Abbreviated Title: Bintrafusp alfa in ONB

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Title: Phase 2 Study of **B**intrafusp **a**lfa in **R**ecurrent/Metastatic **O**lfactory **N**euroblastoma (BARON)

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Drug Name:	Bintrafusp alfa (M7824, MSB0011359C)
IND Number:	154950
Sponsor:	CCR, NCI
Manufacturer:	EMD Serono, Inc.
Supplier:	EMD Serono, Inc.

Commercial Agents: None

PRÉCIS

Background:

- Olfactory neuroblastoma (ONB, also known as esthesioneuroblastoma), is a rare malignant neoplasm of the nasal cavity. At diagnosis, ONB is often locally advanced. It tends to invade locally and has high rates of regional spread to the neck, and distally to the lungs and bones. The 10-year survival rate for ONB is reported at 46%.
- Standard of care treatment is surgical resection followed by adjuvant radiation. In advanced unresectable or metastatic cases, systemic chemotherapy is used off label, with agent selection based on published case series. Genomic profiling of ONB has not yet informed the utilization of an appropriate molecularly targeted treatment.
- High PD-L1 expression by immunohistochemistry was shown in ONB tumor samples, providing a rationale for immune checkpoint blockade in ONB. In addition, high expression of transforming growth factor beta (TGF-β) ligands has been identified in ONB, implying that additional benefit may be achieved by combination of checkpoint blockade with TGF-β inhibition.
- Bintrafusp alfa is a novel bifunctional fusion protein composed of a blocking monoclonal antibody against PD-L1 fused with the soluble extracellular domain of the human TGF-β receptor II (TGF-βRII), acting as a decoy target for TGF-β. The safety profile of bintrafusp alfa in clinical trials to date has been shown to be manageable.

Objective:

- To assess the objective response rate (ORR) to bintrafusp alfa in participants with recurrent/metastatic ONB, immune checkpoint-naïve (CN)

Eligibility:

- Participants must have histologically confirmed recurrent or metastatic ONB, not amenable to potentially curative local therapies.
- Participants should have received at least one line of systemic therapy including a platinum agent, with evidence of disease progression clinically or radiographically.
- Presence of ≥ 1 lesion measurable by RECIST 1.1 criteria
- Age ≥ 18 years, men and women
- Adequate organ function, and without serious comorbidity (e.g., autoimmune disease), that would preclude concurrent systemic treatment.

Design:

- Single-institution, single-arm Phase II trial to determine ORR in participants with recurrent/metastatic ONB treated with bintrafusp alfa.
- Participants will be treated with bintrafusp alfa 1200 mg every 2 weeks for 26 doses.
- The trial will initially enroll 12 checkpoint-naïve (CN) participants; if responses are observed in one or more participants, the second stage will enroll another 9 CN participants to define the response rate to bintrafusp alfa, for a total of 21 CN participants.

- An additional cohort of checkpoint-resistant (CR) participants will be enrolled and evaluated separately. Initially 5 CR participants will be enrolled; if responses are observed in one or more participants, the second stage will enroll another 3 participants, for a total of up to 8 CR participants. Accrual for CR participants will end when the preset number of CN participants has been accrued.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To determine the objective response rate (ORR) to bintrafusp alfa according to RECIST 1.1(1) in participants with immune checkpoint-naïve, recurrent or metastatic Olfactory Neuroblastoma (ONB)

1.1.2 Secondary Objectives

- To assess the safety and tolerability of 1200 mg bintrafusp alfa administered once every 2 weeks in participants with recurrent or metastatic ONB
- To assess Duration of Response (DOR)
- To assess Progression Free Survival (PFS).
- To assess Overall Survival (OS)

1.1.3 Exploratory Objectives

- To perform immune corelative studies in the peripheral blood as well as in the tumor, including, but not limited to immune cell subset quantitative and functional analyses, PD-L1 expression, evaluation of soluble factors and intra-tumoral changes before and after treatment with bintrafusp alfa (studies may be performed in selected participants where adequate samples (blood/tissue) and resources are available)
- To develop *in vitro* organoid ONB models for evaluation of immunotherapeutic approaches in vitro
- To evaluate antitumor efficacy per iRECIST (3)
- To determine the ORR in immune checkpoint-resistant participants
- To assess pharmacokinetics (PK) of bintrafusp alfa and anti-drug antibodies (ADA)

1.2 BACKGROUND AND RATIONALE

1.2.1 Introduction

Olfactory neuroblastoma (ONB), also known as esthesioneuroblastoma, was first described by Berger et al in 1924. (4) It is a malignant neuroectodermal tumor of the nasal cavity developing in the superior portion of the nasal vault, believed to arise from the stem-cell-like basal cells of the olfactory neurosensory epithelium. (5-8) ONB is very rare, with a reported incidence of 0.4 per million(9) and accounts for 3% of all the tumors found in the nasal cavity. (6) The Surveillance Epidemiology and End Results (SEER) 1973-2015 database contains a total of 949 participants with ONB. (10) There is a slight male predilection (54.8%) in population based studies (11), while in terms of age distribution it has been reported as diagnosed in all decades, with a peak in the fifth or sixth decade, and published cases have been largely in whites. (6) A query of the database of the genomics corporation Foundation Medicine compiled a cohort of 75 participants from 2013-2019 (median of 9 participants annually, range 7 – 17 participants), with 44/75 (58.6%) men and 41.3% women, and median age 54.4 years, (range 16-8 years) (unpublished data).

Due to the location of ONB in the sinonasal tract and anterior skull base, the presenting symptoms are often non-specific, including nasal obstruction and epistaxis, thus participants often present at advanced stages. (7, 12) ONB has a propensity for local invasion (i.e., orbit, cranium), and lymph

nodes are involved in up to 10% at diagnosis, while the probability of recurrence in the neck nodes has been reported up to 20-30%, (6, 7, 9, 13) and the reported survival at 15 years being 17% after recurrence of the neck. (14) Distant metastases develop in 12-39% of participants, with a median time-to-distant metastases of 15 months (ranging from 0.75 to 276 months)(14, 15), most commonly to the neck, lungs, and bones, but also drop spinal metastases and brain metastases, with a 2-year survival of 63% (15), and a 5-year survival of 42%. (14)

Comparative genomic hybridization has been employed to analyze the copy number variations in small cohorts of ONB participants. However, while these studies have demonstrated some chromosomal instability, the results generated by various studies have been highly heterogeneous, making correlation analysis and generalizations across studies challenging. (16-22) A comprehensive genomic profiling of 41 recurrent or refractory ONB tumors reported *TP53* mutations in 17% of these samples, followed by *NF1, PIK3CA,* and *CDKN2C,* mutated in <7% of samples of participants. They also reported 4.8% (2/41) with mutations in isocitrate dehydrogenase-2 (*IDH2*), both involving codon R172. (22) An expansion of this study is the aforementioned Foundation Medicine cohort. In this cohort, the microsatellite instability status is available in 64/75 participants, with only one being MSI-high 1/64 (1.56%). The tumor mutation burden (TMB) is 1.7 (test threshold for high: 10 mutations per mega base), with a range of 0 to 7.8 mutations per mega base; the MSI-H sample is an outlier with a TMB of 27 mutations per mega base (unpublished data). The most frequently altered gene is *TP53*, in 24% (18/75) of participants, with *CDKN2C* following, altered in 16% (12/75) participants, while IDH2 is mutated in 4% participants (3/75), two involving the codon R172 and the third involving codon R149 with a missense mutation. A recent multi-omic analysis of 14 ONB tumor samples reported a similar rate of *TP53* mutations (21.4%) and in addition confirmed the presence of mutations in isocitrate dehydrogenase-2 (*IDH2*) R172 codon, in a higher proportion of tumors (7/42 participants, 16.7%). (23)

1.2.2 Current standard of care for ONB

The current treatment paradigm for newly diagnosed local and locoregional ONB involves complete surgical resection, followed by adjuvant radiation therapy, which provides the best overall survival (OS) and progression-free survival (PFS). (8, 24) The extend and route of surgical resection depend upon the location and spread of the disease and may include endoscopic unilateral or bilateral approaches, combined endoscopic and open approach, or craniofacial resection. (7, 25) Surgery is often well tolerated in these participants but post-operative complications may include bleeding, infection such as meningitis, cerebrospinal fluid leak, and tumor recurrence. (25) Adjuvant radiation administered within 6 weeks after primary surgery has shown to be superior than delayed irradiation (administered 6 weeks to 2 months after surgery) in terms of disease-free time and time to recurrence with metastasis. (24) Neoadjuvant chemotherapy with or without radiation therapy has also been used, resulting in decrease of disease-related mortality in participants that responded to it. (26)

For recurrence of ONB in the lymph nodes of the neck, surgery and radiation are used to achieve locoregional control, however the risk of distant metastases is high in these participants. (14, 15) A recent systematic review and meta-analysis of metastatic ONB reported 83 of 678 participants (12%) with a median time-to-distant-metastasis after primary diagnosis of 15 months (range 0.75 – 276 months). Of the 48 studies with enough data for survival analysis, they reported a 6-month survival rate after distant metastasis of 63%, decreasing to 56% for those who received chemotherapy. Across all the studies analyzed by the authors, at total of 21 different

chemotherapies were used, with 66% of the studies implementing a platinum-based regimen, and 37% also including etoposide; there is no tabulation of toxicity data. (15) The same study further concluded that the combination of chemotherapy with surgery and/or radiation was associated with improved survival in the metastatic setting. Sunitinib monotherapy and sunitinib combined with cetuximab have induced complete responses in case reports of two participants (27, 28) but there is no case series describing ONB participants treated with a molecularly targeted agent. In addition, there is no published case series or case report of immunotherapy in ONB.

1.2.3 Immune checkpoint and TGF-β blockade

Tumors evade the immune system via tolerogenic pathways. A well characterized tolerogenic pathway is the programmed death 1 (PD-1)/ programmed death-ligand 1 (PD-L1) checkpoint pathway, which involves interactions between the programmed death 1 (PD-1) molecule on T cells and the programmed death-ligand 1 (PD-L1) present on tumor cells. This interaction leads to suppression of T cell signaling and promotes immune tolerance. Consequently, blockade of the PD-1/ PD-L1 pathway has been exploited therapeutically, and immune checkpoint blockade monoclonal antibodies (ICBMs) have been successful in inducing responses in many different malignancies. The efficacy of PD-L1 monoclonal antibodies in particular has been shown to be predicted by the presence of PD-L1 in the tumor (29-31). However, the response rate is low (~15% objective response across indications), and strategies attempting to increase the efficacy of anti-PD-L1 antibodies include combinations with agents targeting immunomodulatory factors of the tumor microenvironment, (32) such as TGF-β.

TGF-β is a multifunctional cytokine with three isoforms, TGF-β1, TGF-β2, and TGF-β3, which bind to high-affinity cell-surface receptors in a cascade leading to SMAD-mediated transcriptional activation or repression of genes controlling cell growth, differentiation, and migration. In cancer, these result in promoting epithelial-to-mesenchymal transition, invasion, and metastasis (33, 34) but also in local suppression of both T cell and NK cell function. (35-39) In mice, the absence of CD4+ and regulatory T cell-derived TGFβ1 has been shown to inhibit tumor growth, (40) while inhibition of TGF-β in combination with checkpoint blockade has been shown previously to be advantageous. (41, 42)

1.2.4 Bintrafusp alfa drug product, preclinical pharmacology

Bintrafusp alfa (M7824; anti-PD-L1/TGF-βRII) is a novel bifunctional fusion protein composed of a fully human IgG1 mAb against PD-L1 fused to the soluble extracellular domain of human transforming growth factor-beta receptor II (**Figure 1**) that binds TGF-β superfamily ligands, which has been co-developed by the NCI LTIB in collaboration with the CRADA partner EMD Serono. The anti-PD-L1 moiety of bintrafusp alfa is based on avelumab. Functionally, bintrafusp alfa mediates antibody-dependent cellular toxicity, increases expression of T-cell trafficking-related molecules in the tumor cells, enhances antigen-specific and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-specific CD8+ lymphocyte mediated tumor cell lysis, and reduces immunosuppressive activity induced by TGF-β. (43, 44)

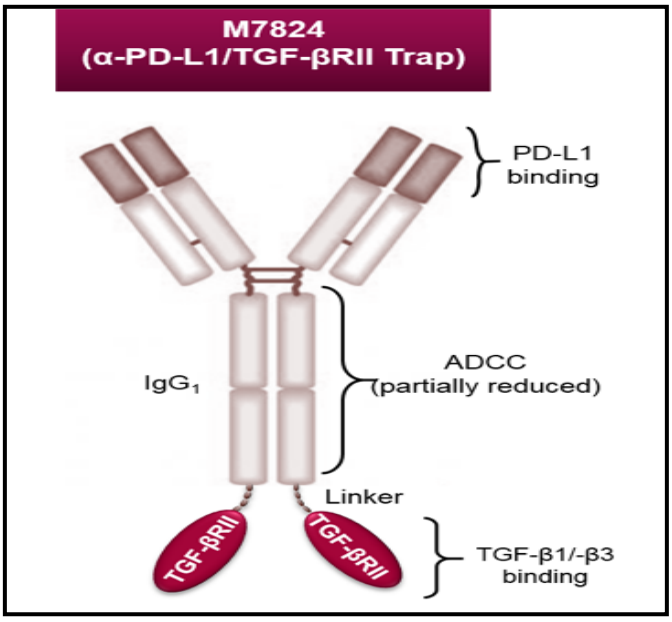


Figure 1: Bintrafusp alfa (PD-L1/TGF-βRII) molecule

Work with the *in vivo* preclinical murine carcinoma models has shown anti-tumor activity of bintrafusp alfa (**Figure 2** A). In these models, bintrafusp alfa accumulates in the tumor microenvironment (**Figure 2**B), decreases TGF-β signaling, as shown by significantly decreased SMAD2 phosphorylation (**Figure 2**C), and increases CS8+ and NK cell activity (**Figure 2**D). (45)

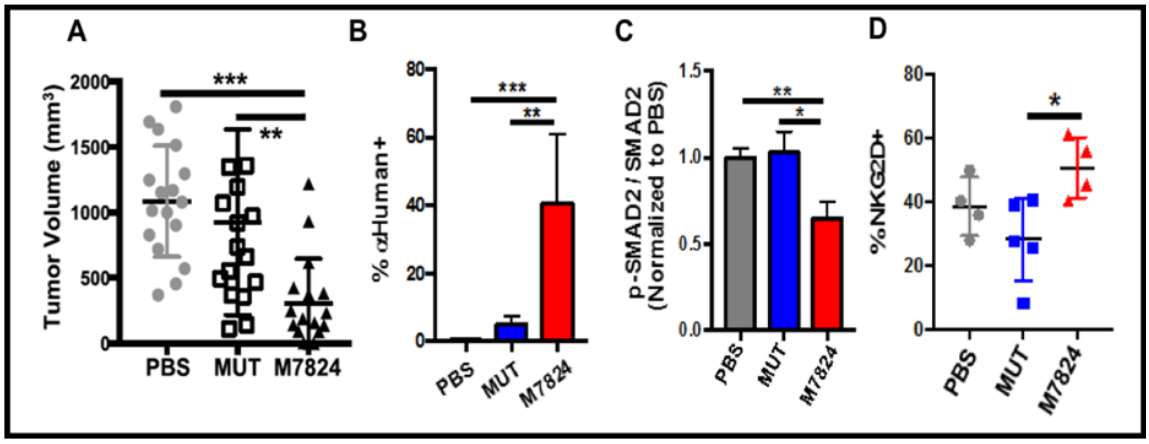


Figure 2: Bintrafusp alfa decreases TGF-β signaling in the tumor microenvironment

(A) Comparison of anti-tumor activity of bintrafusp alfa, and bintrafusp alfa (mut) devoid of PD-L1 binding site in the EMT6 breast cancer model. (B) Accumulation of bintrafusp alfa in the TME resulting in (C) reduction of SMAD2 signaling and (D) increased T- and NK-cell activation.

