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Protocol PI	Xiunig Le, MD
Department	Thoracic Head and Neck Medical Oncology
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A SINGLE-ARM PHASE 2 STUDY TO INVESTIGATE BINTRAFUSP ALFA WITH PLATINUM-PEMETREXED FOR TKI-RESISTANT EGFR-MUTANT NSCLC

Study Center: MD Anderson Cancer Center

Principal Investigator (PI): Xiuning Le, MD PhD
Thoracic Head and Neck Medical Oncology Department
MD Anderson Cancer Center
1515 Holcombe Blvd, Houston 77030 TX, USA
713-792-6980
713-792-1220
Xle1@mdanderson.org

Collaborators: [redacted]
Thoracic Head and Neck Medical Oncology Department
MD Anderson Cancer Center

Statistician
[redacted]
Department of Biostatistics
MD Anderson Cancer Center

[redacted]
Department of Biostatistics
MD Anderson Cancer Center

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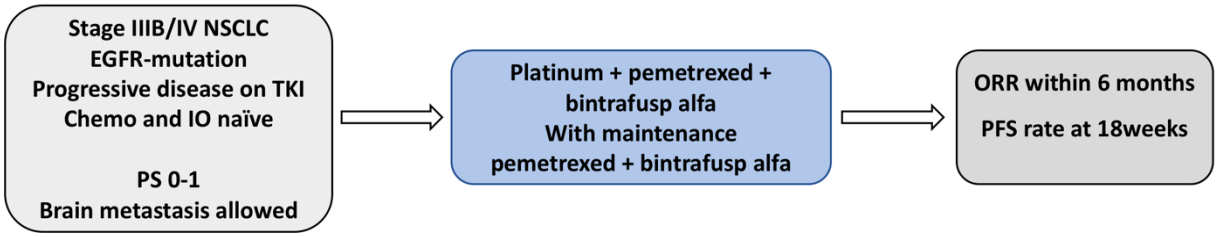
SCHEMA



Key eligibility:
Metastatic EGFR-mutation non-squamous NSCLC
Resistant to EGFR TKI
Naïve to platinum-pemetrexed and anti-PD1/L1 therapy

Sample size:
40

Primary Endpoints:
Best objective response rate (ORR) within 6 months
Landmark progression free survival (PFS) at 18 weeks

Secondary Endpoints:
Safety and tolerability
PFS, disease control rate (DCR), duration of response (DoR), overall survival (OS)

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1. BACKGROUND AND RATIONALE

1.1 Landscape of resistance mechanisms to osimertinib in EGFR-mutant Non-Small Cell Lung Cancer

In the last decade, metastatic EGFR-mutant lung cancers were mostly treated with sequential EGFR tyrosine kinase inhibitors (TKI)[1-3]. Since the FDA approval in April 2018, osimertinib, a third generation EGFR TKI, has become the first line treatment for all newly diagnosed patients with metastatic EGFR-mutant non-small cell lung cancer (NSCLC)[3]. Our group and others examined the resistance mechanisms to osimertinib aiming to identify second line treatment strategies after osimertinib progression[4-6]. In our MD Anderson and Moffitt Cancer Center combine cohort of 118 patients treated with osimertinib, 42 had molecular profiling at progression. T790M was preserved in 21 (50%) patients and lost in 21 (50%). Tertiary mutations in EGFR is a common resistance mechanism in T790M-preserved cases, but not for T790M-loss cases. MET amplification is a most common alteration (14%) that induced resistance in both T790M-preserved and -loss cases[5]. Furthermore, preclinical studies confirmed that acquired MET amplification renders resistance to EGFR TKI, which can be reversed by addition of c-met inhibitors[5,7]. In this cohort, we also found that resistance to osimertinib in T790M-loss cases were mostly mediated by either non-genetic or non-targetable mechanisms, calling for non-TKI strategies as second line treatment for patients who progressed on osimertinib. Given the effectiveness of osimertinib at suppressing T790M positive subclones, it is conceivable that resistance to osimertinib in the first-line setting will be similar to the pattern of T790M-loss cases, where MET amplification and epithelial to mesenchymal transition to be the predominant resistance mechanisms.

1.2 TGF-beta and immune therapy in EGFR-mutant NSCLC

Although immune checkpoint blockade (ICB) has been successfully utilized in treating patients with metastatic NSCLC, the benefit of ICB for patients with advanced EGFR-mutant NSCLC has been limited. Gainor et al reported an objective response rate (ORR) of 3.7% to anti-PD1 monotherapy in EGFR/ALK driven lung cancers[8]. Lee et al showed the anti-PD1/PDL1 therapy was inferior to cytotoxic chemotherapy as the second line treatment for this population of patients[9]. Therefore, EGFR-mutant lung cancers were generally reviewed as immune "cold" tumors. Interestingly, recent data from IMpower150 trial subgroup analysis indicated that combination of VEGF inhibition (bevacizumab) with anti-PD-L1 (Atezolumab) and chemotherapy (carboplatin and paclitaxel) produced prolonged response in patients with EGFR/ALK driven NSCLC[10]. The clinical benefit of PFS was only seen when VEGF inhibition was used in combination with ICB, suggesting an immune modulating effect in the tumor microenvironment and enhances response to anti-PD-1 blockade. These results ignited great excitement as this was the first and only clinical trial showing that EGFR-mutant lung cancer has the potential to be turned to "hot" tumors.

We performed analysis to understand the difference in tumor immune microenvironment (TME) between EGFR-mutant and wildtype (WT) lung cancers. In a retrospective cohort of 94 cases, we compared 14 cases with EGFR mutations to the 80 wildtype tumors[11]. We confirmed that PD-L1 levels were lower in the EGFR-mutant cancers, as were the Granzyme B levels. TGF-β pathway was found to be elevated in the EGFR-mutant group. Furthermore, in cell lines that are resistant to osimertinib, TGF-β signaling is further elevated. The transforming growth factor beta (TGF-β)

signaling family comprises of more than 30 factors and displays diverse spatial and temporal expression patterns during development and oncogenesis[12]. TGF-β has established roles in mediating epithelial-mesenchymal transition (EMT)[13], which was observed in osimertinib-resistant NSCLC. EMT has been suggested as a mechanism of resistance to therapy by our group and others[14]. It was known that elevated TGF-β signal also has a profound impact on tumor immune microenvironment. It acts as a major enforcer of immune tolerance by inhibiting the development and functions of nearly all major components of the innate and adaptive immune cells function[12]. Given the important roles of TGF-β in promoting tumor invasion/metastasis, EMT, fibrosis, and immune tolerance, there has been a growing effort in targeting TGF-β for treating cancers.