The advantage of using the anti-PD-L1/TGF-βRII antibody-ligand fusion protein over using anti-CTLA4 or anti-PD-1/PD-L1 as monotherapy or in combination with an anti-TGF-β monoclonal antibody was shown in preclinical models. (34, 46)

1.2.5 Bintrafusp alfa clinical efficacy and safety

The first-in-human Phase I dose escalation study of bintrafusp alfa in participants with advanced solid tumors was conducted at the CCR (47). This work demonstrated on-target PD-L1 saturation, sequestration of circulating TGF-β, and early evidence of clinical efficacy (**Figure 3**) across all dose-levels, in a cohort of heavily pretreated participants.

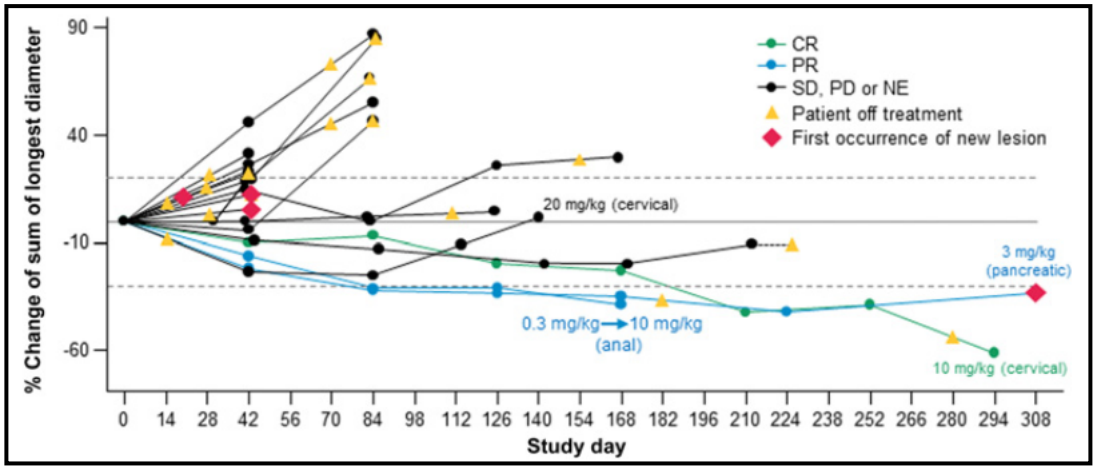


Figure 3: First-in-human Phase 1 trial of bintrafusp alfa. Objective responses in solid tumors.

Further clinical testing in 43 participants with HPV-associated, pre-treated, checkpoint-naive metastatic cancers reported a 38.9% total clinical response rate (complete response, partial response and delayed partial response – the latter being partial response after an initial progression of disease), regardless of PD-L1 expression (**Figure 4**). (48) The reported response rate is notably higher than the 12-24% response rate seen with blockade of PD-1 or PD-L1 alone for HPV-associated malignancies (e.g., cervical, anal, P16+ oropharyngeal) in the literature. (49-54)

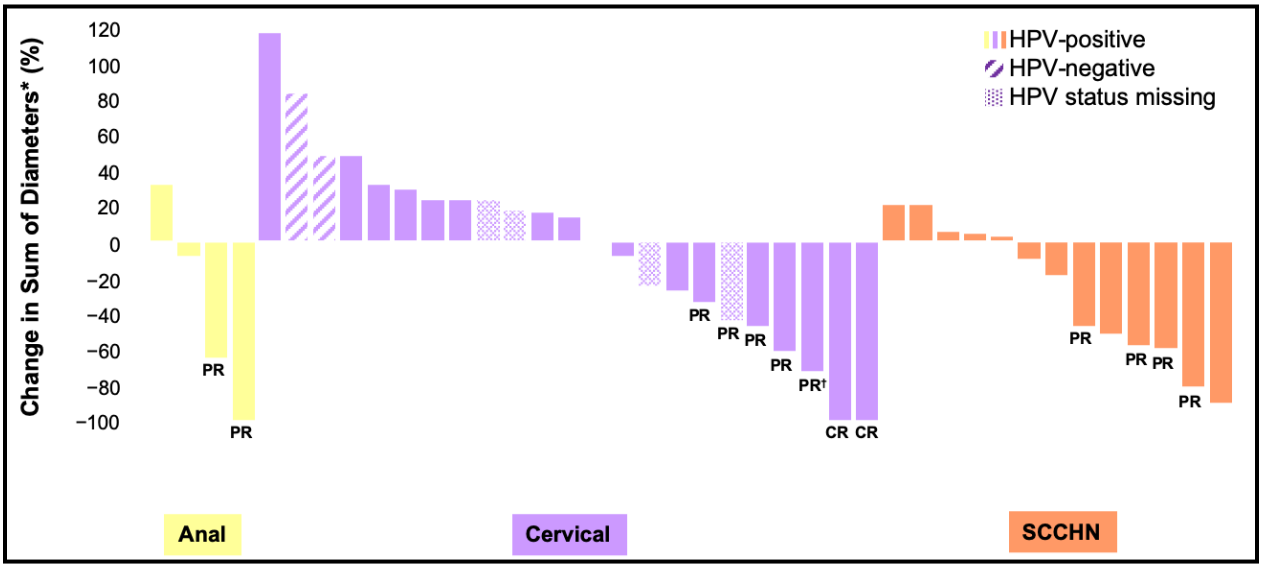


Figure 4: Bintrafusp alfa in participants with metastatic HPV-associated cancers.

Waterfall plot of confirmed best overall responses in participants with immune checkpoint inhibitor-naïve, recurrent/metastatic HPV-positive OPSCC (orange).

In the context of non-HPV-associated malignancies, such as in a population of 80 pretreated (no prior immunotherapy) participants with advanced non-small cell lung cancer, the overall response rate to bintrafusp alfa was 25% in the overall (PD-L1 unselected) population (20/80 participants), 31% (18/58) in the PD-L1+ (≥1%) population and 53.8% (7/13) in the PD-L1 high (≥80%) population. (55) In comparison, in a single-arm trial of 184 pretreated NSCLC participants (no prior immunotherapy), the objective response rate was 12% in the overall population (56), while in a randomized, open-label comparison of avelumab vs. docetaxel in pretreated NSCLC participants reported an objective response rate of 15% (59/396 participants) in the PD-L1 unselected population, 19% in the PD-L1 >=1% population, 25% in the PD-L1 >=50% population, and 31% in the PD-L1 >=80% population. (57)

For data on the safety of bintrafusp alfa, please refer to Section **14.1.2**

1.2.6 Rationale for immune checkpoint blockade and combination with TGF-β blockade in ONB

As discussed in Section **1.2.1**, while the existing data on ONB are retrospective and therefore quite heterogeneous, there is a consensus that the natural history of ONB involves a high rate of locoregional recurrences and distant metastases, which portend a poor prognosis.

Consequently, there is an unmet need for improved systemic treatments, especially for the participants with recurrent and metastatic disease. Chemotherapy in ONB has been reported in case reports, case series, and systematic reviews to result in responses, even complete ones, but there has been no prospective trial of a single regimen or a comparison of different regimens leading to the establishment of a standard of care regimen. Furthermore, there has been no published report of any cytotoxic agent or combination of agents tested in a preclinical model, which might provide data to inform further development of a therapeutic regimen with cytotoxic chemotherapy. In addition, the existing genomic analyses of ONB have revealed a low frequency (16.7%) of a druggable mutation, IDH2 in particular (Section **1.2.1**), which leaves the remaining 83.3% without an option for a targeted agent. We have therefore studied the tumor microenvironment to examine the potential for immunotherapy in ONB.

A recent study of 10 ONB samples reported negative results from immunohistochemistry (ICH) for PD-L1(60), but a subsequent study of ONB examined 36 primary ONB samples with immunohistochemistry for PD-L1 expression on tumor and immune cells and reported 14 samples (39%) having a positive score of ≥1% for expression on both tumor cells and immune cells. (23) The presence of PD-L1 was confirmed by immunohistochemistry studies from the London lab: samples from 10 participants were available, six primary lesion samples (non-paired) and four pairs of primary – metastatic lesion samples. In the non-paired group 4 primary ONB lesion samples demonstrated positive PD-L1 staining (**Figure 5**). (61) In the paired group, all primary lesion samples were negative, but three of the metastatic lesion samples were positive for PD-L1; summarily, for the primary lesions 4 of 10 were positive (40%), and for the metastatic lesions 3 of 4 (75%) where positive; if pooled together, 7 out of 14 (50%) were positive. All PD-L1 positive samples were found to contain PD-1^{+} tumor cells (**Figure 6**).An explanation for the negative initial study for PD-L1 may be randomness due to the small sample size and underlying stratification (primary vs. metastatic).

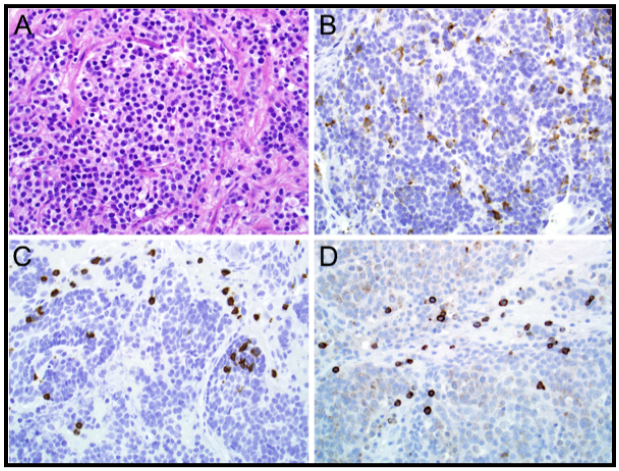


Figure 5 Primary olfactory neuroblastoma.

In a primary olfactory neuroblastoma (**A**, H&E), immunohistochemistry demonstrates PD-L1 expression in a subset of tumor cells (**B**, brown chromagen), PD-1 expression in scattered tumor cells as well as lymphocytes in the tumor and stroma (**C**, brown chromagen), and CD8 expression in lymphocytes in the tumor and stroma (**D**, brown chromagen) (All 40x).

The percentage of tumor cells staining positive for PD-L1, which has been described as the tumor positive score and is a predictive biomarker for response to immune checkpoint blockade in some tumors, is presented in **Table 1**.

Furthermore, PD-L1$^+$ primary and metastatic tumors demonstrated increased PD-1$^+$ infiltrating lymphocytes in the tumor and CD8$^+$ lymphocytes in the tumor and stroma compared to PD-L1 negative tumors ($P<0.05$; **Table 2**).

Tumor infiltrating CD8 and CD4 lymphocytes were also examined in the multi-omic study of ONB by Classe et al, which reported their presence ranging from 0-350 cells per mm^2. In addition, the group of ONB samples with the higher CD8 counts had higher mRNA levels of cytotoxic cell markers, T cell invasion chemokines, immune checkpoints and ligands, as well as suppressive factors, including *TGFB*, **Figure 7**) (23).

PD-L1+ tumor cells (%)										
Primary	0	0	1	5	10	20	0	0	0	0
Metastatic	N/A	N/A	N/A	N/A	N/A	N/A	0	1	2	5

Table 1. PD-L1 positive tumor cells (%).

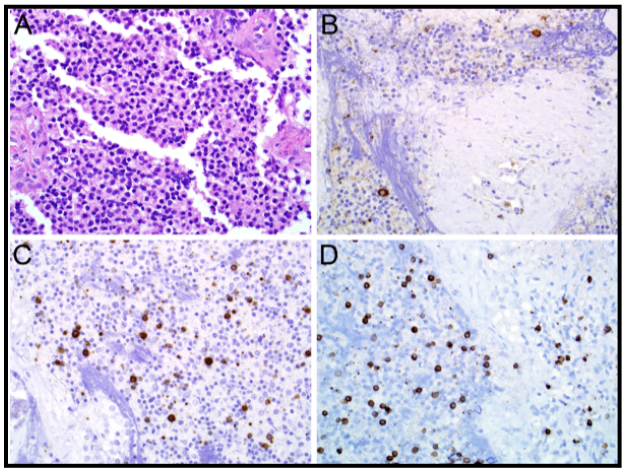


Figure 6 Metastatic olfactory neuroblastoma.

In a metastatic olfactory neuroblastoma (**A**, H&E), immunohistochemistry demonstrates **PD-L1** expression in rare tumor cells (**B**, brown chromagen), **PD-1** expression in occasional tumor cells as well as lymphocytes in the tumor and stroma (**C**, brown chromagen), and CD8 expression in lymphocytes in the tumor and stroma (**D**, brown chromagen) (All 40x).

	Average PD-1$^+$ lymphocytes in tumor ± S.E.M.	Average PD-1$^+$ lymphocytes in stroma ± S.E.M.	Average CD8$^+$ lymphocytes in tumor ± S.E.M.	Average CD8$^+$ lymphocytes in stroma ± S.E.M.
PD-L1$^+$ ONB	8.29 ± 2.97	13.86 ± 5.38	13.86 ± 4.73	15.29 ± 2.66
PD-L1$^-$ ONB	0.71 ± 0.29	3.0 ± 0.62	1.86 ± 0.4	7.14 ± 0.63
Fold increase	11.6 (P<0.05)	4.62 (P=0.068)	7.46 (P<0.05)	2.14 (P<0.05)

Table 2. Correlation between PD-L1 expression and ONB lymphocyte infiltration.

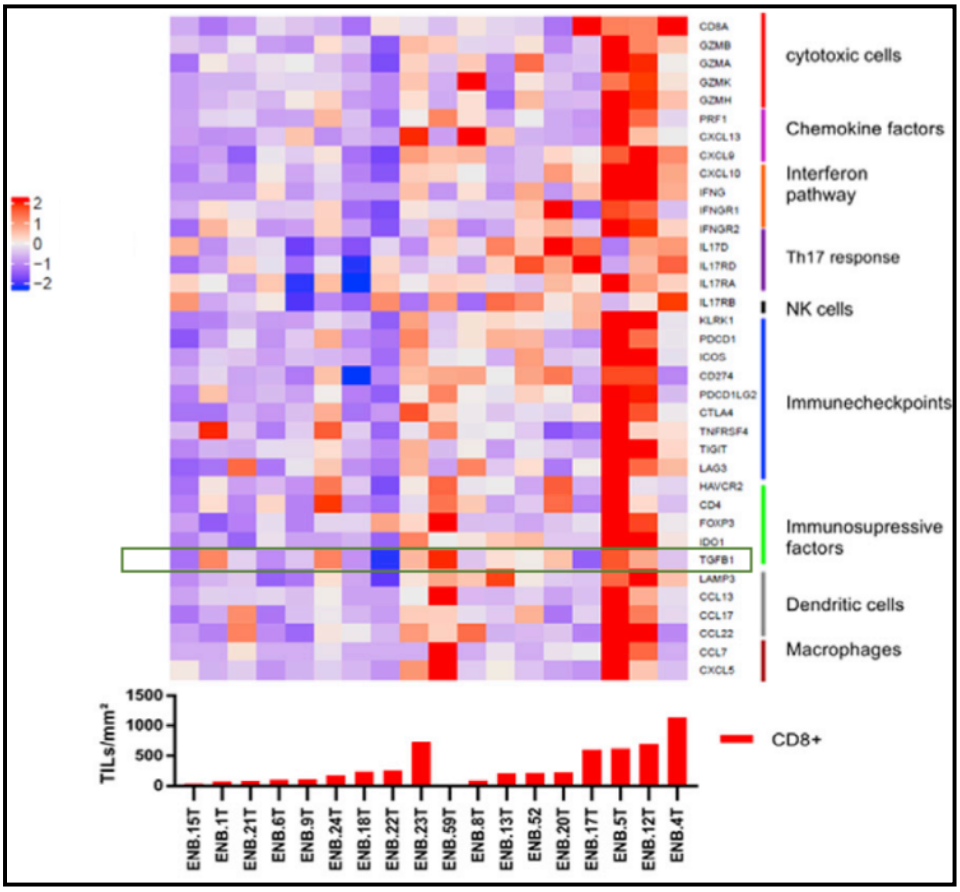


Figure 7 Immune gene expression heatmap and CD8+ TILs in ONB.