1.3 Bintrafusp alfa and preliminary data in NSCLC.

Bintrafusp alfa (M7824) is a first-in-class bifunctional fusion protein composed of the extracellular domain of the human transforming growth factor β receptor II (TGF-βRII or TGF-β "trap") fused via a flexible linker to the C-terminus of each heavy chain of an IgG1 antibody blocking programmed death ligand 1 (anti–PD-L1), designed to target 2 of the key mechanisms of immunosuppression in the tumor microenvironment[15]. This agent is designed to target two major mechanisms of immunosuppression in the tumor microenvironment, through its anti-PDL1 and TGF-β "trap" activities. In phase I studies, M7824 was showed to be safe and tolerable. The RP2D was determined to be 1200mg IV infusion every two weeks. In a recently reported phase 1 study of M7824 in HPV-associated diseases (HNSCC, cervical and anal cancers), 9/16 (56%) patients had response including a durable CR[16]. The expansion cohort of the phase 1 study (NCT02517398) includes 80 patients with advanced NSCLC who had prior platinum doublet therapy but have not received previous immunotherapy. A total of 80 patients were randomized to receive bintrafusp alfa 500 or 1200 mg (n = 40 each). Median follow-up was 51.9 weeks (IQR, 19.6-74.0). The ORR in all patients was 21.3% (17 of 80). The ORR was 17.5% (seven of 40) and 25.0% (10 of 40) for the 500 mg dose and the 1200 mg dose (recommended phase 2 dose), respectively. At the 1200 mg dose, patients with PD-L1-positive and PD-L1-high (≥80% expression on tumor cells) had ORRs of 36.0% (10 of 27) and 85.7% (six of seven), respectively[17]. With the initial observation of efficacy, ongoing study (NCT03840915) is testing the safety and efficacy of M7824 in combination with platinum-doublet in NSCLC. The preliminary results indicate that M7824 administered intra-venously at 2400mg every three weeks in combination with carbo/cisplatin plus pemetrexd (cohort A) is safe and feasible. For this trial (NCT03840915), a safety monitoring committee (SMC) meeting occurred on January 11th, 2021 to review the safety data from all patients enrolled in the study (N=70), including 40 patients treated with cisplatin/carboplatin and pemetrexed + bintrafusp alfa. After the presentation and review of data, the SMC has agreed that the emerging safety profile is in line with the overall benefit/risk that was anticipated based on the clinical experience to date and have recommended to continue the study without modifications.

1.4 Rationale for study design and objectives

Here we hypothesize that Bintrafusp alfa modulate tumor immune microenvironment and work synergistically with chemotherapy therapy to induce response in EGFR-mutant NSCLC. With the established safety and efficacy data, we proposed to perform a phase 2 study to understand the benefit of bintrafusp alfa with chemotherapy in TKI-resistant EGFR-mutant NSCLC. In this trial,

patients who progressed on prior EGFR TKI therapy will receive platinum-pemetrexed chemotherapy in combination with bintrafusp alfa.

The primary objective of this study is to evaluate the efficacy of Bintrafusp alfa-chemotherapy combination. The primary endpoints are the objective response rate at 6 weeks and landmark PFS at 18 weeks. These are appropriate primary efficacy endpoints in this NSCLC population and may be associated with an improvement in OS, delay to time of initiation of subsequent therapies, symptom control, and quality of life. We expect the addition of bintrafusp alfa to chemotherapy render benefit in prolonging disease control. Best objective response rate within 6 months will be evaluated as a co-primary endpoint along with the PFS at 18 weeks. Secondary efficacy endpoints are those that are appropriate to this patient population and include, Disease Control Rate (DCR) [DCR: Complete response (CR) + Partial Response (PR) + Stable disease (SD)] and Duration of Response (DoR) and Overall Survival (OS). Safety and tolerability of bintrafusp alfa with platinum-pemetrexed will also be assessed as a secondary endpoint.

A collection of exploratory biomarker studies will be performed. Tumor samples and ctDNA will be collected at baseline and at the time of progression to evaluate potential mechanisms of resistance. Additional plasma will be collected to understand cytokine and immune microenvironment following therapies. Optional biopsy at progression will be obtained to understand bintrafusp alfa's immune modulation effect to the tumor immune microenvironment.

Overall, the totality of primary, secondary and exploratory endpoints in this study will allow a robust characterization of overall benefit and risk of bintrafusp alfa in combination with platinum-pemetrexed for patients with TKI-resistant advanced EGFR-mutant non-small cell lung cancer (NSCLC)

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Primary Endpoints

The primary objective of this study is to evaluate treatment efficacy of bintrafusp alfa with platinum-pemetrexed in TKI-resistant EGFR-mutant NSCLC. Two co-primary endpoints are the best objective response rate (ORR) within 6 months since initiation of treatment and the landmark progression free survival (PFS) at 18 weeks since initiation of treatment.

2.2 Secondary Objectives and Secondary Endpoints

- The secondary objective is to assess safety and tolerability of bintrafusp alfa platinum-pemetrexed combination and to study other clinical efficacy parameters. The secondary endpoints are the type and grade of toxicities, time to resolve toxicities, the best response rate, duration of response, disease control rate, progression-free survival, and overall survival.

2.3 Exploratory Objectives

- To explore the association of baseline genomic profiles (from tumor, germline DNA, and ctDNA) with clinical benefit in patients treated with bintrafusp alfa platinum-pemetrexed combination.

- To explore resistance mechanisms to bintrafusp alfa platinum-pemetrexed combination. At C3D1 and at the time of progression, patients will undergo ctDNA genomic tests and an optional biopsy to explore resistance mechanisms to bintrafusp alfa platinum-pemetrexed combination.

- To determine the immunomodulatory effects of bintrafusp alfa platinum-pemetrexed combination. We have shown TGF-beta elevation is associated with TKI resistance. We will investigate if bintrafusp alfa treatment will suppress TGF-beta and favorably modulate the tumor immune microenvironment (TME). Plasma will be collected before treatment, after treatment, as well as at the time of disease progression. Plasma TGF-beta level and cytokine profiling will be performed to identify potential correlative markers for response and resistance. At the time of progression, patients will undergo an optional biopsy. The purpose of this additional tissue acquisition is for molecular analysis and comparison with the initial specimen, to determine if there are changes in molecular alterations or pathways that shed light on TME modulation.

3. PARTICIPANT SELECTION

For entry in this study, all eligibility criteria MUST be met.

3.1 Inclusion Criteria

1. Age equal or greater than 18 years old and willing to give their signed consent

2. Histologically or cytologically confirmed non-squamous, non-small cell lung cancer

3. Locally advanced or metastatic disease, not amenable to curative surgery or radiotherapy.

4. Patients must have one of the following:
   - NSCLC which harbours *EGFR* Exon 19 deletion.
   - NSCLC which harbours *EGFR* L858R mutation.
   - NSCLC which harbours *EGFR* G719X, S768X, L861X mutation, and other activating uncommon mutations in exon 18-21.
   - NSCLC which harbours *EGFR* exon20 insertion
   - NSCLC which harbours *EGFR* T790M mutation

   EGFR deletion/mutation must be documented by a Clinical Laboratory Improvement Amendments (CLIA) certified test

5. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (**Appendix A**)

6. At least one target lesion, not previously irradiated and not chosen for biopsy during the study screening period, that can be accurately measured at baseline at equal or greater than 10mm in the longest dimension by RECIST 1.1.