Using whole-transcriptome RNA-Seq data from the study by Classe et al, we can compare the levels of mRNA for *CD274, TGFB1, TGFB2, and TGFB3* in ONB with those in some of the tumors included in TCGA (**Figure 8**). We can observe that the CD274 mRNA levels in ONB are quite comparable to those in cutaneous melanoma, cervical squamous carcinoma, and head and neck squamous carcinoma, tumors where ICBMs have been approved by the FDA. We can also observe that mRNA levels for the genes of the TGF-β ligands (TGFB1, TGFB2, TGFB3) are

higher than in cutaneous melanoma, cervical squamous carcinoma, and head and neck squamous carcinoma, tracking those of breast cancer, a tumor which has resisted immunotherapy thus far.

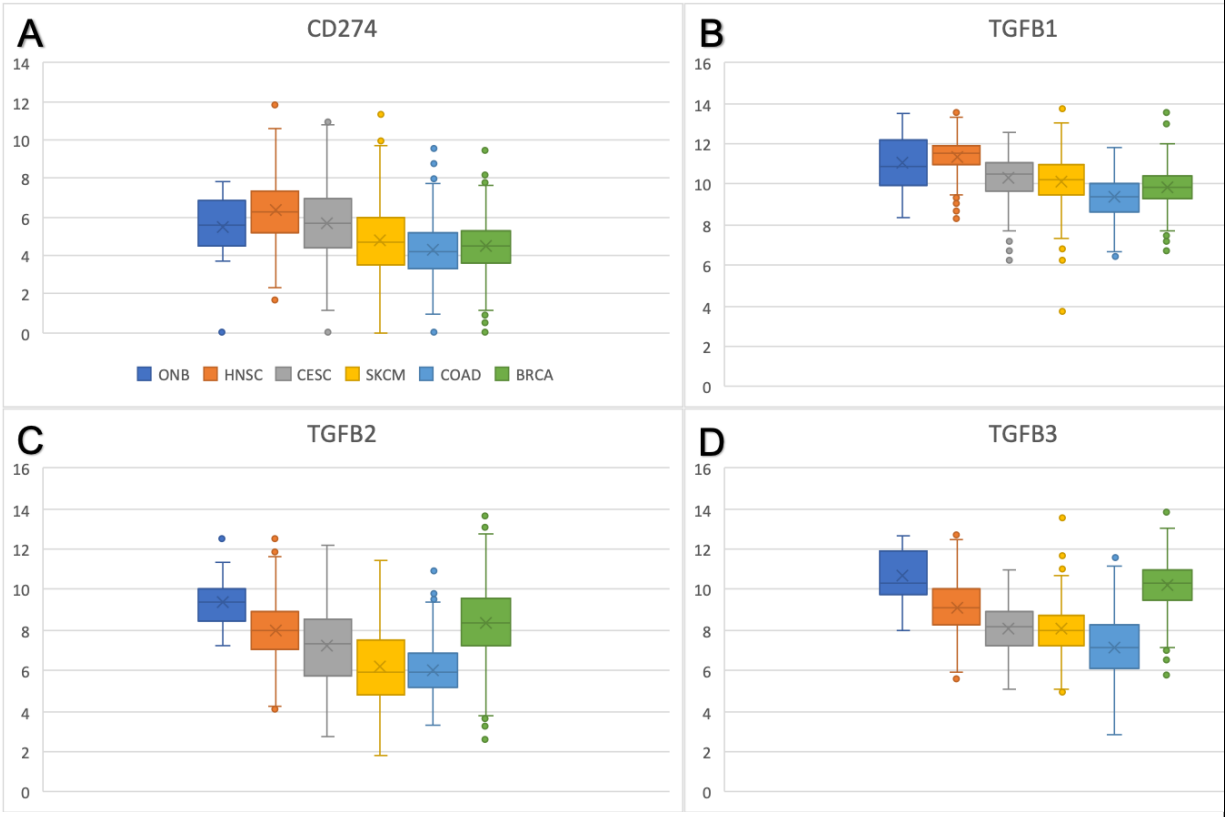


Figure 8 CD274 and TGFB ligands mRNA in ONB and other types of tumors

Gene-level transcription estimates (log2(x+1) transformed RSEM normalized counts). ONB: Olfactory neuroblastoma, HNSC: head and neck squamous cancer, CESC: cervical squamous cancer, SKCM: cutaneous melanoma, COAD: colon adenocarcinoma, BRCA: breast cancer. Results in part based upon data generated by the TCGA Research Network: https://www.cancer.gov/tcga.

Thus, a proportion of ONB primary and metastatic tumors express PD-L1 and possesses an associated infiltrate of PD-1^{+} and CD8^{+} lymphocytes, which may render them susceptible to immune checkpoint blockade, while at the same time they also have high levels of mRNA for TGF-β ligands, which may drive immunosuppression in the microenvironment. Taken together, these data suggest that choosing bintrafusp alfa, which combines blockade of PD-L1 and TGF-β signaling, rather than a-PD-L1, is a rational therapeutic strategy for ONB.

1.2.7 Bintrafusp alfa dose and schedule rationale

The dose of bintrafusp alfa is derived from previous experience using this drug in multiple studies here at the National Institutes of Health. Thus, 1200mg will be administered intravenously once every 2 weeks.

1.2.8 Rationale for performing exploratory studies

Due in part to the rare nature of ONB and to the lack of development of *in vitro* or *in vivo* models to study this disease, few exploratory studies have been reported in the literature. This underscores

the importance for the development of models to study this disease as described in this proposal. These exploratory studies will provide critical insight into the biology of this disease and help to guide the development and refinement of subsequent clinical trial protocols in the future.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Histologically or cytologically confirmed recurrent or metastatic ONB not amenable to potentially curative local therapies. Review of tissue samples by Pathology at the NIH is preferred.

2.1.1.2 Participants must have measurable disease, per RECIST 1.1. See Section **6.3** for the evaluation of measurable disease. A previously treated lesion by radiotherapy can be chosen as the target lesion only if progression in the respective lesion has been demonstrated during or following radiotherapy.

2.1.1.3 Participants should have received at least one line of systemic therapy including a platinum agent, with evidence of disease progression clinically or radiographically.

2.1.1.4 Men or Women ≥18 years of age on day of signing informed consent. Because no dosing or adverse event data are currently available on the use of bintrafusp alfa in participants <18 years of age, children are excluded from this study.

2.1.1.5 ECOG performance status (PS) ≤2 (see **Appendix A**).

2.1.1.6 Participants must have adequate organ and marrow function as defined below:

Absolute neutrophil count (ANC)	≥1,500/mcL
Hemoglobin	≥ 9 g/dL (transfusions allowed)
Platelets	≥ 100,000/mcL
Serum Creatinine **OR** Measured CrCl or eGFR by CKD-EPI formula may be used to estimate CrCl/eGFR	≤ 1.5 × ULN **OR** ≥ 30 mL/min/1.73m^2 for participant with creatinine levels > 1.5 × institutional ULN
Serum **total** bilirubin **OR** **Direct** bilirubin	≤ 1.5 × upper limit of normal (ULN) **OR** ≤ ULN for participants with **total** bilirubin levels > 1.5 × ULN
AST(SGOT) and ALT(SGPT)	≤ 2.5 × ULN

2.1.1.7 The effects of immunotherapy on the developing human fetus are unknown. Therefore, participants must use effective methods of contraception (such as implants, injectables, combined oral contraceptives, IUDs, sexual abstinence or vasectomized partner).

- Women of child-bearing potential (**WOCBP**: any woman who has experienced menarche and has not had hysterectomy or bilateral oophorectomy or is not postmenopausal (amenorrheic 12 months or more following cessation of exogenous hormonal treatments; if <50 years old need follicle stimulating hormone FSH in the post-menopausal range)) must agree to use highly effective contraception prior to study entry and for up to 65 days following the last dose of study treatment.
- Men must agree to use highly effective contraception prior to study entry and up to 125 days following the last dose of study treatment.
- Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

2.1.1.8 Participants with bone metastases or hypercalcemia on intravenous bisphosphonate treatment, zolendronic acid, denosumab, or similar agents are eligible to participate and may continue this treatment.

2.1.1.9 Participants with treated CNS ONB lesions are eligible if follow-up brain imaging after at least a month following central nervous system (CNS)-directed therapy shows no evidence of progression.

2.1.1.10 Participants with new or progressive non-intraparenchymal CNS ONB lesions are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.

2.1.1.11 Human immunodeficiency virus (HIV)-positive participants must have CD4 count ≥ 200 cells per cubic millimeter at enrollment, be on stable antiretroviral therapy for at least 4 weeks and have no reported opportunistic infections or Castleman's disease within 12 months prior to enrollment.

2.1.1.12 For participants with serological evidence of chronic hepatitis B virus (HBV) infection, the HBV DNA viral load must be undetectable on suppressive therapy, if indicated.

2.1.1.13 For participants with serological evidence of HCV infection, the HCV RNA viral load must be negative to be eligible for study participation.

2.1.1.14 Ability of participant to understand and the willingness to sign a written informed consent document.

2.1.1.15 Must co-enroll in the following two studies. A separate inform consent will be obtained from participant for these studies.

- 21-C-0009: "A Natural History Study of Children and Adults with Olfactory Neuroblastoma," and
- 18-DC-0051: "Biospecimen procurement for NIDCD clinical protocols"

2.1.2 Exclusion Criteria

2.1.2.1 Anticancer treatment, concurrent or prior (chemotherapy, monoclonal antibody, cytokine therapy, immune therapy, targeted small molecule therapy) or any

investigational drug, within 4 weeks or 5 half-lives (whichever shorter) prior to the first drug administration. All residual treatment-related toxicities must have resolved or be minimal and not constitute a safety risk. **Note:** Palliative radiotherapy is permitted concurrently or within the pretreatment period. Subjects receiving bisphosphonates or denosumab are eligible provided treatment was initiated at least 14 days before treatment.

2.1.2.2 Participants who received prior checkpoint blockade therapy and were taken off treatment for serious adverse events related to immuno-therapy are excluded.

2.1.2.3 Major surgery within 4 weeks prior to the first drug administration (minimally invasive procedures such as diagnostic biopsies are permitted).

2.1.2.4 Active or prior documented autoimmune or inflammatory diseases that might deteriorate on immunostimulatory agent (including colitis or Crohn's disease, systemic lupus erythematosus, sarcoidosis, vasculitis, Grave's disease, hypophysitis, uveitis, rheumatoid arthritis etc.), **except** the following:

- Type I diabetes mellitus
- Chronic skin conditions that do not require systemic therapy (including eczema, vitiligo, alopecia, psoriasis)
- Hypothyroidism (e.g., post-Hashimoto thyroiditis) stable, on hormone replacement
- Mild autoimmune disease not active in the last 5 years may be eligible after consultation with the principal investigator.

2.1.2.5 Current use of immunosuppressive medication within 14 days before the first dose of the study medication, **except** the following:

- Intranasal, inhaled, topical glucocorticoids; locally injected glucocorticoids (i.e. intra-articular, intra-ocular)
- Systemic glucocorticoids at physiologic doses (generally ≤ 10 mg prednisone or equivalent per day)
- Glucocorticoids as premedication for contrast-enhanced studies is allowed prior to enrollment and on study.

2.1.2.6 Uncontrolled intercurrent chronic or acute illness including, but not limited to the following, that may limit interpretation of results or increase risk to the participant in the judgment of the investigator:

- Bleeding diathesis or recent (<3 months) clinically significant bleeding event.
- Prior organ transplantation including allogenic stem-cell transplantation
- Impaired cardiovascular function or clinically significant cardiovascular disease, including, but not limited to, any of the following:
  - cerebral vascular accident/stroke (< 3 months prior to enrollment),
  - acute coronary syndromes (including myocardial infarction < 6 months prior to enrollment, unstable angina),

  - Congestive Heart Failure (≥ New York Heart Association Classification Class III); CHF Class II must have been stable for 3 months prior to enrollment
  - history or presence of clinically significant cardiac arrhythmia including resting bradycardia, uncontrolled atrial fibrillation or paroxysmal supraventricular tachycardia (controlled arrhythmias, e.g. stable atrial fibrillation, may be allowed at the discretion of the investigator),
  - history of myocarditis
- History of idiopathic pulmonary fibrosis, drug-induced or idiopathic pneumonitis, active interstitial lung disease, blood oxygen saturation <90% at rest (on ambient air).
- Clinically significant hepatic disease.
- Active infection requiring systemic therapy (minor infections may be allowed at the discretion of the investigator).

2.1.2.7 Subjects unwilling to accept blood products as medically indicated.

2.1.2.8 Vaccination with live vaccines within 4 weeks of the first dose of treatment and while on study is prohibited. Inactivated vaccines may be administered.

2.1.2.9 History of allergic reactions or hypersensitivity attributed to compounds of similar chemical or biologic composition to bintrafusp alfa. Participants with history of severe hypersensitivity reaction to monoclonal antibodies (grade ≥ 3 NCI-CTCAE v5) will be evaluated by the allergy/immunology team prior to enrollment.

2.1.2.10 History of second malignancy within 3 years of enrollment except for the following: adequately treated localized basal cell or squamous skin cancer, cervical carcinoma in situ, superficial bladder cancer, other localized malignancy which has been adequately treated or malignancy which does not require active systemic treatment (e.g. low risk CLL).

2.1.2.11 Pregnant or breastfeeding women are excluded from this study because the study medications have not been tested in pregnant women and there is potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with the study medications, breastfeeding should be discontinued if the mother is treated on this protocol.

2.1.3 Recruitment Strategies

The study may be abstracted to a plain language announcement posted on NIH website, on NIH social media forums, and on www.clinicaltrials.gov. A link to the clinical trial from www.clinicaltrials.gov will be placed on the investigators' NIH research websites. Following IRB approval of the recruitment materials, this study may be posted at national conferences including AACR, ASCO, North America Skull Base Society (NASBS) meeting, American Rhinologic Society (ARS) meeting, American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) meeting, American Head and Neck Society (AHNS) meeting, local sinonasal/skull base CME courses and/or symposia, and may also be shared with the organizations including Rare as One, NASBS, ARS, AAO-HNS, AHNS, National Organization for Rare Disorders (NORD), Genetic Alliance, Global Genes, TRAIN, and HRA who may advertise it further. the Office for Participant Recruitment services will be utilized to and the study will be added to the Research Match site (www.researchmatch.org).

Outside physicians may directly refer participants for screening to the study and participants may be self-referred. Study participants may also be recruited from the population of participants screened for or participating in the ONB natural history protocol.

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed after the subject has signed the study consent or the consent for study 01-C-0129 (provided the procedure is permitted on that study) on which screening activities may also be performed.

Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

<u>Any time prior to initiation of study therapy:</u>

- Histologic confirmation by the NCI Laboratory of Pathology: archival tumor samples will be requested from each participant; if there is no available tumor sample or pathology report, a biopsy may be performed to confirm the diagnosis.

  NOTE: Pathology report of histologic confirmation by Johns Hopkins Pathology (Dr. Lisa Rooper) may be accepted as evidence of histologic confirmation at the discretion of the PI.

<u>Within 3 months prior to initiation of study therapy:</u>

- HBV, HCV, HIV serologies: may include viral load for HCV, HBV and HIV if clinically indicated. CD4 testing may also be required for HIV+ participants.

<u>Within 28 days prior to initiation of study therapy:</u>

- Clinical evaluations:
  - Medical history, complete review of concomitant medications and symptoms/side effects; assessment of performance status per ECOG.
  - Physical examination, including height (at screening only), weight, vital signs (i.e., temperature, blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry).
- Laboratory evaluations

- Complete blood count (CBC) with differential.
- Serum biochemical profile:
  - Acute care panel (Na+, K+, Cl-, CO2, creatinine, glucose, urea nitrogen)
  - Mineral panel (albumin, calcium total, magnesium total, phosphorus)
  - Hepatic panel (AST/GOT, ALT/GPT, total bilirubin, direct bilirubin, alkaline phosphatase)
- Troponin I
- Amylase, lipase
- Creatine kinase (CK/CPK)
- Thyroid function tests: thyroid stimulating hormone (TSH) and free thyroxine (FT4)
- Lymphocyte phenotype TBNK (T, B, and natural killer cells)
- Urinalysis
- 24-hour urine collection for creatinine clearance (if needed to measure CrCl in cases where serum creatinine > 1.5 X ULN)

- Imaging tests: (**NOTE:** external imaging may be used for screening; however, NIH reading will be used to determine eligibility, and baseline imaging performed at NIH will be required):
  - CT of skull base, neck, chest, abdomen and pelvis, or MRI.
  - Brain MRI or CT, if clinically indicated.
  - PET/CT (FDG or Dotatate)
  - Nuclear bone scan for individuals with known/suspected bone lesions
- Cardiac evaluation:
  - 12-lead EKG

Within 1 week prior to enrollment:

- Urine or serum pregnancy test (β-HCG) for WOCBP (see Inclusion Criteria **2.1.1.7** for definition of WOCBP).

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at:

https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.3.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a laboratory test abnormalities or non-measurable disease may be rescreened.

2.3.2 Treatment Assignment

Cohorts

Number	Name	Description
1	Cohort 1	Participants with recurrent or metastatic ONB, checkpoint-naïve
2	Cohort 2	Participants with recurrent or metastatic ONB, checkpoint-resistant

Arms

Number	Name	Description
1	Arm 1	Treatment with Bintrafusp alfa

Arm Assignment

Participants in Cohorts 1 and 2 will be assigned to Arm 1.

2.4 BASELINE EVALUATION

All participants are required to complete baseline evaluations within the below designated intervals prior to the first planned dosing of the study drug.

Tests performed during screening or on another NIH protocol within the designated time frame before first dose of the study drug do not need to be repeated for the baseline evaluation, unless otherwise indicated:

Within 28 days prior to first dose:

- Baseline research tumor biopsy (optional; does not need to be repeated if biopsy was done during screening or if performed on another NIH protocol)
    - If intranasal disease is present and amenable, endoscopic endonasal tumor biopsy will be performed in an out-participant clinic setting.
    - Core needle biopsy of metastatic disease will be performed, if present and amenable (see Section **5.2.2**).

Within 14 days prior to the first dose:

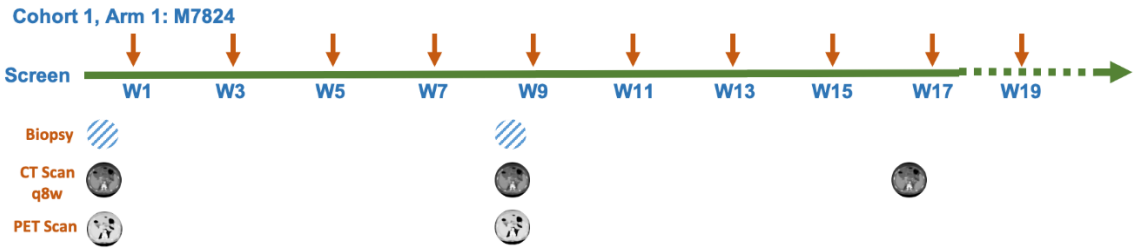
- Clinical evaluations:
    - Medical history (interim, signs and symptoms); review of concomitant medications and symptoms/side effects; assessment of performance status
    - Physical examination, including weight, vital signs (i.e., temperature, blood pressure, heart rate, respiratory rate, oxygen saturation with pulse oximetry), and skin assessment
- Laboratory evaluations:
    - Urine or serum pregnancy test (β-HCG) for WOCBP (see Inclusion Criteria **2.1.1.7** for definition of WOCBP)

- CBC with differential
- Coagulation panel: PT, INR, PTT/aPTT
- Serum biochemical profile:
  - Acute care panel (Na+, K+, Cl-, CO2, creatinine, glucose, urea nitrogen)
  - Mineral panel (albumin, calcium total, magnesium total, phosphorus)
  - Hepatic panel (AST/GOT, ALT/GPT, total bilirubin, direct bilirubin, alkaline phosphatase)
- CRP
- LDH
- Amylase, lipase
- Urinalysis
- Thyroid function tests: thyroid stimulating hormone (TSH) and free thyroxine (FT4)
- Research blood samples for correlative studies. Please refer to Section **5** for details.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a single-site, open-label Phase 2 study of bintrafusp alfa in up to 21 checkpoint-naïve (CN) participants with recurrent or metastatic ONB (see Schema 1). Up to 8 checkpoint-resistant (CR) participants will be enrolled as an additional cohort in parallel with CN participants and evaluated separately; accrual for CR participants will end when the preset number of CN participants has been accrued.



Schema 1: Treatment and response assessment schedule**.**

3.1.1 Treatment period

Participants will be treated with bintrafusp alfa 1200 mg intravenous (IV) every two weeks, for a total of 26 doses, at which point the drug will be withheld. Treatment will continue until completion of 26 doses, disease progression, unacceptable toxicity, or other stopping criterion per Section **3.4.1**.

The primary endpoint of ORR per RECIST 1.1. criteria will be augmented with secondary endpoints including safety, tolerability and PFS, and with exploratory correlative studies.

All ongoing testing and procedures will take place per the Study Calendar (Section **3.7**).

Participants who complete 26 doses of bintrafusp alfa will have the drug withheld and will be followed with surveillance imaging per Section **3.1.3**. However, participants who achieve

complete response, partial response, stable disease without significant toxicity may continue treatment beyond 26 doses of bintrafusp alfa at the discretion of the investigator.

3.1.2 Retreatment

Participants with evidence of disease progression following treatment discontinuation after 26 doses will be allowed re-treatment with bintrafusp alfa using the same dosing regimen, while the trial is ongoing. Retreatment will start after repeat of baseline evaluation and clinical assessment. The second course of treatment will follow the same principles of up to 26 doses, with post-completion imaging surveillance per Section **3.1.3**.

3.1.3 End-of-Treatment

An End-of-Treatment visit should take place as soon as possible within 14 days of the decision to discontinue treatment prematurely before completion of 26 doses (See **Study Calendar** for further details and assessments).

3.1.4 Post-Treatment Follow-Up: Safety and Long-term

A safety follow-up visit will be scheduled within 28 days (+/- 7 days) following last treatment (See **Study Calendar** for further details and assessments).

Subsequent post-treatment follow-up will occur every 3 months (+/- 2 weeks) starting after the safety visit, for the first year, then every 6 months (+/- 4 weeks) for years 2 – 5, and then annually (+/- 6 weeks) thereafter, at the discretion of the investigator (See **Study Calendar** for further details and assessments).

3.2 STUDY ACCRUAL STOPPING RULE

Once the 6th participant had reached the 6 months follow up period (or potentially would have reached the 6 months follow-up if the participant died prior to the 6 months follow-up), the study will be halted for a DSMB review of the available data if more than 85% of participants have PD $\leq$ 6 months following the first dosage. In the absence of literature information on response rates with other treatments in the second-line, his threshold comes from the considerations of acceptable response rates used for sample size determination in Section **10.2**.

3.3 DRUG ADMINISTRATION

3.3.1 Dosage of bintrafusp alfa

Participants will receive bintrafusp alfa 1,200mg IV over 60 minutes (+/- 20 minutes) once every 2 weeks. Bintrafusp alfa will be administered as a flat dose of 1,200 mg independent of body weight (starting dose and all subsequent dose administrations).

3.3.2 Preparation of bintrafusp alfa

Visually inspect the vial for particulate matter and discoloration. Bintrafusp alfa is a clear, colorless to slightly yellow solution. Discard the vial if the solution is cloudy, discolored, or contains particulate matter. Further dilute the bintrafusp alfa in 0.9% sodium chloride to a final concentration between 0.16 mg/mL to 9.6 mg/mL. Gently invert the bag to mix the diluted solution and avoid foaming or excessive shearing. Inspect the solution to ensure it is clear, colorless, and free of visible particles. Discard any partially used or empty vials.

3.3.3 Administration of bintrafusp alfa

Infusion: Administer the diluted solution via IV infusion with a mandatory 0.2 micron in-line filter over 60 minutes. Infusions may be done peripherally or via central venous access device (not required by study). Prior to infusion via port, the primary port material must be an approved material as indicated in "PowerPort Material Analysis for M7824 Administration," a CCR pharmacy document. Do not co-administer other drugs through the same intravenous line. After administration, a flush of the line with 0.9% NaCl is recommended but not mandatory.

Please refer to **Appendix B** for administration rates following an infusion-related reaction.

Premedication: To mitigate potential infusion-related reactions, premedication with an antihistamine and with acetaminophen (for example, 25-50 mg diphenhydramine and/or 500-650 mg acetaminophen) within approximately 30 to 60 minutes prior to the infusion of bintrafusp alfa is optional and at the discretion of the investigator. The premedication regimen may be modified per local site procedures and based on participant-specific factors.

For prophylaxis of flu-like symptoms, a NSAID, for example, ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each dose of bintrafusp alfa IV infusion, in participants without contraindications to NSAIDs (including allergy to class, renal function impairment, concurrent glucocorticoids).

Setting: Bintrafusp alfa should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Glucocorticoids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

NOTE: Treatment with bintrafusp alfa is planned to be administered on an outpatient basis. At the discretion of the investigator (e.g., for additional monitoring, participant social reasons, scheduling logistics, etc.), participants may be treated on an inpatient basis. Any such cases of **elective hospital admission** are not considered reportable serious adverse events per Section **8.1.2**.

Observation period: Participants must be monitored for infusion-related reactions after bintrafusp alfa infusions for a minimum of 30 minutes for the first 4 infusions and as clinically indicated thereafter.

Reported adverse events and potential risks are described in Section **14.1.2**. Participants will be encouraged to report any and all adverse events.

3.4 DOSE MODIFICATIONS

3.4.1 Discontinuation

Treatment with bintrafusp alfa will be discontinued in participants experiencing specific adverse events; subjects will remain on study for follow up of survival. Treatment will be discontinued in any participant in the case of:

- Any Grade 4 or higher adverse drug reactions (ADRs) graded according to NCI CTCAE v5.0 and assessed as possibly related to that agent by the Investigator, except for laboratory values that are asymptomatic or resolve to Grade ≤ 1 or baseline grade within 7 days without medical intervention.

- Any Grade 3 ADRs possibly attributed to any agent **except** for any of the following:
    - Transient (≤ 48 hours) Grade 3 nausea and vomiting, headache, flu-like symptoms, fever, controlled with appropriate medical management.
    - Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
    - Endocrinopathy that can be medically managed with hormone replacement.
    - Keratoacanthoma and squamous cell carcinoma of the skin. Suspicious skin lesions will be evaluated by dermatology and managed per recommendations (**Appendix B**: Recommendations for Management of IRRs and AEs, Table C), including potential removal of the lesion.
    - Grade 3 laboratory test abnormalities that resolve to Grade ≤ 1 or to baseline Grade within 7 days with appropriate medical management or Grade 3 laboratory test abnormalities that are determined not to be clinically significant or asymptomatic.
    - Grade 3 anemia with Hgb <8.0 g/dL that is clinically manageable with PRBC transfusions does not require treatment discontinuation.
    - Any Grade 3 ADR which in the opinion of the investigator is not clinically relevant or can be managed with minimal risk to the participant (e.g. placement of a pleural catheter for recurrent inflammatory pleural effusions).

3.4.2 Dose delay

- Bintrafusp alfa should be withheld for Grade ≥ 2 epistaxis or any Grade ≥ 2 toxicity possibly attributed to the study agent until resolution to Grade ≤ 1 unless the toxicity in the opinion of the investigator is not clinically relevant or can be medically managed with minimal risk to the participant. Should a clinically relevant grade 2 or 3 toxicity persist for more than 4 weeks, consideration should be given to discontinuing treatment at the discretion of the investigator.
- Laboratory abnormalities which are clinically non-significant and/or unrelated to the agent in the judgement of the investigator, will not lead to dose delays.
- Grade 3 fatigue, headache, nausea, emesis that resolve to Grade ≤ 1 with appropriate medical management will not lead to dose delays.
- Management recommendations for infusion-related adverse reactions are found in **Appendix B**: Recommendations for Management of IRRs and AEs, Table A Management of Infusion-related Reactions and should be followed along with institutional standards.
- Immune-related adverse reactions (irAE) should lead to treatment modifications and management per the summarized NCCN recommendations found in in **Appendix B**: Recommendations for Management of IRRs and irAEs, Table B Management of immune-related adverse events. Investigators may refer to the relevant guidelines available by ASCO (62), SITC (63), NCCN (64), and ESMO (65).
- For non-medical logistical reasons, unrelated acute illnesses, or palliative radiation, scheduled assessments and dosing can be delayed up to 2 months. Following this interval treatment may resume, and where at all possible, dosing should be restarted to keep in line with the original treatment schedule.

- Local tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected lesions will not be considered adverse event or lead to dose interruptions.

3.4.3 Monitoring post-biopsy

For biopsy performed in the ENT clinic, monitoring will be per the ENT surgeon performing the biopsy. If the biopsy is done in Interventional Radiology, the standard clinical recovery procedures for patient safety will apply.

3.4.4 Dose reductions

Bintrafusp alfa doses may be reduced to a 600 mg or 300 mg flat dose per investigator discretion (e.g., for ≥ grade 1 hemorrhage due to bintrafusp alfa).

3.5 ASSESSMENTS ON TREATMENT

Upon confirmation of eligibility and successful registration, and following completion of the Screening/Baseline visits, participants will begin treatment with bintrafusp alfa.

Following initial agent administration on Week 1, pre-dose assessments may be performed up to 5 days prior to the day of scheduled administration, except where otherwise noted. Results of all applicable procedures and tests are to be reviewed prior to each scheduled administration. Additional clinical and other appropriate evaluations may be performed as clinically indicated.

Refer to the Study Calendar (Section **3.7**) for an overview of all tests and procedures to be conducted during screening/ baseline, on study/ during treatment, upon discontinuation of treatment, and during follow up.

3.6 STUDY INTERVENTION COMPLIANCE

Adherence to the protocol will be verified by reviewing the Medical Administration Record (MAR) section of the medical record, which will serve as source documentation.

3.7 STUDY CALENDAR

Procedure	*Screening*[1]	*Baseline* [2]	*Week 1*	*Subsequent Weeks (2N+1)*[3, 14]	*End of treatment*[4, 14]	*Post Treatment Follow-up*[14]	
						Safety[5]	*Long Term*[6]
Treatment							
Bintrafusp alfa [7]			X	X			
Assessments							
Histologic confirmation	X						
Height	X						
Medical History and Performance Status	X	X					
Physical Exam (including weight, signs & symptoms, skin assessment)	X	X	X	X	X	X	
Vital signs (including pulse oximetry), weight	X	X	X	X	X	X	
HIV, HCV, HBV	X						
NIH Advance Directives Form[8]		X					
12-lead EKG	X				X	X	
CBC with differential	X	X	X	X	X	X	
Biochemical profile (acute care, mineral, hepatic panels)	X	X	X	X	X	X	
Coagulation profile (PT, INR, PTT/aPTT)		X					
Troponin I	X						
Creatine kinase (CK/CPK)	X						
CD4 (if indicated)	X						
Lymphocyte phenotype TBNK (T, B, and natural killer cells)	X						
LDH		X					
CRP		X	X	X			
TSH, Free T4, lipase, amylase	X	X	X	X[9]			
Tumor markers		X		X[15]			
Urinalysis	X	X					
24-hour urine collection (if indicated)	X						
Pregnancy test (urine/serum HCG in WOCBP)	X	X	X	X			

Procedure	***Screening***[1]	***Baseline***[2]	***Week 1***	***Subsequent Weeks (2N+1)***[3, 14]	***End of treatment***[4, 14]	***Post Treatment Follow-up***[14]	
						Safety[5]	***Long Term***[6]
Tumor imaging and assessment	X			X[10]			X
PET/CT scans[13]	X						
Adverse Events			X	X	X	X	
Concomitant Medications		X	X	X	X	X	
Correlative Research Studies (Section **5.1)**							
Tumor tissue (biopsy)[11]		X		X			
Blood samples[12]		X		X	X		
Telephone follow-up						X	X

1. Screening evaluations performed within 28 days prior to the first drug administration, unless specified in Section **2.2.2**
2. Baseline evaluation performed within 14 days prior to the first drug administration.
3. Every odd numbered week for up to 51 weeks. Allowance for scheduling changes: Brief changes (up to 1 days earlier or up to 3 days later) in bintrafusp alfa administration and indicated evaluations may occasionally be required due to travel delays or restrictions, airport closure, inclement weather, family responsibilities, security alerts, government holidays, complications of disease not attributable to disease progression or protocol therapy, etc. These delays will not be considered protocol deviation. The timing of subsequent bintrafusp alfa administrations will be adjusted to maintain a minimum interval of 11 days between bintrafusp alfa administrations. Any dose that cannot be accommodated within this window will be skipped and the dose not made up. In the event of a durable PR or CR after one year on trial, further treatment may be held (even if a total of 26 doses has not been given) and scheduled assessments may be performed at 3-month (+/- 2 weeks) intervals at the discretion of the investigator.
4. End of Treatment visit (EOT): within 14 days of the decision to discontinue treatment prematurely before completion of 26 doses. Clinical Center clinic visit preferred; if the participant cannot return to the Clinical Center for this visit, a request will be made to collect required clinical labs (specify as needed) from a local physician or laboratory. If this is not possible, participants may be assessed by telephone/email for symptoms. Does not need to be completed if drug is withheld after 26 doses.
5. 28 days (+/- 7 days) following last treatment. Clinical Center clinic visit preferred; if the participant cannot return to the Clinical Center for this visit, they may be assessed by telephone/email for adverse events.