7. Patients must have received at least one line of EGFR tyrosine kinase inhibitor (TKI) treatment, if an FDA-approved treatment exist for the EGFR mutation. Patients whose tumor harboring EGFR T790M mutation must have received prior osimertinib (or another EGFR TKI with demonstrated activity against T790M mutation). Patients who received more than one EGFR TKIs are eligible. Up to two lines of TKIs are allowed.

8. Patients must have adequate hematologic, coagulation, hepatic, and renal function. All laboratory tests must be obtained less than 4 weeks from study entry. This includes:
   A. ANC >/= 1,500/mm3
   B. platelet count >/=100,000/mm3
   C. HgB ≥ 9 g/dL
   D. Creatinine ≤ 1.5x ULN
   E. INR ≤ 1.5 and partial thromboplastin time (PTT) (PTT/aPTT) < 1.5 x upper limits of normal [ULN]. Patients receiving warfarin must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to first dose of protocol therapy.
   F. Total Serum Bilirubin ≤ 1.5 x ULN (Patients with known Gilbert Syndrome, a total bilirubin ≤ 3.0 x ULN, with direct bilirubin ≤ 1.5 x ULN)
   G. SGOT, SGPT ≤ 3 X ULN if no liver metastasis present
   H. SGOT, SGPT ≤ 5 X ULN if liver metastasis present

9. Patients with history of HIV: stable on ART for at least 4 weeks, no documented evidence of multi-drug resistance, viral load of < 400 copies/ml and CD4+ T-cells ≤ 350 cells/μL.

10. Patients with history of HBV/HCV: participant on a stable dose of antiviral therapy, HBV viral load below the limit of quantification. HCV viral load below the limit of quantification.

11. Females of childbearing potential must not be breast feeding and must have a negative serum or urine pregnancy test within 7 days of starting of treatment. The patient must agree to use adequate contraception for a minimum of two weeks prior to receiving study medication until 65 days after discontinuation of the study medication. Acceptable methods of contraception include total and true sexual abstinence, hormonal contraceptives that are not prone to drug-drug interactions (IUS Levonorgestrel Intra Uterine System (Mirena), Medroxyprogesterone injections (Depo-Provera)), copper-banded intra-uterine devices, and vasectomized partner. All hormonal methods of contraception should be used in combination with the use of a condom by their sexual male partner. Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause). Women will be considered post-menopausal if they have been amenorrheic for the past 12 months without an alternative medical cause. The following age-specific requirements must also apply: Women < 50 years old: they would be considered post-menopausal if they have been amenorrheic for the past 12 months or more following cessation

of exogenous hormonal treatments. The levels of Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) must also be in the post-menopausal range (as per the institution). Women ≥ 50 years old: they would be consider post-menopausal if they have been amenorrheic for the past 12 months or more following cessation of all exogenous hormonal treatments, or have had radiation-induced oophorectomy with the last menses > 1 year ago, or have had chemotherapy-induced menopause with >1 year interval since last menses, or have had surgical sterilization by either bilateral oophorectomy or hysterectomy.

12. Non-sterilized males who are sexually active with a female partner of childbearing potential must use adequate contraception for the duration of the study and 125 days after the last dose of study medication. Adequate contraception methods include: birth control pills (e.g. combined oral contraceptive pill), barrier protection, and abstinence. Patients should not father a child for 125 days after completion of the study medication. Patients should refrain from donating sperm from the start of dosing until 125 days after discontinuing the study medication. If male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of the study medication.

3.2 Exclusion Criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Previous treatments with cytotoxic chemotherapy or checkpoint immunotherapy or combination of chemo-immunotherapy for metastatic disease. If the patient had prior chemotherapy as neoadjuvant or adjuvant therapy, the completion of treatment must be greater than 6 months until the beginning of the treatment on trial.

2. Previous treatment with any anti-TGF-beta medications.

3. Spinal cord compression or brain metastases unless asymptomatic or stable for at least 2 weeks prior to start of study treatment.

4. Persisting Grade > 1 CTCAE 5.0 toxicity (except alopecia and vitiligo) related to prior therapy; however, sensory neuropathy Grade ≤ 2 is acceptable

5. Current use of immunosuppressive medication, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids at doses ≤ 8 mg/day of dexamethasone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)."

6. Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.

7. Any evidence of current interstitial lung disease (ILD) or pneumonitis or a prior history of ILD or non-infectious pneumonitis requiring high-dose glucocorticoids.

8. No previous malignant disease within the last 3 years except for a. superficial/non-invasive bladder cancer, or basal or squamous cell carcinoma *in situ* treated with curative intent; b. endoscopically resected GI cancers limited to the mucosal layer without recurrence in > 1 year.

9. No prior organ transplantation including allogenic stem-cell transplantation, except transplants that do not require immunosuppression.

10. Active infection requiring systemic therapy.

11. Live vaccination that has received or will receive within 30 days prior to the first administration of study intervention. Seasonal flu vaccines that do not contain a live virus are permitted. COVID-19 vaccines are permitted.

12. Known severe hypersensitivity [Grade ≥ 3 NCI CTCAE 5.0]) to investigational product or any component in its formulations, any history of anaphylaxis, or recent, within 5 months, history of uncontrollable asthma.

13. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

14. History of bleeding diathesis or recent major bleeding events (i.e. Grade ≥ 2 bleeding events in the month prior treatment)

15. Males and females of reproductive potential who are not using and effective method of birth control and females who are pregnant or breastfeeding or have a positive (urine or serum) pregnancy test prior to study entry. Females who are pregnant or breast-feeding.

16. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirement.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. ETHICAL CONSIDERATIONS

4.1 Institutional Review Board (IRB)

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other written

information to be provided to the subjects. The investigator should also provide the IRB with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The instigator should provide the IRB with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institutional procedures.