6. Subsequent Post-treatment follow-up: Every 3 months (+/- 2 weeks), starting after the safety visit for the first year, followed by every 6 months (+/- 4 weeks) for years 2-5, and then annually (+/- 6 weeks) thereafter at the discretion of the investigator. Follow-ups may be done by phone/email or by clinic visit at the discretion of the investigator. Follow-up via telephone/email will include survival, adverse events, and assessment of further tumor therapy; furthermore, routine outside blood, urine, and imaging results may be collected and used for analysis at the discretion of the investigator. Any other evaluations and tests should be performed as clinically indicated. Participants who have not progressed on treatment will be scanned until progression. Those that completed the previous 26-doses course and have progression will be invited for an additional course (26 doses) at the time of progression.

7. Bintrafusp alfa administered IV at flat dose of 1,200 mg.

8. As indicated in Section **12.3**, all subjects will be offered the opportunity to complete an NIH advance directive form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended but is not required.

9. Every 6 weeks.

10. Imaging (Section **6.3**) will be performed every 8 weeks (+/- 1 week). In the event of a PR or CR, tumor imaging assessments may be performed every 3 months (+/- 2 weeks) at the discretion of the investigator. Tumor assessment should be continued beyond end of treatment in participants who have not experienced PD until they experience PD in order to assess PFS. Additional imaging to be performed at the investigator's discretion. Imaging performed in outside facilities maybe utilized in the case of travel restrictions or delays, airport closures, inclement weather, family responsibilities, security alerts and government holidays, etc. Nuclear bone scan or imaging may be done for individuals with known/suspected bone lesions at screening; in these cases bone scans should be done in follow-up for response assessments.

11. Optional biopsies: at baseline (within 2 weeks prior to first treatment) and within 2 weeks of first imaging restaging; optional biopsy at/near progression, where clinically feasible.

12. Where feasible, blood samples for Correlative Research Studies (see Section **5**) will be collected at baseline, W1, W3, W9, and at the EOT. Collection can occur +/- 3 days for any specified timepoint. May also be collected at restaging visits/at time of biopsies per PI discretion.

    Where feasible, samples for PK analysis/ADA will be drawn prior to infusion on W1, W3 and W9 and/or with EOT labs if participant comes off treatment prior to any of these timepoints.

13. PET/CT (FDG or Dotatate) scans will be done at screening and at the time of first treatment response evaluation (w8). Then a third one at/near radiographic progression (if there is progression). Effort will be made to keep the same PET/CT type, depending on logistics and availability.

14. Any visits for which administration of trial medication is not planned such as treatment held for AEs, EOT and post-treatment follow-up, assessment may be a telehealth (remote) visit with a member of the study team (e.g., if the patient is not able to return to the NIH CC). Remote visits will be conducted in compliance with NIH guidelines and FDA regulations. A patient may be referred to their local provider or asked to come to the NIH CC for an in-person assessment, if clinically indicated, and at the discretion of the PI. In the case of any visits with participants' local providers, records will be requested. Labs may be drawn locally (interlaboratory variability is not a concern, as these are routine, standardized laboratory tests).

15. Tumor markers (Chromogranin and Neuron Specific Enolase) to be drawn with each restaging.

3.8 COST AND COMPENSATION

3.8.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants received at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medications that are not part of this study will not be provided or paid for by the NIH Clinical Center.

3.8.2 Compensation

There will be no compensation provided in this study.

3.8.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.9 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 28 days after the last dose of study therapy. Additional visits and follow up will continue as per Section **3.7**. Participants who refuse to return for this visit will be asked to review any safety concerns by phone within this time period.

3.9.1 Criteria for removal from protocol therapy

- Participant requests to be withdrawn from active therapy.
- Unacceptable Toxicity as defined in Section **3.4.1** that require treatment discontinuation.
- Completion of treatment.
- **Disease Progression:** Clinical or radiographic progression of disease, except where per investigator clinically appropriate and the participant is achieving clinically meaningful benefit from treatment with bintrafusp alfa (See also Section **3.9.1.1**).
- Intercurrent illness that prevents further administration of the treatment.
- Start of another systemic anticancer treatment or participation in another investigational therapeutic trial. Focal palliative radiotherapy, ablation, or surgery to a site of disease will not necessitate removal from protocol therapy.
- Investigator discretion.
- Non-compliance with study treatment or procedure requirements.
- Positive pregnancy test.
- Study is cancelled for any reason.
- Permanent loss of capacity to give consent.

Participants who are off-treatment but still on-study will have remaining study procedures completed as indicated by the study protocol.

3.9.1.1 Treatment Beyond Progression

Response patterns to immunotherapy have included observations of clinical response after initial increases in tumor burden (termed "pseudo-progression"). Consequently, it is preferable that where clinically appropriate, participants remain on treatment past initial radiographic progression until disease progression is confirmed by subsequent imaging, 4 to 6 weeks (preferably 6 weeks but not later) after progression has been determined per RECIST1.1. (1) If progression is based on the occurrence of a new lesion in an area not scanned at Baseline, a further on-study scan 6 weeks later should be considered before performing the 28-day Safety follow-up visit. Clinically appropriate context entails the following:

- There are no new or concerning symptoms.
- There is no decline in ECOG PS.
- The Investigator does not consider it necessary to administer urgent salvage medical intervention.

3.9.2 Off-Study Criteria

- Participant requests to be withdrawn from study.
- Screen failure.
- Participant lost to follow up.
- Death.
- Investigator discretion.
- Study is cancelled for any reason.

3.9.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 4 consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 4 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

3.9.4 Trial discontinuation

- Evidence of inefficacy of the investigational drug (evidence of inefficacy may arise from this trial or from other trials).
- Occurrence of significant previously unknown adverse reactions or unexpected intensity or incidence of known adverse reaction (unfavorable safety findings may arise from clinical or non-clinical examinations, e.g., toxicology).
- Sponsor decision that continuation of trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of participants, making completion of trial unlikely within acceptable time frame.
- Discontinuation of development of the investigational drug.
- Termination or suspension upon request of health authorities.

4 CONCOMITANT MEDICATIONS/MEASURES

Subjects must be instructed to inform the investigators of the current or planned use or all other medications during the study (including prescription medications, over-the-counter medications, vitamins and herbal and nutritional supplements).

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over the counter (OTC) medications, herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. All concomitant medications received starting from 30 days prior to the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.

4.1 ACCEPTABLE MEDICATIONS/MEASURES

All routine and appropriate treatments and supportive care (including blood products) that the investigator considers necessary for a participant's welfare or symptom alleviation may be administered at the discretion of the investigator in keeping with the community standards of medical care.

Palliative radiotherapy to non-targeted lesions delivered in a normal organ-sparing technique may be administered during the trial. The assessment of PD will not be based on the necessity for palliative radiotherapy.

Traditional herbal or homeopathic or natural medicines should be **avoided**. Ingredients for such medicines have not been fully studied, and their use may result in unanticipated drug-drug interactions that may cause toxicity or confound assessment of toxicity. Herbal medications include, but are not limited to St. John's Wort, kava, ephedra, gingko biloba, yohimbe, saw palmetto, black cohosh, ginseng, turmeric, and curcumin.

4.2 PROHIBITED MEDICATIONS

Medications or vaccinations specifically prohibited in the exclusion criteria (see Section **2.1.2**) are not allowed during the ongoing trial. If there is a clinical indication for a prohibited medication/measure during the trial, discontinuation from trial therapy may be required, but the participant may remain on study for follow up. The following treatments should **not** be administered during the trial:

- Other immunotherapies or immunosuppressive drugs (for example, chemotherapy or systemic glucocorticoids except for prophylaxis or treatment of allergic reactions, endocrine replacement therapy as low dose prednisone [≤ 10 mg daily] or equivalent, for the treatment of irAEs, or for short courses (≤ 14 days) as appropriate medical therapy for unrelated medical conditions (e.g., asthma). Glucocorticoids with no or minimal systemic effect (topical, inhalation) are allowed.
- Prophylactic use of glucocorticoids for infusion related reactions. **NOTE:** Glucocorticoid administration prior to CT scans in participants with intravenous contrast allergy is allowed.
- Any live vaccine therapies for the prevention of infectious disease. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Administration of inactivated vaccines is allowed (for example, inactivated influenza vaccines, recombinant zoster vaccine, or locally approved COVID vaccines).
- Systemic anticancer treatment.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 SUMMARY

A description of research correlative studies including a brief statement of rationale and processing information is provided below. The list is not all inclusive and studies may or may not be performed in select participants based on investigator discretion and available resources. Studies may include, but are not limited to, the following:

Test / Assay	Collection Details (approx. volume, tube type[1])	Collection Time (+/- 48hrs)	Location of Specimen Analysis	Storage
Tumor Tissue				
Sequencing, gene expression analysis, proteomics, and methylation	FFPE / snap frozen tissue	See **Study Calendar**	NIDCD or NFGCF	NIDCD tissue repository
Immune markers (IHC)			GMB TIME Lab, London Lab	
Organoid cultures	Tumor tissue		London Lab	
Cell line and participant derived xenograft development			London Lab and NCI PDM	
RNA expression level of 770 genes			LTIB and NFGCF	
T cell clonality (ImmunoSeq)				
Blood Samples				
WBC DNA Sequencing[3]	60-80 mL blood for PBMCs, Sodium Heparin tubes (green top)	See **Study Calendar**	NFGCF	CSP
Standard and 123 immune cell subsets (FACS)			LTIB	
Functional Analysis of immune cell subsets (FACS)				
Antigen Specific Immune Response (Cytokine Staining Assay)				
T cell clonality (ImmunoSeq)			LTIB and NFGCF	

RNA expression level of 770 genes				
Soluble factors (incl. sCD27, sCD40L, ELISA)	8 mL blood for serum, SST		LTIB	
Circulating free tumor DNA(PCR)	10 mL (Streck tubes)		LTIB and NIH Core Facility	CSP
Extracellular/ exosome DNA	10 mL (Streck tubes)		Dr. Jenifer Jones Lab	
Pharmacokinetics/ADA(ELISA)	8 mL blood for serum (SST)		EMD Serono	CSP
TGFβ1 levels (ELISA/bead based multiplex assay)	10 mL EDTA lavender top tube		LTIB	CSP

[1] Tubes/media may be adjusted at the time of collection based upon materials available or to ensure the optimal samples are collected for planned analyses.

[2] LTIB: Laboratory of Tumor Immunology, NIDCD: National Institute of Deafness and Craniofacial Disorders, NFGCF: NCI Frederick Genomic Core Facility; NCI Participant-Derived Models Repository: NCI PDM; SST: serum separation tubes

[3] Control for sequencing studies of tumor, circulating tumor DNA, and extracellular/exosome DNA

Research blood samples will be sent to the Clinical Services Program – Leidos Biomedical Research, Inc. (CSP) for barcoding, initial processing and storage. Tissue will be sent to the NIDCD tissue repository. From these facilities, coded, linked samples will be sent to the designated labs for analysis upon request

5.2 SAMPLE COLLECTION AND PROCESSING

For the planned analyses described below, laboratories may share resources or collaborate if appropriate. Portions of all samples may be banked for future research analyses; prospective consent will be obtained during the informed consent process.

For adult subjects: The amount of blood that may be drawn from adult participants for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period.

5.2.1 Peripheral blood collection

Subjects will have approximately 130 mL of peripheral blood drawn at each time point specified in Study Calendar **3.7** (six to eight, 10-mL green top sodium heparin tubes for PBMC samples, two 8-mL serum-separating tube for serum samples, three 10-mL lavender EDTA tubes).

5.2.1.1 Immune Phenotyping – PBMCs

Where possible, exploratory immunologic studies will be conducted to evaluate the study drug's effect on the immune response before and after treatment, to gain insight into potential biomarkers, and help improve the administered therapy. Blood will be collected as per **Study Calendar**. The following immune assays may be performed at the Laboratory of Tumor Immunology and Biology (LTIB) at the NCI's Center for Cancer Research (CCR) in select participants where adequate samples are available:

1. PBMCs may be analyzed for changes in standard immune cell types (CD4 and CD8 T cells, natural killer [NK] cells, regulatory T cells [Tregs], myeloid-derived suppressor cells [MDSCs], and dendritic cells) as well as 123 immune cell subsets, using multi-color flow cytometry.
2. PBMCs from selected subjects may be analyzed for function of specific immune cell subsets, including CD4 and CD8 T cells, NK cells, Tregs, and MDSCs using flow-based assays.
3. PBMCs may be analyzed for tumor antigen-specific immune responses using an intracellular cytokine staining assay. PBMCs will be stimulated in vitro with overlapping 15-mer peptide pools encoding tumor-associated antigens; control peptide pools will involve the use of human leukocyte antigen peptide as a negative control and CEFT peptide mix as a positive control. CEFT is a mixture of peptides of CMV, Epstein-Barr virus, influenza, and tetanus toxin. Post-stimulation analyses of CD4 and CD8 T cells will involve the production of IFN-γ, IL-2, TNF, and the degranulation marker CD107a. If sufficient PBMCs are available, assays may also be performed for the development of T cells to other tumor-associated antigens.
4. Changes in T-cell clonality score using Adaptive Biotechnologies TCR-seq assay.
5. Changes in inflammatory gene signature using Nanostring's nCounter Human PanCancer Immune Profiling Panel.

5.2.1.2 Soluble Factors

Samples for soluble factor analysis will be collected as per Study Calendar (Section **3.7**).

Where possible, sera and/or plasma may be analyzed pre- and post-therapy for the following soluble factors: sCD27, sCD40 ligand using commercial ELISA kits. Also, sera and/or plasma

may be analyzed for changes in cytokines (IFN-γ, IL-10, IL-12, IL-2, IL-4, etc.), chemokines, antibodies, tumor-associated antigens, and/or other markers using ELISA or multiplexed assays (e.g., Mesoscale, Luminex, cytokine bead array).

5.2.2 Tumor tissue samples

Archival tumor samples will be requested, where available. For participants with lesions amenable to biopsy, tumor biopsies will be performed (see Section **2.4** and Study Calendar **3.7**). Selection of site for biopsy will be as per Section **2.4**; an attempt will be made for site-matching between pre-treatment and on-treatment tumor biopsies. The biopsy will be performed per routine standard of care, by ENT/Surgery consultants or Interventional Radiology, with Imaging guidance (e.g., ultrasound or CT) as appropriate. Conscious sedation may be used, if warranted, and the use and risks to the participant are minimal. Endoscopy, CT or other imaging guidance will be used as appropriate. If these procedures are not considered to be of minimal risk to the participant, the biopsy will not be performed, and this will not be reported as a deviation of the protocol. The participant will consent at the time of the procedure. For the biopsies, if the participant refuses, the refusal will be documented in the medical record and in the research record.

Tumor samples will be sent to the Laboratory of Pathology for disease evaluation; remaining samples will be used for research. Tissue samples for research may also be stored in the NIDCD tissue repository.