4.2 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.
In situations where consent cannot be given by subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate. The approved informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

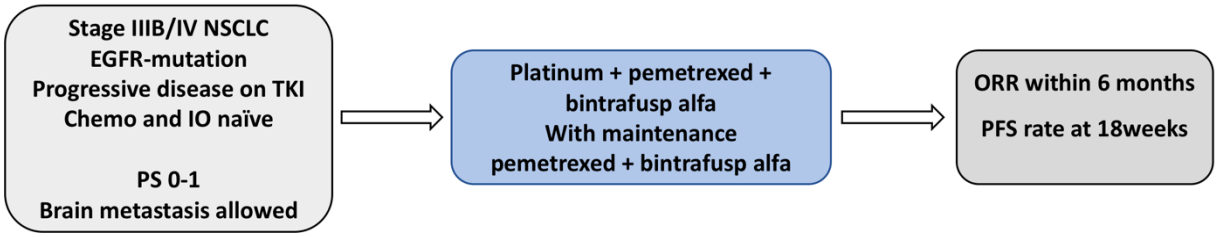
1) Obtain the IRB written approval of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
2) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
3) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
4) Obtain an informed consent signed and personally dated by each subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. All participants will be registered in the Clinical Oncology Research System (CORe)

5. STUDY DESIGN

5.1 Study Design

This is a single-arm open-label phase 2 study that will enroll EGFR-TKI resistant advanced or metastatic *EGFR*-mutant NSCLC patients who are chemotherapy and immunotherapy naïve. All subjects will receive bintrafusp alfa with platinum-pemetrexed chemotherapy. If no progression, bintrafusp alfa and pemetrexed maintenance therapy is allowed.

Figure 1. Study schema



5.2 Subject Screening

Subjects will be screened and eligible subjects will be offered treatment. Investigator(s) should keep a subject screening log of subjects considered for the study. The screening log will be kept electroinically in the department clinical trial shared drive for the study monitor to review.

The Investigator(s) will:

- Obtain signed informed consent from the potential subject, or their guardian or legal representative before any study specific procedures are performed.
- Determine subject eligibility.
- Re-screening is allowed.

5.3 Treatments and Visits

Please see **Section 6** for calendar (**Table 1**).

5.4 Discontinuation, Withdrawal and Termination of the Study

5.4.1 Discontinuation:

Subjects may be discontinued from study treatment in the following situations:

1. Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
2. Adverse events that are prolonged unresolved.
3. Pregnancy
4. Severe non-compliance with the study protocol as judged by the investigator
5. Subject incorrectly initiated on study treatment
6. Objective disease progression or subject is no longer receiving clinical benefit
7. Lost to follow up.

5.4.2 Withdrawal:

Subjects may withdraw from study treatment in the following situations:

1. Eligibility criteria not fulfilled
2. Death
3. Withdrawal of consent. If a subject wish to withdraw their consent to both treatment and study assessments, they should be asked if they are willing to continue with survival follow-up (which can be conducted by telephone). If a subject wish to withdraw their consent to further participation in the study entirely, including survival follow-up, this should be clearly documented in the subject notes and in the clinical study database.

5.4.3 Termination:

The study may be terminated if, in the judgment of principal investigator and review committee, trial subjects are placed at undue risk because of clinically significant findings that:

1. Meet individual stopping criteria or are otherwise considered significant
2. Are assessed as causally related to investigational product
3. Are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the electronic database. All reasons for discontinuation of treatment must be documented.

5.5 Duration of Follow Up

Participants will be followed every 4 months after removal from protocol therapy for one year or until death, whichever occurs first. Participants removed from protocol therapy for prolonged unresolved adverse event(s) will be followed until resolution or stabilization of the adverse event, and every 4 months after removal from protocol therapy for one year or until death, whichever occurs first.

6. CALENDAR

Each cycle is defined as 21 days.

Baseline evaluations, including *EGFR* mutation status, are to be confirmed prior to start of protocol therapy. Scans must be done $\leq$4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 5 days prior to initiation of the next cycle of therapy.

Office visits are required once at screening, and day one of each cycle. During the office visit, laboratory tests as well as physical exam will be performed to identify adverse effects. CT or PET scans will be performed every two cycles (within 7 days) for evaluation of disease status. Laboratory tests need to be performed within 7 days during each cycle before giving next dose of treatment.

Study assessments and agents should be administered within ± 7 days of the protocol-specified date, unless otherwise noted.

Table 1. Study calendar

	Screening 4wks	C1 D1 +/- 7 days	C2 D1 +/- 7 days	C3 D1 +/- 7 days	C4 D1 +/- 7 days	C5 D1 +/- 7 days	C6 D1 +/- 7 days	C7 D1 +/- 7 days	C8 D1 +/- 7 days	C9 D1 +/- 7 days	C10 D1 and more	Discontinuation Visit[c]
Bintrafusp alfa[A]		X	X	X	X	X	X	X	X	X	X	
Carboplatin[B]		X	X	X	X							
Pemetrexed[C]		X	X	X	X	X	X	X	X	X	X	
Informed consent	X											
Confirmation of EGFR status	X											
Demographics	X											
Medical history	X											
Pregnancy test	X[b]											
Serum chemistry [g,h]	X[a]	X	X	X	X	X	X	X	X	X	X	
CBC with diff [g,h]	X	X	X	X	X	X	X	X	X	X	X	
Physical exam	X	X	X	X	X	X	X	X	X	X		X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Height	X											
Weight	X	X	X	X	X	X	X	X	X	X	X	X
Performance status	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event evaluation	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medications	X	X	X	X	X	X	X	X	X	X	X	X
Tumor measurements	X[d]			X		X		X		X		X [i]
Tissue collection	X[e]											X (optional)
ctDNA collection	X[f]			X								X
Plasma collection	X[f]			X								X

A: Bintrafusp alfa 2400mg iv on day 1 of every 21-day cycle
B: Carboplatin (AUC 4-5) every three weeks on day 1 of the 21-day cycle for up to 4 cycles. Cisplatin is allowed if the treating physician deems appropriate.
C. Pemetrexed (400-500mg/m^2) every three weeks on day 1 of the 21-day cycle. Folic acid and vitamin B12 will be given according to the standard practice.

a: Alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, SGOT [AST], SGPT [ALT], sodium.
b: Urine or blood pregnancy test (women of childbearing potential). This is only required at screening.
c: Off-study evaluation. Note: follow up visits or other contact are required in order to identify SAEs during the 30 days following the end of study treatment. Survival follow up via telephone is every 4 months for 1 year or until death.
d: Tumor measurement by PET or CT using RECIST 1.1. Tumor measurements are taken before C3D1, and every two cycles in subsequent cycles. Brain MRI is performed at investigator's discretion.
e: Optional biopsy at the time of disease progression.
f: ctDNA and plasma collections are required at baseline, C3 and at the off study evaluation.
g; Labs might be repeated within 5 days prior to the next cycle for patients with deteriorating conditions.
h: Lab tests need to be performed within 7 days during each cycle prior to the next dose.
i: Subjects who discontinue study medication for reasons other than objective disease progression will continue RECIST 1.1 assessments for objective progression.

6.1 Screening Period (up to 4 weeks)

At screening, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects who do not meet these criteria must not be enrolled into the study. Demographic data and other characteristics will be recorded and will include date of birth or age, gender, smoking history, race and/or ethnicity according to local regulations.

Informed consent will be obtained.

The following information and items will be collected at screening.

6.1.1 Archival tumor sample (if available):

All subjects will be asked to provide consent to supply a sample of their archival tumor blocks if a sample taken at the time of diagnosis is available. Any archival biopsy samples taken following previous lines of therapy will also be requested, if available. In each case the previous subject treatment must be clearly indicated for each sample provided. Tumor samples will preferably be in the form of a formalin fixed paraffin embedded block (sample derived from the diagnostic tumor or a metastatic site). If this is not possible, 10-20 slides of freshly prepared unstained 5micron sections from the archival tumor block may be provided.

6.1.2 Blood for ctDNA and plasma biomarkers:

All subjects are required to provide two baseline blood samples, one for ctDNA and the other for plasma biomarkers.

6.1.3 Performance Status

The performance status of all patients will be graded according to the ECOG PS scale.

6.1.4 Clinical Laboratory Tests

Clinical laboratory tests will be performed to assess eligibility for enrolment and will be repeated according to study calendar included in this section. Laboratory tests can be repeated more frequently, if clinically indicated.

6.1.5 Symptoms and Toxicity Assessment

The symptoms and adverse events of all patients will be graded at scheduled intervals according to the NCI CTCAE, v5.0. Patients will be monitored continuously throughout the study for the occurrence of adverse events. Planned medical interventions will not be considered an adverse event.

6.1.6 Radiology Assessments

CT chest (with/without abdomen/pelvis), PET-CT, and CT brain / MRI brain will be obtained according to Study Calendar included in **Table 1**. Response and progression will be evaluated in

the study using the international criteria proposed by the RECIST committee, and will be performed by the radiology collaborator(s) on trial in a blind fashion.

6.1.7 Pregnancy test

Pregnancy test (blood or urine tests are acceptable based on the site's standard clinical practice) for women of childbearing potential only.

6.2 Treatment Period

6.2.1 Bintrafusp alfa

A cycle of treatment is defined as 21 days. On day one of each 21-day cycle, bintrafusp alfa at 2400mg is administered via intra-venous infusion. Safety tests (vitals, weight, laboratory tests) and clinical visits are required every cycle.

6.2.2 Carboplatin

A cycle of treatment is defined as 21 days. On day one of cycles 1-4, carboplatin (AUC4-5) is administered via intra-venous infusion. Safety tests (vitals, weight, laboratory tests) and clinical visits are required every cycle.

Cisplatin is allowed if the treating physician deems appropriate.

6.2.3 Pemetrexed

A cycle of treatment is defined as 21 days. On day one of each 21-day cycle, pemetrexed is administered via intra-venous infusion. Safety tests (vitals, weight, laboratory tests) and clinical visits are required every cycle.

If pemetrexed is permanently interrupted due to toxicities, bintrafusp alfa continuation is allowed. Similarly, if bintrafusp alfa is permanently interrupted, pemetrexed continuation is allowed.

If a subject continues to receive treatment with bintrafusp alfa and/or pemetrexed beyond RECIST 1.1 defined progression they must continue to follow the treatment visit schedule and assessments excluding study specific RECIST 1.1 assessments.

6.3 Follow-up Period

6.3.1 Discontinuation visit

A discontinuation visit will be performed at the time when treatment is permanently stopped. This is an office visit. Other than clinically indicated laboratory tests, ctDNA and plasma biomarker samples will be collected. Optional biopsy will be discussed.

6.3.2 Progression follow-up

Subjects who discontinue study medication for reasons other than objective disease progression will continue RECIST 1.1 assessments for objective progression.

6.3.3 Survival follow-up

Assessments for survival should be made every 4 months following objective disease progression for one year or until death, whichever occurs first. Survival information may be obtained via telephone contact with the subject, the subject's family or caretaker or by contact with the subject's current physician.

7. STUDY DRUGS

7.1 Carboplatin

7.1.1 Introduction

Carboplatin is a platinum compound alkylating agent which covalently binds to DNA; interferes with the function of DNA by producing interstrand DNA cross-links. Carboplatin is apparently not cell-cycle specific. It is commonly used (off-label) for non-small cell lung cancers, including EGFR-mutant NSCLC.

7.1.2 Dose selection

Doses for adults are commonly calculated by the target AUC using the Calvert formula, where Total dose (mg) = Target AUC x (GFR + 25). If estimating GFR instead of a measured GFR, the FDA recommends that clinicians consider capping estimated GFR at a maximum of 125 mL/minute to avoid potential toxicity. Antiemetics may be recommended to prevent nausea and vomiting; carboplatin is associated with a moderate to high emetic potential (dose/AUC dependent). For Non-small cell lung cancer (off-label use), target AUC 5 every 3 weeks (in combination with pemetrexed) was widely accepted and utilized[18].

7.1.3 Adverse events

Percentages reported with single-agent therapy.
>10%:

Central nervous system: Pain (23%)

Endocrine & metabolic: Hyponatremia (29% to 47%), hypomagnesemia (29% to 43%), hypocalcemia (22% to 31%), hypokalemia (20% to 28%)

Gastrointestinal: Vomiting (65% to 81%), abdominal pain (17%), nausea (without vomiting: 10% to 15%)

Hematologic & oncologic: Bone marrow depression (dose related and dose limiting; nadir at ~21 days with single-agent therapy), anemia (71% to 90%; grades 3/4: 21%), leukopenia (85%; grades 3/4: 15% to 26%), neutropenia (67%; grades 3/4: 16% to 21%), thrombocytopenia (62%; grades 3/4: 25% to 35%)

Hepatic: Increased serum alkaline phosphatase (24% to 37%), increased serum AST (15% to 19%)

Hypersensitivity: Hypersensitivity (2% to 16%)

Neuromuscular & skeletal: Weakness (11%)

Renal: Decreased creatinine clearance (27%), increased blood urea nitrogen (14% to 22%)

1% to 10%:

Central nervous system: Peripheral neuropathy (4% to 6%), neurotoxicity (5%)

Dermatologic: Alopecia (2% to 3%)

Gastrointestinal: Constipation (6%), diarrhea (6%), dysgeusia (1%), mucositis (≤1%), stomatitis (≤1%)
Hematologic & oncologic: Bleeding complications (5%), hemorrhage (5%)
Hepatic: Increased serum bilirubin (5%)
Infection: Infection (5%)
Ophthalmic: Visual disturbance (1%)
Otic: Ototoxicity (1%)
Renal: Increased serum creatinine (6% to 10%)

<1%, postmarketing, and/or case reports (Limited to important or life-threatening): Anaphylaxis, anorexia, bronchospasm, cardiac failure, cerebrovascular accident, dehydration, embolism, erythema, febrile neutropenia, hemolytic anemia (acute), hemolytic-uremic syndrome, hypertension, hypotension, injection site reaction (pain, redness, swelling), limb ischemia (acute), malaise, metastases, pruritus, skin rash, tissue necrosis (associated with extravasation), urticaria, vision loss.