5.2.2.1 RNA and T-cell Receptor Clonality Analysis of Blood and Tumor Tissue

Where possible, RNA expression and T-cell receptor clonality analysis will be done on the peripheral blood as well as archived tumor tissue or optional biopsies to help further evaluate changes in immune response and RNA expression levels with treatment as well as to determine tumor and infiltrating lymphocyte characteristics which may be predictive of response to treatment. In addition, these analyses will also be used to gauge resistance mechanisms and additional targets for future therapy. Coded, linked samples may be analyzed for RNA expression levels using the Nanostring platform and T-cell receptor clonality using the ImmunoSeq platform (LTIB and NCI Frederick Genomic Core Facility).

5.2.2.2 Bintrafusp alfa Pharmacokinetics

Serum PK measurements of Bintrafusp alfa (schedule per **Study Calendar**) may be measured. Coded, linked samples will be shipped to EMD Serono for analysis under existing CRADA, to collect data which will provide insight into population PKs of bintrafusp alfa in participants receiving these novel combinations.

5.2.2.3 ADA

Anti-Drug Antibody (ADA) development may lead to loss of efficacy of administered monoclonal antibodies. Measuring titers (schedule per **Study Calendar**) will examine if lack of efficacy of bintrafusp alfa is due to ADA development. Serum samples may be analyzed by EMD Serono with ELISA, under existing CRADA.

5.2.2.4 Analyses of Tumor Tissue for Immune Markers

Study of immune infiltration as well as immune mediated pathways such as PD-L1 status within the tumor microenvironment pre vs. post treatment by IHC and/or multiplex immunofluorescence may be performed by the GMB TIME Lab or by Dr. Nyall London (NIDCD). Where available, archival tumor samples may be requested for pre-treatment analysis (preferably tissue samples

from the last 6 months). For participants with lesions amenable to biopsy, biopsies may be performed as described in Section **5.2.2**.

5.2.3 Sequencing, gene expression analysis, proteomics, and methylation

Studies characterizing the mutations, gene expression profile, protein analysis, and methylation status of ONB specimens will be performed at the NIDCD genomics core facility. Tissue samples for research will be stored and obtained from the NIDCD tissue repository.

5.2.4 Organoid cultures

Organoid cultures will be established from tissue specimens in the lab of Dr. Nyall London. This will be performed as recently described (67). Specimens directly from either core needle biopsy or endoscopic nasal biopsy will be utilized to generate these organoids *in vitro*. The organoids will be utilized to test novel immunotherapeutic approaches as well as interrogate and investigate alternative mechanisms of tumorigenesis such as epigenetic regulators and assess the effects of small molecule inhibition of these pathways.

5.2.5 Blood genomic material

WBC DNA as a control for sequencing studies as well as circulating tumor DNA and extracellular vesicle/exosome DNA will be analyzed in this portion of the protocol. Blood will be collected according to the study calendar and transferred to the LTIB. Genomic material may be used as a control for sequencing studies. Furthermore, serum and genomic materials may be collected to study circulating tumor DNA.

5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed.

Samples will not be sent outside the National Institutes for Health (NIH) without appropriate approvals and/or agreements, if required.

5.3.1 Sample Management and Storage at Clinical Services Program – Leidos Biomedical Research, Inc. (CSP)

Clinical Services Program – Leidos Biomedical Research, Inc.
Attn: Theresa Burks
1050 Boyles Street
Bldg. 496/Room 121
Frederick, MD 21702

On days samples are drawn, Jen Bangh at CSP (part of NCI Frederick Central Repositories) should be notified (phone: [301] 846-5893; fax [301] 846-6222). She will arrange same-day courier delivery of the specimens.

All data associated with the participant samples is protected by using a secure database. All Clinical Support Laboratory Staff receive annual training in maintaining records' confidentiality. All samples drawn at the NIH Clinical Center will be transported to the Clinical Support Laboratory at the Frederick National Laboratory for Cancer Research by couriers.

Samples will be tracked and managed by Central Repository database, where there is no link to personal identifiable information. All samples will be stored in either a -80ºC freezer or vapor

phase liquid nitrogen. These freezers are located at NCI Frederick Central Repository in Frederick, Maryland.

NCI Frederick Central Repositories (managed under a subcontract) store, among other things, biological specimens in support of NIH clinical studies. All specimens are stored in secure, limited-access facilities with sufficient security, backup, and emergency support capability and monitoring to ensure long-term integrity of the specimens for research.

Specimens are stored in accordance with applicable HHS and FDA Protection of Human Subjects Regulations in accordance with the subcontractor's Federal-wide Assurance. The subcontractor's role limited to clinical research databases and repositories containing participant specimens. The subcontractor does not conduct or have any vested interest in research on human participants but does provide services and support the efforts of its customers, many of which are involved in research on human participants.

It is the intent and purpose of the subcontractor to accept only coded, linked samples and sample information. To the limit of our ability, every effort will be made to ensure that protected information is not sent electronically or by hard copy or on vial labels.

Sample data is stored in the Biospecimen Inventory System II (BSI). This inventory tracking system is used to manage the storage and retrieval of specimens as well as to maintain specimen data. BSI is designed for controlled, concurrent access. It provides a real-time, multi-user environment for tracking millions of specimens. The system controls how and in what order database updates and searches are performed. This control prevents deadlocks and race conditions. For security, BSI has user password access, 3 types of user access levels, and 36 user permissions (levels of access) that can be set to control access to the system functions. BSI provides audit tracking for processes that are done to specimens including shipping, returning to inventory, aliquoting, thawing, additives, and other processes. BSI tracks the ancestry of specimens as they are aliquoted, as well as discrepancies and discrepancy resolution for specimens received by the repository. If a specimen goes out of the inventory, the system maintains data associated with the withdrawal request. Vials are labeled with a unique BSI ID which is printed in both eye-readable and bar-coded format. No participant-specific information is encoded in this ID.

Investigators are granted view, input, and withdrawal authority only for their specimens. They may not view specimen data or access specimens for which they have not been authorized. Access to specimen storage is confined to repository staff. Visitors to the repositories are escorted by repository staff at all times.

5.3.2 Procedures for Storage of Specimens in NIDCD

All participants will also be consented for study #18-DC-0051 entitled "Biospecimen procurement for NIDCD clinical protocols". Procedures detailed in this protocol will be followed regarding tumor tissue management. In brief, following enrollment, subjects will be registered and assigned a code in CTDB under which the limited demographic and clinical information will be stored. Only the code will be used on the specimens to electronically log the specimens using a task-specific bar-code technology software which has full security and audit functions consistent with NIH requirements. Samples and the limited demographic and clinical information will not contain PII. Data should be entered within 2 weeks of participant enrollment onto the protocol. The access to the code keys will be limited to those designated by the Primary Investigator and will be kept in a secured, locked location.

Samples will be stored in freezers, liquid nitrogen containers or tissue cartridge shelves in the NIDCD Core laboratory, located in building 10 on the NIH campus, secured by locked doors.

NIDCD Biospecimen Tissue Core
Building 10, Room 7S244
Attn: Christian Samaniego Dávila, PhD
Notify Christian Samaniego of all incoming specimens:
Phone: 301-827-6894, cell: 240-495-9775, email: christian.samaniego@nih.gov
Backup contact #1: Nyall London: Cell: 801-5477-7851, email: nyall.london@nih.gov
Backup contact #2: Clint Allen: Cell: 979-324-5307, email: clint.allen@nih.gov

Access to samples from a protocol for research purposes will be by permission of the Principal Investigator of that protocol in order to be used (1) for research purposes associated with protocol objectives for which the samples were collected, or (2) for a new research activity following submission and IRB approval of a new protocol and consent, or (3) for use only as unlinked or coded samples under the Office of Human Subjects Research Protections (OHSRP) Exemption Form guidelines stipulating that the activity is exempt from IRB review. The use of all samples will be fully tracked and audit lists of when each sample was used and who used it can be generated upon need or request.

Samples, and associated data, will be stored permanently unless the participant withdraws consent. If researchers have samples remaining once they have completed all studies associated with the protocol and participant consent has not been withdrawn, samples may be kept permanently for possible use in future IRB approved investigations.

5.3.3 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described above. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

If the participant withdraws consent the participants data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section **7.2**.

5.4 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.4.1 Description of the scope of genetic/genomic analysis

The research correlates for this study are expected to include DNA/RNA sequencing of tumors, including circulating tumor (ct) DNA. In addition, whole exome sequencing may include evaluation for known cancer-related mutations.

5.4.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

For any genetic studies performed, the results will be deposited in a database such as dbGaP per NIH requirements. Although there is controlled access to such a database, such a submission

carries theoretical risks of revealing the identity of the subject. This is discussed in the consent. Confidentiality for genetic samples will be maintained as described (Section **6.1**).

5.4.3 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists).

5.4.4 Genetic Counseling

Subjects who remain on the study will be contacted at this time with a request to provide a blood sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH (at our expense) to have genetic education and counseling to explain this result. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, study day 1, through 28 days after the subject received the last product administration. After 28 days, only adverse events which are serious and related to the study investigational agent need to be recorded.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the participant's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in Section **7.2.1**.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows

- Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center)
- Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository: clinicaltrials.gov, dbGaP
- BTRIS (automatic for activities in the Clinical Center)
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

When will the data be shared?

- Before publication.
- At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE ASSESSMENT

For the purposes of this study, during the study participants should be re-evaluated for response every 8 weeks (+/- 1 week), according to the **Study Calendar**.

The Investigator may perform scans in addition to a scheduled trial scan for medical reasons or if the Investigator suspects PD.

Tumor assessments may include the following evaluations: physical examination (with photograph and measurement of skin lesions, as applicable); cross-sectional imaging using computed tomography (CT) or magnetic resonance imaging (MRI) scan of the skull base, neck, chest, abdomen, and pelvis; nuclear bone scan for subjects with known/suspected bone lesions; and CT of the skull base and MRI of brain (at baseline and follow ups as clinically warranted based on symptoms/findings per investigator discretion). The preferred method of disease assessment is CT with contrast. If CT with contrast is contraindicated, CT of the chest without contrast and MRI scan of the skull base, neck, abdomen/pelvis is preferred.

Radiologic imaging: Brain MRI/CT at the baseline and if needed at follow ups. CT scan of skull base, neck, chest, abdomen, and pelvis. or MRI.

In addition, PET (FDG or Dotatate) scan will be acquired at the time of first treatment response evaluation, and at/near radiographic progression, where clinically feasible. PET scan may also be acquired per investigator discretion to characterize metabolic activity of lesions (target/non-target/new) beyond cross-sectional measurement-based response categories, such as in cases of, discordant response among lesions, durable partial response, or other indeterminate radiological changes.

For each participant, the Investigator will designate 1 or more of the following measures of tumor status to follow for determining response: CT or MRI images of primary and / or metastatic tumor masses, physical examination findings, and the results of other assessments.

The measure(s) to be chosen for sequential evaluation during the trial have to correspond to the measures used to document the progressive tumor status that qualifies the subject for enrollment.

Post-baseline response assessments should follow the lesions identified at baseline. The same modality of assessment (e.g., CT) used to identify/evaluate lesions at baseline should be used throughout the course of the study unless subject safety necessitates a change (e.g., allergic reaction to contrast media).

To assess the primary endpoint of objective response, tumor lesions will be categorized at baseline to target and non-target lesions and used for comparison with subsequent measurements according to the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).(1)

All available images collected during the trial period will be considered. Results for the evaluations will be recorded with as much specificity as possible so that pre- and post-treatment results will provide the best opportunity for evaluating tumor response.

Per RECIST 1.1 initial disease progression should be confirmed by imaging after 4 to 6 weeks (preferably 6 weeks, but not later than 8 weeks).

Per RECIST 1.1 any CR or PR should be confirmed by a repeat imaging assessment no sooner than 4 weeks (preferably at the scheduled 6-week interval). Participants who obtain a confirmation scan do not need to undergo the next scheduled imaging assessment if it is due <4 weeks later; imaging may resume at the subsequent scheduled timepoint.

If progression is based on the occurrence of a new lesion in an area not scanned at Baseline, a further on-study scan 6 weeks later should be considered before performing the 28-Day Safety Follow-up visit.

6.3.1 Disease Parameters

At baseline, tumor lesions will be selected and categorized as target or non-target lesions, defined as described below.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

A sum of the longest diameters (SLD) of the non-nodal target lesions will be calculated and reported as the baseline SLD.

6.3.1.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as:

- By CT scan:
    - Scan slice thickness 5 mm or under: as ≥10 mm
    - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: ≥10 mm.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

6.3.1.2 Target lesions

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: The RECIST 1.1 guidelines has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

MRI is also acceptable in certain situations (e.g., for body scans), as detailed per Section **2.4** and **6.3**. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should preferably be the same as was used at baseline and the lesions measured/assessed on the same pulse sequence. Ideally, the same type of scanner should be preferably used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET/CT: At present, the low dose or attenuation correction CT portion of a combined PET/CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET/CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and **should not be used** as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when

biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is **mandatory** to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.3.3 Response Criteria

Tumor responses to treatment will be assigned based on the evaluation of the response of target, non-target, and new lesions according to RECIST 1.1.

6.3.3.1 Target Lesions Evaluation

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

6.3.3.2 Non-Target Lesions Evaluation

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, *not a single lesion increase*.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.3.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria (See **Appendix C**: Best Overall Response per RECIST 1.1).

6.3.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.3.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

6.3.7 Immune-Related Response Criteria

As an exploratory endpoint antitumor activity will also be evaluated according to iRECIST. (3)

Using iRECIST criteria the following will be incorporated into assessment:

1. An increase in the sum of target lesions of more than 20%, unequivocal increase in non-target lesions or new lesions result in iUPD (unconfirmed progressive disease); iUPD can be assigned multiple times as long as iCPD (confirmed progressive disease) is not confirmed at the next assessment.

2. Progression is confirmed in the target lesion category if the next imaging assessment after iUPD (4–8 weeks later) confirms a further increase in sum of measures of target disease from iUPD, with an increase of at least 5 mm. Progression is confirmed in the non-target lesion category if subsequent imaging, done 4–8 weeks after iUPD, shows a further unequivocal increase in non-target lesions. Progression is confirmed in the new lesion category if at next assessment additional new lesions appear or an increase in size of previously seen new lesions is seen (≥5 mm for sum of new lesion target).

3. However, the criteria for iCPD (after iUPD) are not considered to have been met if complete response, partial response, or stable disease criteria (compared with baseline and as defined by RECIST 1.1) are met at the next assessment after iUPD. The status is reset (unlike RECIST 1.1, in which any progression precludes later complete response, partial response, or stable disease). iCR, iPR, or iSD should then be assigned; and if no change is detected, then the timepoint response is iUPD.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each participant while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore a separate submission for these reports is not necessary.

In addition to those reports, deaths not reported to the OHSRP/IRB that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis (approximately weekly) when participants are being actively treated on the trial to discuss each participant. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior participants.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in Section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each participant to ensure safety and data accuracy. The principal investigator will personally conduct or supervise

the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.4.2 Data Safety Monitoring Board (DSMB)

The DSMB is an independent group of at least 3 experts that monitors participant safety and advises The Sponsor. DSMB members will be separate and independent of study staff participating in this trial and should not have scientific, financial, or other conflicts of interest related to this trial. The DSMB will consist of members with appropriate expertise to contribute to the interpretation of data from this trial. A quorum will consist of a simple majority.

The DSMB will review cumulative safety data and interim analysis data (see Section **10.4.5)** generated in review timeframe from this trial at least annually.

The DSMB will meet when trial halting criteria (see Section **3.2**) are met, or as requested by the sponsor or PI.

The DSMB will have a final review meeting at the end of the study.

Procedures for DSMB reviews/meetings will be defined in the DSMB charter. The DSMB will review applicable data, including, but not limited to, enrollment, demographics, dosing data, clinical laboratory data, and safety data, at scheduled timepoints during this trial as defined in the DSMB charter. The DSMB will review blinded aggregate data in the open session of the DSMB meetings.

Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by the Sponsor. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study product administration, and to continue, modify, or terminate this trial.

8 SPONSOR PROTOCOL / SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2)).

8.1.2 Serious Adverse Event (SAE)

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

- Death;
- A life-threatening adverse event (see Section **8.1.3**);
- In participant hospitalization or prolongation of existing hospitalization:

- A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
- A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for participant convenience) is not considered a serious adverse event.
- Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.