7.1.4 Drug ordering and accountability

Carboplatin will be prescribed as the standard of care (SoC). The investigator is responsible for obtaining the drug when prior-authorization is needed

7.2 Pemetrexed

7.2.1 Introduction

Pemetrexed is an antifolate; it disrupts folate-dependent metabolic processes essential for cell replication. Pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltransferase (GARFT), and aminoimidazole carboxamide ribonucleotide formyltransferase (AICARFT), the enzymes involved in folate metabolism and DNA synthesis, resulting in inhibition of purine and thymidine nucleotide and protein synthesis.

7.2.2 Dose selection

For the initial treatment of advanced or metastatic NSCLC: 500 mg/m^2 on day 1 of each 21-day cycle (in combination with platinum) for 4 cycles or until disease progression or unacceptable toxicity.

If there is no progression after completion of 4 cycles of carboplatin-pemetrexed, maintenance treatment at 500 mg/m^2 on day 1 of each 21-day cycle is allowed, until disease progression or unacceptable toxicity.
Due to the mechanism of action, vitamin supplements during the pemetrexed treatment is required: (1) folic acid 400 to 1,000 mcg orally once daily (starting prior or at the same time with treatment initiation; continue daily during treatment and for 21 days after last pemetrexed dose) and (2) vitamin B_{12} 1,000 mcg intra-muscular injection prior or at the same time with treatment initiation and then every 3 cycles.

7.2.3 Adverse events

>10%:

Central nervous system: Fatigue (18% to 34%)
Dermatologic: Desquamation (≤14%), skin rash (≤14%)
Gastrointestinal: Nausea (12% to 31%), anorexia (19% to 22%), vomiting (6% to 16%), stomatitis (≤15%), diarrhea (5% to 13%)
Hematologic & oncologic: Anemia (15% to 19%; grades 3/4: 3% to 5%), neutropenia (6% to 11%; grades 3/4: 3% to 5%)
Respiratory: Pharyngitis (≤15%)

1% to 10%:

Cardiovascular: Edema (5%)
Central nervous system: Neuropathy (sensory: 9%; motor: ≤5%)
Dermatologic: Pruritus (7%), alopecia (6%), erythema multiforme (≤5%)
Gastrointestinal: Constipation (6%), abdominal pain (1% to <5%)
Hematologic & oncologic: Thrombocytopenia (8%; grades 3/4: 2%), febrile neutropenia (<5%)
Hepatic: Increased serum alanine aminotransferase (8% to 10%), increased serum aspartate aminotransferase (7% to 8%)
Hypersensitivity: Hypersensitivity reaction (<5%)
Infection: Infection (1% to <5%), sepsis (1%)
Ophthalmic: Conjunctivitis (≤5%), increased lacrimation (1% to <5%)
Miscellaneous: Fever (8%)

<1%, postmarketing, and/or case reports: Bullous rash, cardiac arrhythmia, colitis, depression, esophagitis, gastrointestinal obstruction, hemolytic anemia, interstitial pneumonitis, pain, pancreatitis, pulmonary embolism, radiation recall phenomenon, renal failure syndrome, Stevens-Johnson syndrome, supraventricular cardiac arrhythmia, syncope, toxic epidermal necrolysis, ventricular tachycardia

7.2.4 Drug ordering and accountability

Pemetrexed will be prescribed as the standard of care (SoC). The investigator is responsible for obtaining the drug when prior-authorization is needed

7.3 Bintrafusp alfa (M7824)

7.3.1 Introduction

Bintrafusp alfa (MSB0011359C, M7824) is a first-in-class bifunctional fusion protein composed of the extracellular domain of the human transforming growth factor β receptor II (TGF-βRII or TGF-β "trap") fused via a flexible linker to the C-terminus of each heavy chain of an IgG1 antibody blocking programmed death ligand 1 (anti–PD-L1), designed to target 2 of the key mechanisms of immunosuppression in the tumor microenvironment. Bintrafusp alfa is the proposed international nonproprietary name for M7824.

Bintrafusp alfa is designed to target tumors via colocalized, simultaneous blocking of two nonredundant immunosuppressive pathways—the TGF-β and PD-L1 pathways, which might potentially result in improved clinical benefit.

Bintrafusp alfa was shown to have full biological activity in vitro including the ability to block PD-L1and neutralize TGFβ simultaneously. In experiments investigating the combination of bintrafusp alfa with standard of care therapies in mouse tumor models, bintrafusp alfa separately enhanced the antitumor effects of standard of care therapies including targeted therapies (in combination with receptor tyrosine kinase inhibitor pazopanib or anti-VEGF antibody), immuno-oncology therapies (anti-CTLA4), of radiation therapy, and in combination with chemotherapy such as 5-fluorouracil and oxaliplatin (FOLFOX), gemcitabine, cisplatin, and doxorubicin.

7.3.2 Dose selection

For all toxicity studies, a no observed adverse effect level (NOAEL) of 140 mg/kg (maximum feasible dose) was established. The only notable clinical effect observed in all studies was a decrease in red blood cell (RBC) counts and related parameters (hemoglobin [Hgb] and hematocrit) from all treated groups; evaluation of peripheral blood smears did not demonstrate evidence of an immune-mediated hemolytic process.

Bintrafusp alfa is being developed as an immuno-oncology agent for treatment in a number of tumor types, including non-small cell lung cancer (NSCLC). The results from 2 Phase I studies (global study EMR200647-001 and MS200647-0008 in Asia) are summarized in the IB. Both studies have a dose escalation phase (following a standard “3 + 3” design) followed by a parallel-group expansion phase in selected solid tumor indications. Maximum tolerated dose (MTD) was not reached in either study at doses tested up to 30 mg/kg q2w. Each study had 1 dose-limiting toxicity (DLT) in 1 participant at the 20 mg/kg dose level. With no DLTs at other dose levels up to 30 mg/kg, M7824 at 30 mg/kg is considered tolerable.

The dose for the expansion cohorts of both studies has been selected as 1200 mg/infusion (flat dose) iv once every 2 weeks for all cohorts except second-line (2L) NSCLC cohort and the 2L HCC dose ascending cohorts. The flat dose approach and selection of the recommended Phase II dose (RP2D; 1200 mg q2w or 2400 mg q3w when administered concomitantly with chemotherapies using q3w regimens) for bintrafusp alfa is supported by population pharmacokinetics (popPK) and exposure-response modeling and simulation.

7.3.3 Adverse events

The safety summary for this Investigator’s Brochure includes data (as of 24 August 2018) from a total of 689 participants, including:

Data from 36 participants enrolled in the dose escalation part of EMR200647-001;

Data from 23 participants enrolled in the dose escalation part of MS200647-0008 (14 participants) and in the ascending-dose 2L HCC expansion cohort (9 participants);

Pooled data from a total of 630 participants enrolled in the dose expansion cohorts of EMR200647-001 and MS200647-0008, including 584 participants who received flat dose of M7824 at 1200 mg q2w, 40 participants with 2L NSCLC who received flat dose of M7824 at 500 mg q2w and 6 participants with 2L HCC who received M7824 at 3 mg/kg q2w.