- 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 participant or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the participant or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death (21CFR312.32).

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.0.

8.1.5 Relationship to Study Product

All Aes will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.6 Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product(s) and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events to characterize and understand them in association with the use of these investigational products.

Only AESIs that match the definition of SAE will be reported as other SAEs within 7 days from the knowledge of event. Other non-SAE AESIs should not be reported to OSRO but only collected in the clinical database.

The adverse events related to following, regardless of site, will be collected as an AESI to enable evaluation of potential risk factors, such as site/past radiation/associated infection at site/recent instrumentation and other variables such as time to onset, exposure history, grade of bleeding, anatomical sites, etc. can be collected.

- Mucosal bleeding
- Cutaneous lesions possibly due to TGF-beta

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to Section **6.1**.

8.3 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form.

All SAE reporting must include the elements described in Section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 WAIVER OF EXPEDITED REPORTING TO CCR

As overall survival, which includes death or hospitalization due to disease progression are part of the study objectives, and captured as an endpoint in this study, they will not be reported in expedited manner to the sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to Section **8.3**.

Hospitalization that is deemed to be due to disease progression, and not attributable to the intervention will not be reported as an SAE. The event, and the assessment that it was caused by disease progression will be documented in the medical records. The causality assessment of hospitalization will be re-evaluated any time when new information is received. If the causality assessment changes from disease progression to related to the study intervention, SAE report will be sent to the Sponsor in an expedited manner according to Section **8.3**. If there is any uncertainty whether the intervention is a contributing factor to the event, the event should be reported as AE or SAE as appropriate.

8.5 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

Reporting will be per the collaborative agreement.

8.6 REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.6.1 Maternal exposure

If a participant becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy becomes known.

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (Section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented.

8.6.2 Paternal exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 125 days after the last dose of bintrafusp alfa.

Pregnancy of the participant's partner is not considered to be an AE. The outcome of all pregnancies occurring from the date of the first dose until 125 days after the last dose should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse

reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.8 SPONSOR PROTOCOL DEVIATION REPORTING

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and,
- that the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit

(SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site. Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable) and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESIS

10.1.1 Primary Efficacy Endpoint

To assess Overall Response Rate (ORR) according to RECIST 1.1.

10.1.2 Secondary Efficacy Endpoints

To assess:

- Safety and tolerability of bintrafusp alfa in participants with recurrent or metastatic ONB
- Progression Free Survival
- Duration of response
- Overall Survival

10.2 SAMPLE SIZE DETERMINATION

There is no published literature on the anticipated efficacy of any specific treatment for participants with ONB. In these rare participants, the objective will be to determine if a modest response rate is possible while keeping the study size small. Thus, in immune checkpoint-naïve participants, this trial will be conducted using a Simon optimal two-stage phase II trial design (Simon R, Controlled Clinical Trials 10:1-10, 1989) to rule out an unacceptably low response rate (CR+PR) of 5% (p0=0.05) in favor of an improved response rate of 20% (p1=0.20). With alpha=0.10(one sided alpha; equals two-sided alpha = 0.20; probability of accepting a poor treatment=0.10) and beta = 0.20 (probability of rejecting a good treatment=0.20), the first stage will enroll 12 evaluable participants, and if 0 of the 12 has a response, then no further participants will be accrued. If 1 or more of the first 12 participants has a response, then accrual would continue until a total of 21 evaluable participants have been treated. As it may take up to several months to determine if a participant has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. If there are 1-2 participants with a response out of 21 participants, this would likely be an uninterestingly low response rate. If there were 3 or more of 21 (14.3%) who experienced a response, this would be sufficiently interesting to warrant further study in later trials. Even if there are fewer than 3 responses, this will provide information on degree of efficacy of a single agent in a rare disease where there is currently no published

information. Under the null hypothesis (5% response rate), the probability of early termination is 54.0%.

It is expected that approximately 6-8 participants per year may enroll on this trial. Thus, in order to enroll up to 21 evaluable CN participants, it is expected that accrual will be completed within 3 to 4 years. We will also enroll up to 8 immune checkpoint-resistant (CR) participants; this cohort will be evaluated separately for OR. Accrual for CR participants will occur in two stages: initially 5 CR participants will be enrolled; if responses are observed in one or more participants, the second stage will enroll another 3 participants. Accrual for CR participants will end when the needed number of CN participants have been accrued. To allow for a small number of inevaluable participants, the accrual ceiling will be set at 32 participants (21 in the main CN cohort, 8 in the exploratory CR cohort, and 3 additional participants for inevaluable).

10.3 POPULATIONS FOR ANALYSES

Intention to treat: any subjects who enroll onto the trial and provide consent and who receive at least one dose of bintrafusp alfa will be included in the efficacy and safety evaluations. Only the immune checkpoint-naïve participants will be included in the primary endpoint analysis. The CN and CR populations will be reported separately for the secondary and exploratory endpoints.

10.3.1 Evaluable for Toxicity

All participants will be evaluable for toxicity from the time of their first treatment with bintrafusp alfa.

10.3.2 Evaluable for Objective Response

Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated in Section **6.3** (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

10.3.3 Evaluable Non-Target Disease Response:

Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.4 STATISTICAL ANALYSES

10.4.1 Analysis of the Primary Endpoints

The fraction of evaluable participants who experience a response will be reported along with a 95% two-sided confidence interval.

10.4.2 Analysis of the Secondary Endpoint(s)

PFS will be determined using the Kaplan-Meier method and will be reported along with 95% confidence intervals. PFS will be defined as the time from the date of first treatment to the date of disease progression or death (any cause) whichever occurs first. Subjects who do not have disease progression or have not died at the end of follow up will be censored at the last known date the subject was progression free.

OS will be evaluated using Kaplan-Meier methods. OS will be defined as the time from the date of first treatment to the date of death (any cause). Subjects who are alive at the end of follow up will be censored at the last known date alive.

Duration of Response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that PD or death is objectively documented and is evaluated using the Kaplan-Meier method. Analysis of safety and tolerability is as described in the Section **10.4.3.**

10.4.3 Safety Analyses

The fraction of participants who experience a toxicity, by grade and type of toxicity, will be tabulated. In addition, overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 5 for the study population in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented either in a Table or a Listing.

10.4.4 Baseline Descriptive Statistics

Baseline demographic characteristics will be reported.

10.4.5 Planned Interim Analyses

As indicated in the two-stage design (Section **10.2**), the number of responses after 12 evaluable checkpoint naïve participants have been treated will be noted and will be used to determine if enrollment to the second stage of accrual may proceed. After the first restaging scan of the last evaluable patient required for the interim analysis, enrollment to the checkpoint naïve cohort will be halted to allow for an analysis by the study statistician. An interim analysis report will be created by the study statistician to document the number of responses in the first stage and will be reviewed by the PI and study team. The memo will be provided to and approved by the study sponsor prior to continuation of accrual. Alternatively, if the required number of responses is observed before that time, the memo may be generated, reviewed and provided to the study sponsor at that point without a pause in accrual.

The interim analysis report will also be provided to the DSMB.

10.4.6 Tabulation of Individual Participant Data

Individual responses may be depicted using a waterfall plot or a spider diagram. In addition, to assess feasibility, the participant description of symptomatic adverse events (complimentary to clinician reported CTCAE) and missing data will be tabulated.

10.4.7 Exploratory Analyses

The exploratory objectives are intended to collect data for use in planning future scientific investigations or clinical research. These analyses are expected to be performed only using descriptive techniques, reporting descriptive statistics including confidence intervals when appropriate. Any statistical tests performed for evaluation of exploratory objectives will be done without formal adjustment for multiple comparisons, but in the context of the number of tests performed.

11 COLLABORATIVE AGREEMENTS

11.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

A CRADA (02666) is in place with EMD Serono for the supply of bintrafusp alfa.

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

Subjects from all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. Efforts will be made to extend accrual to a representative population. Due to impaired cellular immunity which may affect the efficacy of treatment, participants with poorly controlled HIV as well as patents with detectable viral loads of hepatitis B and C will be excluded.

As there is a risk of severe bleeding with this study drug, participants must be willing to receive blood transfusions if medically necessary for their own safety. Participants must be able to receive blood transfusions in order to minimize the risks of receiving bintrafusp alfa.

12.2 PARTICIPATION OF CHILDREN

Individuals under the age of 18 will not be eligible to participate in this study because of unknown toxicities in pediatric participants.

The effects of bintrafusp alfa on the developing human fetus are unknown. For this reason and because immunotherapeutic agents as well as other therapeutic agents used in this trial may be teratogenic, women of child-bearing potential and men must agree to use highly effective contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and up to 65 days for women and 125 days for men following the last dose of any study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

12.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to provide consent are excluded from enrolling in the protocol. However, it is possible that subjects enrolled in the protocol may permanently lose the capacity to consent for themselves during the course of this study. In the event this occurs, the subjects will be removed from treatment and remain in the study to be followed-up for overall survival. Due to the rarity of ONB, it is important to keep any enrolled subjects in follow-up for overall survival to learn more about the outcome of the disease. All subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study.

Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation to assess ongoing capacity of the subjects and to identify a LAR, as needed.

Please see Section **12.6.1** for consent procedure.

12.4 Evaluation of Benefits and Risks/Discomforts

Participants will receive evaluation of their disease at the National Cancer Institute's Clinical Center. The potential benefit to a participant that goes onto study is a reduction in the bulk of their tumor which may or may not have a favorable impact on symptoms and/or survival.

Potential adverse reactions attributable to the administration of the study drug utilized in this trial are discussed in Section **14.1.2**. All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. Participants will be examined and evaluated prior to enrollment. All evaluations to monitor the treatment of participants will be recorded in the medical record. If participants suffer any physical injury as a result of the participation in this study, immediate medical treatment is available at the Clinical Center, National Cancer Institute, Bethesda, Maryland.

Although no compensation is available, any injury will be evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations.

12.5 Risk/Benefit Assessment

12.5.1 Known Potential Risks

12.5.1.1 Potential Risks Associated with Bintrafusp alfa

Potential adverse reactions attributable to the administration of the study drugs utilized in this trial are discussed in Section **14.1.2.** Risks include the possible occurrence of any of a range of side effects which are listed in the Consent Document or this protocol document. Frequent monitoring for adverse effects will help to minimize the risks associated with administration of the study agents.

Participants may be harmed from being in this study by toxicity due to the drug or combination of drugs given during this study. M7824 is similar to immune check point inhibitors. There are preliminary data to suggest that not all patients benefit from immune check point inhibitors nor M7824. Additionally, there are preliminary data to suggest that an unexpectedly rapid progression of disease occurs in some patients receiving immunotherapy such as immune checkpoint inhibitors.

12.5.1.2 Risk of Optional Biopsies

All care will be taken to minimize risks that may be incurred by tumor sampling. There are potential risks associated with this procedure including pain or bleeding caused by the anesthesia needle as well as the biopsy procedure itself. An allergic reaction to the local anesthetic may occur. There may be bruising at the site of biopsy. Continuous bleeding and infection are rare and very often is easily controlled. Potential risks and discomforts will be minimized to the greatest extent possible by using personnel with appropriate training and monitoring.

12.5.1.3 Risks Due to Radiation

The study will involve radiation from the following sources:

- Up to 7 CT scans (C/A/P) per year for disease assessment
- Up to 3 FDG or Dotatate PET/CT scans per year for disease assessment
- 3 CT-guided biopsies

- Up to 2 bone scans

Subjects in this study may be exposed to approximately 14.28 rem maximum annually.

The radiation exposure that participants may get in this study will expose them to the roughly the same amount of radiation as 47.6 years of background radiation. The risk of getting cancer from the radiation exposure in this study is 1.4 out of 100 (1.4%) and of getting a fatal cancer is 0.7 out of 100 (0.7%).

Note: As the FDG PET/CT scans have a higher possible radiation exposure than Dotatate PET/CT, this scan was used in the possible maximum radiation exposure above and in the informed consent document.

12.5.1.4 Risks Due to Contrast Agents for CT

Contrast agents can cause allergic reactions and kidney damage. Allergic reactions can include mild itching associated with hives but can also result in a serious life-threatening emergency from difficulty breathing. If this occurs, it is treatable.

12.5.1.5 Risks Due to MRI

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection.

There are no known long-term risks of MRI scans.

12.5.1.6 Risks Due to Gadolinium as a Contrast Agent in MRI

During part of the MRI, people receive gadolinium, a contrast agent, through an intravenous (IV) catheter (small tube). It will be done for research purposes.

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. The risks due to gadolinium have been explained in detail in the consent document.

12.5.1.7 Risks Due to EKG

Other than possibly experiencing some minor skin irritation from the electrodes there are no anticipated risks related to complete the electrocardiogram

12.5.1.8 Blood Sampling Risks

Risks of blood draws include pain and bruising in the area where the needle is placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

12.5.1.9 Non-Physical Risks of Genetic Research

- Risk of receiving unwanted information: Anxiety and stress may arise as a result of the anticipation that unwanted information regarding disease related DNA sequencing or disease tendencies, or misattributed paternity. Participants will be clearly informed that the data related to DNA sequencing and genetic analysis is coded, investigational and will not be shared with participants, family members or health care providers.
- Risk related to possibility that information may be released: This includes the risk that data related to genotype, DNA sequencing or risk for disease tendency or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the participants, family members or health care providers, this risk will be included in the informed consent document.
- Risk to family or relatives: Family members or relatives may or may not want to be aware of familial tendencies or genetic risks of disease which may cause anxiety about possible future health problems. As previously noted, participants will be notified of any medically significant and actionable incidental findings. Study results will not be shared with participants.

12.5.2 Known Potential Benefits

As per Section **12.4** the potential benefit to a participant that goes onto study is a reduction in the bulk of their tumor which may or may not have favorable impact on symptoms and/or survival.

12.5.3 Assessment of Potential Risks and Benefits

Metastatic or refractory/recurrent ONB need improved therapy options. Studies suggest that a portion of ONB PD-L1 expression and presence of an associated inflammatory infiltrate. Thus, ONB may be susceptible to checkpoint inhibition. The information gained from this study will allow us to determine that bintrafusp alfa are tolerated in participants with metastatic or recurrent ONB. Furthermore, additional secondary outcomes will allow us to probe into the possibility of improvement in disease progression with bintrafusp alfa. Lastly, information gained from experimental aims will allow us to potentially improve treatment options in the future.

A number of clinically appropriate strategies to minimize risks to participants have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, and management guidelines.

The potential benefit to a participant that participates in this study is better control of their tumor growth and disease recurrence which may or may not have a favorable impact on symptoms and/or survival.

Potential adverse reactions attributable to the administration of the study drug utilized in this trial are discussed in Section **14.1.2**. All care will be taken to minimize side effects, but they can be unpredictable in nature and severity.

12.6 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time

as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the subject will sign the document with a hand signature using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at:

https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825

12.6.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in Section **12.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **12.6**.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI)

will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe the site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, and data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NCI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore,

the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the National Cancer Institute Center for Cancer Research (NCI CCR). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

14.1 BINTRAFUSP ALFA (M7824, MSB0011359C) (IND # 154950)

14.1.1 Source/Acquisition and Accountability

Bintrafusp alfa is manufactured and supplied for the trial by EMD Serono Research and Development Institute.

14.1.2 Toxicity

Most of the observed AEs with bintrafusp alfa are similar with class effects of monoclonal antibody blockade of the anti-PD-1/PD-L1 axis, with additional cutaneous side effects presumed to be related to TGF-β signaling modulation. The safety data summarized from April 2020 include data on the pooled expansion cohorts (630 participants): treatment-related (TR) treatment-emergent adverse events (TEAEs) were reported in 426 (67.6%) participants. (47) Most TR

TEAEs were low grade (Grade 1 or 2), while Grade ≥ 3 TR TEAEs occurred in 142 participants (22.5%), and immune related adverse events (irAEs) occurred in 137 (21.7%) participants.

Treatment-related TEAE Leading to Permanent Treatment Discontinuation by System Organ Class and Preferred Term in ≥ 2 participants in the Pooled Analysis of Dose Expansion Cohorts

System Organ Class (SOC) Preferred Term (PT)	EMR200647-001 N = 539 n (%)	MS200647-0008 N = 91 n (%)	Overall N = 630 n (%)
Related TEAE leading to permanent treatment discontinuation	38 (7.1)	12 (13.2)	50 (7.9)
Skin and subcutaneous tissue disorders	11 (2.0)	2 (2.2)	13 (2.1)
Rash maculo-papular	3 (0.6)	1 (1.1)	4 (0.6)
Eczema	1 (0.2)	1 (1.1)	2 (0.3)
Rash	2 (0.4)	0	2 (0.3)
Investigations	6 (1.1)	3 (3.3)	9 (1.4)
Alanine aminotransferase increased	3 (0.6)	1 (1.1)	4 (0.6)
Lipase increased	2 (0.4)	1 (1.1)	3 (0.5)
Aspartate aminotransferase increased	1 (0.2)	1 (1.1)	2 (0.3)
Gamma-glutamyltransferase increased	1 (0.2)	1 (1.1)	2 (0.3)
Gastrointestinal disorders	7 (1.3)	0	7 (1.1)
Colitis	3 (0.6)	0	3 (0.5)
Respiratory, thoracic and mediastinal disorders	5 (0.9)	1 (1.1)	6 (1.0)
Pneumonitis	3 (0.6)	0	3 (0.5)
Dyspnoea	2 (0.4)	0	2 (0.3)
Blood and lymphatic system disorders	4 (0.7)	1 (1.1)	5 (0.8)
Anaemia	1 (0.2)	1 (1.1)	2 (0.3)
Eosinophilia	2 (0.4)	0	2 (0.3)
Renal and urinary disorders	3 (0.6)	0	3 (0.5)
Acute kidney injury	3 (0.6)	0	3 (0.5)
Endocrine disorders	2 (0.4)	0	2 (0.3)
Adrenal insufficiency	2 (0.4)	0	2 (0.3)
Source: ADAE 30OCT2018 12:04 Outputid: t31.doc.			

TEAEs leading to death occurred in 79 (12.5%) participants with similar rates in EMR200647-001 and MS200647-0008; 7 deaths were due to treatment-related TEAE:1 participant had dyspnea, hemolysis and thrombocytopenia, 1 participant had an intracranial tumor hemorrhage, 1 participant had pneumonia, 2 participants died of interstitial lung disease, 1 participant due to sudden death, and 1 due to septic shock.

Common TEAEs (occurring in more than 10% of participants) were:

- Anemia (29%)
- Decreased appetite (25%)

- Fatigue (tiredness) (22%)
- Pruritus (itching) (21%)
- Dyspnea (shortness of breath) (21%)
- Constipation (19%)
- Nausea (19%)
- Pyrexia (fever) (19%)
- Asthenia (weakness, fatigue) (17%)
- Diarrhea (16%)
- Abdominal pain (15%)
- Vomiting (14%)
- Cough (13%)
- Headache (12%)
- Epistaxis (12%)
- Rash (11%)
- Elevation of aspartate aminotransferase (AST, liver enzyme) (11%)
- Leg or arm swelling (10%)

Skin-related adverse events which were possibly due to TGF-β inhibition, occurred in 11% of participants and included keratoacanthomas (7%), squamous cell carcinoma of the skin (3%), and hyperkeratosis (1%) and are important identified risks with bintrafusp alfa.

Anemia, alterations in would healing or repair of tissue damage, and embryofetal toxicity remain important potential risks.

At least 2 instances of nodular regenerative hyperplasia have been observed with the use of this agent.

In addition, mucosal bleeding events (e.g. gum bleeding, nose bleeds, coughing up blood, blood in urine or stool) are a potential risk for bintrafusp alfa, included in the informed consent document.

Infusion-related Reactions (including reactions, signs and symptoms) occurred in 38 (6%) participants in the pooled safety analysis, and all IRRs were of Grade 1 or 2 intensity; most of the IRRs had an onset after the first or second infusion; those with onset after the third infusion (or later) were less frequent. Consequently, the administration of premedication is not required. As per Section 3.2.3, if an Investigator deems necessary to administer a premedication to a particular participant, an antihistamine (e.g. 25 to 50 mg diphenhydramine) and paracetamol (acetaminophen, 500 to 650 mg intravenously or equivalent oral dose) 30 to 60 minutes prior to bintrafusp alfa infusion is recommended. Premedication should be administered for subsequent bintrafusp alfa doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

In addition, immune-mediated side effects might be possible (immune- related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus, pituitary disorders), immune-related nephritis and renal dysfunction and other immune-related AEs (arthralgias, arthritis, myositis, myocarditis, Guillain-Barré syndrome, uveitis, thrombocytopenia, dry eyes, dry mouth, psoriasis, neuritis). Per IB, in the pooled expansion cohorts the incidence of all immune-related AEs was 21.7% (123 of 630 participants), with Grade 3 and 4 events being 8.5% (53 participants), 2.9% (18 participants) leading to discontinuation and 0.3% (2 participants) leading to death.

Please refer to the IB for detailed toxicity information.

14.1.3 Formulation and preparation

Bintrafusp alfa is provided as a sterile liquid formulation and packaged at a 10 mg/mL concentration in USP/ Ph Eur type I 50R vials that are filled with drug product solution to allow an extractable volume of 60 mL (600 mg/60 mL). The vials are closed with rubber stoppers in serum format complying with USP and Ph Eur with an aluminum crimp seal closure. Each single-use vial contains 600mg of bintrafusp alfa, formulated as 10mg/mL of active, 6% (w/v) Trehalose, 40 mM NaCl, 5 mM Methionine, 0.05% (w/v) Tween 20, 10 mM LHistidine at pH 5.5.

The liquid formulation is diluted directly with 0.9% sodium chloride solution for injection. The estimated volumes of delivery are anticipated to be no more than 250mL. The verified concentration range in the infusion solution is 0.16 mg/mL to 9.6 mg/mL.

14.1.4 Stability and Storage

Bintrafusp alfa must be stored at 2℃ to 8℃ until use. Product stored at room temperature for extended periods of time might be subject to degradation. Bintrafusp alfa must not be frozen. Rough shaking of the reconstituted solution must be avoided.

The chemical and physical in-use stability for the infusion solution of bintrafusp alfa in 0.9% sodium chloride for injection has been demonstrated for a total of 72 hours at room temperature; however, from a microbiological point of view, the diluted solution should be used immediately and is not intended to be stored unless dilution has taken place in controlled and validated aseptic conditions. No other drugs should be added to the infusion containers containing bintrafusp alfa. See Manual of Preparation of approved ancillary supplies.

14.1.5 Administration procedures

See Section **3.3.3**.

14.1.6 Incompatibilities

Not available.

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16 LIST OF ABBREVIATIONS

Abbreviation	Term
AACR	American Association for Cancer Research
AAO-HNS	American Academy of Otolaryngology-Head and Neck Surgery
ACAT	Ability to Consent Assessment Team
ADA	anti-drug antibodies
ADR	adverse drug reactions
AE	Adverse Event/Adverse Experience
AESI	Adverse Event/Experience of Special Interest
AHNS	American Head and Neck Society
ALT	alanine transaminase
ANC	Absolute neutrophil count
ARS	American Rhinologic Society
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BARON	Bintrafusp alfa in Recurrent/Metastatic Olfactory Neuroblastoma
β-HCG	Beta human growth hormone
BSI	Biospecimen Inventory System
BTRIS	Biomedical Translational Research Information System
CAP or C/A/P	Chest, abdomen, pelvis
CBC	Complete blood count
CCR	Center for Cancer Research
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CFR	Code of Federal Regulations
CK	Creatine kinase
CLIA	Clinical Laboratory Improvement Amendment
CN	checkpoint-naïve
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COV	Close-out Visit
CR	checkpoint-resistant
CR	Complete Response
CSP	Clinical Services Program
CRADA	Cooperative Research and Development Agreement
CRIS	Clinical Research Information System
CRF	Case Report Form
CT	Computed Tomography
ct DNA	Circulating tumor DNA
CTCAE	Common Terminology Criteria for Adverse Events
dbGaP	database of Genotypes and Phenotypes
DNA	Deoxynucleic acid

Abbreviation	Term
DOR	Duration of Response
ECG / EKG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay)
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	Flash frozen, paraffin embedded
EOT	End of treatment
FT4	free thyroxine
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMB	Genitourinary malignancies branch
GMP	Good Manufacturing Practices
GOT	Glutamic oxaloacetic transaminase
GPT	glutamate pyruvate transaminase
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HHS	Health and Human Services
HIV	Human immunodeficiency virus
H&P	History and Pathology
IB	Investigator's Brochure
ICBMs	immune checkpoint blockade monoclonal antibodies
ICH	International Conference on Harmonisation
iCPD	confirmed progressive disease
IHC	Immunohistochemistry
IMV	Interim Monitoring Visit
IND	Investigational New Drug
INR	International Normalized Ratio
irAE	Immune-related adverse reactions
IRB	Institutional Review Board
IRBO	Institutional Review Board Office
iRECIST	immune Response Evaluation Criteria in Solid Tumors
IRR	Immune-related reaction
iUPD	unconfirmed progressive disease
IV	Intravenous
LAR	Legally Authorized Representative
LTIB	Laboratory of Tumor Immunology
MAR	Medical Administration Record
MDSC	myeloid-derived suppressor cell
MRI	Magnetic Resonance Imaging
MUGA	multi-gated acquisition scan

Abbreviation	Term
N	Number (typically refers to subjects)
NASBS	North America Skull Base Society
NCI	National Cancer Institute
NCI PDM	NCI Participant-Derived Models Repository
NCT	National Clinical Trial (number)
NFGCF	NCI Frederick Genomic Core Facility
NIDCD	National Institute of Deafness and Craniofacial Disorders
NIH	National Institutes of Health
NK	natural killer cells
NORD	National Organization for Rare Disorders
NSAID	Non-steroidal anti-inflammatory drugs
NSCLC	Non- small cell lung cancer
OHSRP	Office for Human Subjects Research Protections
ONB	Olfactory Neuroblastoma
ORR	objective response rate
OS	Overall survival
OSRO	Office of Sponsor and Regulatory Oversight
OTC	over the counter
PBMC	peripheral blood mononuclear cell
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PD-1	programmed death 1
PD-L1	programmed death-ligand 1
PET	Positron Emission Tomography
PFS	Progression-free survival
PI	Principal Investigator
PK	pharmacokinetics
PR	Partial Response
PS	Performance Status
PT	Prothromibn time
PTT/aPTT	Partial Thromboplastin Time/activated Partial Thromboplastin Time
QA	Quality Assurance
QC	Quality Control
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious Adverse Event/Serious Adverse Experience
SAV	Site Assessment Visit
SIV	Site Initiation Visit
SEER	Surveillance Epidemiology and End Results
SD	Stable Disease
SLD	sum of the longest diameters

Abbreviation	Term
SOP	Standard Operating Procedure
SST	serum separation tubes
TBNK	T, B, and natural killer cells
TEAE	treatment-emergent adverse events
TGF-β	transforming growth factor beta
TGF-βRII	human TGF-β receptor II
TR	treatment-related
TRAIL	tumor necrosis factor-related apoptosis-inducing ligand
TSH	thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Women of child-bearing potential

17 APPENDICES

17.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

17.2 APPENDIX B: RECOMMENDATIONS FOR MANAGEMENT OF IRRS AND AES

TABLE A MANAGEMENT OF INFUSION-RELATED REACTIONS

NCI-CTCAE 5.0 Grade	**Treatment Modification for Infused Agent (Bintrafusp alfa)**
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Consider decreasing the infusion rate of the particular agent by 50% and monitoring closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤ 24 hours.	Consider temporarily discontinuing infusion of the particular agent. Consider resuming infusion of the particular agent 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 Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the infusion immediately and disconnect infusion tubing from the subject. For grade 3 events: Consider withdrawing immediately from treatment with that particular agent and not offering any further treatment with that agent based upon if the clinical condition can be safely managed. For grade 4 events: Withdraw immediately from treatment and do not offer further treatment with that agent.

If the infusion rate of bintrafusp alfa has been decreased by 50% or interrupted due to an infusion reaction, keep it decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgment.

If hypersensitivity reaction occurs, the subject should be treated according to the best available medical practice.

TABLE B Management of immune-related Adverse Events

Recommended guidance and management for specific irAEs as provided in the current NCCN guideline available at http://www.nccn.org.

According to American Society of Clinical Oncology Clinical Practice Guideline (Brahmer 2018), treatment of irAEs is mainly dependent upon severity as defined by NCI-CTCAE v5.0. In general, management by NCI-CTCAE v5.0 grading is listed below:

- Grade 1: study intervention should be continued with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities.
- Grade 2: study intervention may be suspended for some 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 intervention 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 intervention is recommended, with the exception of endocrinopathies that have been controlled by hormone replacement.

Permanent treatment discontinuation is required in case of immune-related Grade 4 rash/inflammatory dermatitis, nephritis, autoimmune hemolytic anemia, hemolytic uremic syndrome, aplastic anemia, immune thrombocytopenia, and acquired thrombotic thrombocytopenic purpura.

For Grade 4 immune-related lymphopenia, permanent treatment discontinuation will be required, if lymphopenia is considered immune-related in nature, no clear alternative explanation exists for the event, and it does not resolve within 14 days. Permanent treatment discontinuation is not required when the AE is manifested by a single laboratory value out of normal range without any clinical correlates. In this case, treatment should be held until the etiology is determined. If the event is not considered immune-related and resolves to Grade $\leqslant$ 1, restarting treatment may be considered.

For organ/system specific management guidelines, see the current NCCN guideline available at http://www.nccn.org.

TABLE C Management of TGF-β mediated Skin Adverse Events

Skin assessment must be performed at baseline and at least every 6 weeks during treatment and at the end of treatment or 28 (±5 days) days post-treatment safety follow-up (if not performed in the previous 6 weeks).

- Hyperkeratosis
- Keratoacanthoma
- Cutaneous squamous cell carcinoma (cSCC)
- Basal cell carcinoma
- Actinic keratosis

Management

- Baseline skin assessment with detailed medical history
- Discontinuation or termination not required in most cases. Continuation of treatment should be evaluated by the Investigator.
- Emollients may be used
- Develop diagnostic and treatment plan in collaboration with Investigator and dermatologist
- Treatment follow-up will depend on number and localization of lesions.
    - Single lesion: full excision may be recommended
    - Multiple lesion or location not suitable for full excision: Mohrs surgery, cryotherapy or other standard treatment options depending on pathology. Topical retinoids may be used after discussion with Investigator.
- Close clinical follow-up for re-evaluation, resolution and potential recurrence should be implemented
- In general, treatment of TGF-β mediated skin lesions should be based on local guidelines/standard of care.

Additional consideration: Keratoacanthoma lesions may resolve spontaneously without surgical intervention within weeks after discontinuing bintrafusp alfa. Consult with Medical Monitor as needed for management of TGF-β mediated skin lesions.

Management of Mucosal/Non-tumor and Tumor Bleeding

Mucosal Bleeding	
• Events of mild to moderate severity are a potential risk for bintrafusp alfa. • In general, these reactions resolve without discontinuation of treatment. • Events may include, but are not limited to the following: o Epistaxis o Hemoptysis o Gingival bleeding o Hematuria	
Non-tumor Bleeding	
Grading	Management
Grade 2	• If resolves to Grade ≤ 1 by the day before the next infusion, study intervention may be continued • 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.
Grade 3	• Permanently discontinue treatment unless an alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic events, etc.) • 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 • Permanently discontinue treatment if the Investigator considers the participant to be at risk for additional severe bleeding.

Guideline on Alterations in Wound Healing or Repair of Tissue Damage

• Alterations of wound healing and tissue damage repair are considered an important risk for bintrafusp alfa • Management should be discussed with Medical Monitor for participants requiring surgery on study. • It is recommended to hold study intervention for approximately 4 weeks post major surgery for observation. • Post-operative wound healing should be closely monitored

17.3 APPENDIX C: BEST OVERALL RESPONSE PER RECIST 1.1

RECIST version 1.1 will be used in this study for assessment of tumor response.(1)

For Participants with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		