Of the 630 participants enrolled in the expansion cohorts of EMR200647-001 and MS200647-0008, 615 (97.6%) participants experienced TEAE, treatment-related Grade ≥ 3 TEAEs occurred in 142 (22.5%) participants, treatment-related SAEs were reported in 93 (14.8%) participants, and 50 (7.9%) participants had treatment discontinuations due to treatment-related TEAEs. Death due to treatment-related TEAEs, as assessed by the Investigator, occurred in 7 participants (1.1%) from 8 to 182 days following the last dose of M7824. The emerging safety profile of M7824 from EMR200647-001 and MS200647-0008 including 689 patients across tumor types investigated is manageable and consistent with other therapies targeting either PD-(L)1 or TGFβ pathways.

Treatment-emergent AEs of special interest (AESI) for bintrafusp alfa are: infusion-related reactions (IRRs), immune-related adverse events (irAEs), skin lesions possibly due to TGFβ inhibition and treatment-related anemia. Since 23 July 2017, IRRs (including hypersensitivity), irAEs /autoimmune disorders, and skin lesions with hyperkeratosis, keratoacanthoma, cutaneous squamous cell carcinoma possibly due to TGFβ inhibition are considered to be important identified risks with bintrafusp alfa. Anemia, alterations in wound healing or repair of tissue damage and embryofetal toxicity remain important potential risks. In addition, mucosal bleeding events are a potential risk for bintrafusp alfa. Respective risk mitigation measures have been implemented in the protocols.

7.3.4 Clinical efficacy

Bintrafusp alfa has shown preliminary efficacy in NSCLC. The expansion cohort of the phase 1 study (NCT02517398) includes 80 patients with advanced NSCLC who had prior platinum doublet therapy but have not received previous immunotherapy. A total of 80 patients were randomized to receive bintrafusp alfa 500 or 1200 mg (n = 40 each). Median follow-up was 51.9 weeks (IQR, 19.6-74.0). The ORR in all patients was 21.3% (17 of 80). The ORR was 17.5% (seven of 40) and 25.0% (10 of 40) for the 500 mg dose and the 1200 mg dose (recommended phase 2 dose), respectively. At the 1200 mg dose, patients with PD-L1-positive and PD-L1-high (≥80% expression on tumor cells) had ORRs of 36.0% (10 of 27) and 85.7% (six of seven), respectively[17]. With the initial observation of efficacy, ongoing study (NCT03840915) is testing the safety and efficacy of M7824 in combination with platinum-doublet in NSCLC.

7.3.5 Drug ordering and accountability

EMD serono will supply bintrafusp alfa for this trial.

The investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity).

1) If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product.

2) If the study drug(s) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures.

7.3.6 Storage and dispensing

The investigator should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as per product information and the Investigator Brochure and per local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The relevant Drug Product (DP) presentation is a liquid formulation in Type I glass vials, closed with a rubber septum and sealed with an aluminum crimp seal closure. The investigational product, Bintrafusp alfa is available as a sterile, clear, colorless and non-pyrogenic solution for intravenous infusion.

Each single-use vial contains 600 mg of Bintrafusp alfa, formulated as 10 mg/mL of active, 6% (w/v) Trehalose, 40 mM NaCl, 5 mM Methionine, 0.05% (w/v) Tween 20, 10 mM L-Histidine at pH 5.5. This product requires further dilution prior to IV infusion.

EMD Serono will package and distribute the IMP to sites via their distribution vendor - Fisher Clinical Services. The IMP will be shipped in transport cool containers (2oC to 8oC) that are monitored with temperature control devices.

Bintrafusp alfa drug product must be stored in the original packaging (protected from light) at refrigerated conditions (2- 8°C, 36-46°F) until use, with a temperature log maintained daily. The storage condition is based on data from ongoing long-term stability studies with Bintrafusp alfa.

Bintrafusp alfa drug product stored at room temperature (15-25°C, 59-77°F) or higher temperatures for extended periods of time might be subject to degradation.

Bintrafusp alfa drug product must not be frozen.

7.3.7 Destruction

Sponsor/Investigator drug destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed.

- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.

8. DOSING MODIFICATIONS

8.1 Toxicity management and dose modification for bintrafusp alfa

a. Treatment modification for symptoms of infusion-related reactions (Table 2)
b. Management of immune-mediated adverse reactions (Table 3)
c. Management of potential TGF-β mediated skin adverse events (Table 4A)
d. Other potential risks (Table 4B – 4D)
    i. Management of treatment-related anemia
    ii. Management of mucosal bleeding and tumor related bleedings
    iii. Guidance on wound healing alterations

Table 2. Treatment Modification of bintrafusp alfa for Symptoms of Infusion-Related Reactions including Immediate Hypersensitivity

NCI-CTCAE Grade	Treatment Modification for bintrafusp alfa
Grade 1 - mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	• Stop the infusion of the study intervention caused IRR • Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator. • If symptoms resolve quickly or decrease to Grade 1, resume infusion at 50% of original rate with close monitoring of any worsening signs and symptoms, otherwise dosing held until resolution of symptoms with mandated premedication for the next visit schedule. • If symptoms worsen to Grade 3 or 4, follow treatment modification guidelines accordingly.
Grade 3 or Grade 4 – severe or life-threatening ○ Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. ○ Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop bintrafusp alfa infusion immediately and disconnect infusion tubing from the participant with additional appropriate medical measures. • Monitor closely until deemed medically stable by the attending investigator. • Hospitalization may be indicated.

IRR=infusion-related reactions, IV=intravenous, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, NSAIDs=nonsteroidal anti-inflammatory drugs.

Once the bintrafusp alfa infusion is interrupted or rate reduced to 50% of previous infusion rate, it must remain decreased for all subsequent infusions. For Grade 3 or 4 IRRs, bintrafusp alfa discontinuation is mandated.

For all types and grades of infusion reactions, details about drug physical constitution, method of preparation, and infusion must be recorded.

Additional recommendation: critical instructions include the requirement that treatment must be permanently discontinued for the following Grade 4 irAE toxicities: rash/inflammatory dermatitis, nephritis, autoimmune hemolytic anemia, hemolytic uremic syndrome, aplastic anemia, immune thrombocytopenia, acquired TTP, and in certain circumstances, lymphopenia.

Management of immune-mediated adverse reactions (Table 3)

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, colitis and hepatitis. Permanent discontinuation is also required for Grade ≥ 3 pneumonitis and Grade ≥ 3 nervous system irAEs.

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 ≤ 1, restarting treatment may be considered.

Table 4A 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.

OTHER POTENTIAL RISKS

Table 4B Management of Treatment-Related Anemia

• Hematology assessment must be performed at baseline, prior to each bintrafusp alfa dose, at the end of treatment visit and at 28 (±5 days) days post-treatment safety follow-up. • Participants must enter the study with Hgb values at least 9g/dl • All relevant hematological testing for treatment-related anemias should be done prior to a blood transfusion, if clinically feasible
Diagnostic Work-up

• Baseline Anemia Evaluation
  ○ CBC with emphasis on red cell indices
• If indicated and at clinical discretion, the following should be considered:
  ○ Iron studies
  ○ Serum Folate and Vit B12 values
  ○ Coagulation factors
  ○ Fecal occult blood
  ○ Urinalysis
  ○ Hormone panel: TSH, Erythropoietin
  ○ Peripheral blood smear

Further recommendation

• Suspected Hemolysis
  ○ bilirubin, LDH, Coombs test, haptoglobin
• Suspected bleeding
• :
  ○ Consider imaging/interventional radiology consultation as indicated
  ○ Consider imaging and/or endoscopy as clinically indicated
• Suspected aplastic anemia:
  ○ Hematology consultation
  ○ Consider bone marrow aspiration/morphologic evaluation

Additional consideration: Treatment-related Anemia is an important identified risk for bintrafusp alfa. In general, blood transfusions and erythroid growth factors are permitted as clinically indicated.

Abbreviation: CBC: complete blood count, TSH: thyroid stimulating hormone, LDH: lactate dehydrogenase

Table 4C 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:
  ○ Epistaxis
  ○ Hemoptysis
  ○ Gingival bleeding
  ○ 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.

Table 4D

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

8.2 Toxicity management and dose modifications for carboplatin/pemetrexed

The toxicity management for SoC carboplatin and pemetrexed will be by the investigator's discretion. Dose adjustment following drug inserts is recommended.

See carboplatin FDA insert

See pemetrexed FDA insert

9. ADVERSE EVENTS AND REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

9.1 Definitions

9.1.1 Adverse event

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug. The term AE is used to include both serious and non-serious adverse events.

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

The term "disease progression" should not be reported as an adverse event term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the patient and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the patient through the completion of final study procedures.
- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present before the AE reporting period

- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies).

The following are NOT considered AEs:

- Pre-existing condition: A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- Pre-planned or elective hospitalization: A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- Diagnostic Testing and Procedures: Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.
- Asymptomatic Treatment Related Lymphocytosis: This event should also not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.
- Any adverse event clearly attributable to disease progression

9.1.2 Severity criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 5 (CTCAE v5) will be used for grading the severity (intensity) of AEs. The CTCAE v5 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a patient experience any AE not listed in the CTCAE v5, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the patient's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the patient, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the patient's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the patient to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in patient death

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events, assigning the attribution and assessing the severity of the AE, the causal relationship between any events and the clinical study procedure, activities or device. Additionally, the Investigator is responsible for providing appropriate treatment for the

event and for adequately following the event until resolution for all adverse events for subjects enrolled.

AEs will be recorded as per the guidelines for phase II on the table below:

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

9.1.3 Causality (Attribution)

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to the sponsor and EMD Serono in accordance with the agreed process

Not Related: Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.

Unlikely: The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.

Possibly Related: There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes. These AEs will be reported as related if the investigator believes it is more likely than not that the investigational product caused the AE.

Related: The AE is clearly related to use of the investigational product.

8.1.5 Unexpected adverse events

An "unexpected" AE is an AE that is not listed in the Investigator's Brochure/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be "unexpected" (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the Investigator's Brochure/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

9.2 Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

9.2.1 Serious Adverse Events (SAE) Reporting requirements for MD Anderson Sponsor Single Site IND protocols.

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

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Adverse Events for Drugs and Devices".
- Serious adverse events will be captured from the time of the first protocol-specific

intervention, until 90 days after the last dose of drug, unless the participant withdraws consent.

- Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- All SAEs, expected or unexpected/ initial or follow up, must be reported to the IND Office **within 5 working days of knowledge of the event** regardless of the attribution**.**
- Death or life-threatening events that are unexpected, possibly, probably or definitely related to drug must be reported (initial or follow up) to the IND Office **within 24 hours of knowledge of the event**
- Additionally, any serious adverse events that occur after the 90 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.
- The electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MD Anderson IRB.
- All events reported to the supporting company must also be reported to the IND Office

- **Reporting to FDA:**
- Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.

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

- SAEs will also be forwarded to EMD Serono as required within the applicable contract excuted between EMD Serono and Sponsor-investigator. The SAE will be reported to EMD Serono by fax: +49-6151-72 6914 and email: ICSR_CT_GPS@merckgroup.com.

9.2.2 Assessment of adverse events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation time points during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded. Each recorded adverse event or serious adverse event will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

9.2.3 Adverse Event Reporting Period

All AEs whether serious or non-serious, will be captured from the time signed and dated ICF is

obtained until 30 days following the last dose of treatment or until the initiation of alternative anticancer therapy.

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported.

All Grade 3 – 5 adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").
All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself.

9.2.4 Other events requiring reporting

Overdose

An overdose is defined as a subject receiving a dose of bintrafusp alfa in excess of that specified in this protocol. If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. The investigator will use clinical judgment to treat any overdose.

Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.
A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 65 days after the last dose of bintrafusp alfa. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 125 days after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.
Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of bintrafusp alfa (up to 65 days for a female and 125 days for a male) must be reported. Any occurrence of pregnancy must be reported per SAE reporting timelines. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing will need to be reported per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a

serious adverse event.

Pregnancy will be submitted to the IND Office via eSAE application as "Other Important Medical Event".

Paternal Exposure
Pregnancy of the subject's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.
To capture information about a pregnancy from the partner of a male subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 6 months after dosing ends should be followed up and documented.

Other Malignancies
All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

10. CORRELATIVE STUDIES

10.1 Tissue and Blood Repository

As part of the study, a tissue and blood sample repository will be created. The objective of this tissue sample repository will be to provide material for the correlative studies proposed to evaluate the endpoints proposed, and for future evaluations of other relevant biomarkers that may be associated with clinical outcomes. A written informed consent will be obtained from patients enrolled in this study so that these samples may be analyzed in the future for biomarkers not described in this protocol.

10.2 Tissue

Archived tissue for diagnosis will be requested. Next-generation sequencing (NGS) will be applied to the archived tissue to detect co-mutations.

If biopsy is performed at the time of disease progression, tissue will be requested. NGS will be applied to the archived tissue to detect resistance mechanisms.

No mandatory biopsy at the time of progression.

10.3 ctDNA

Plasma ctDNA will be collected at screening or C1D1 (pre-treatment), C3D1 (On-treatment), and

at the time of disease progression (post-treatment). NGS profiling will be performed to identify potential mechanisms of resistance and to aid selection of next line of treatment.

20ml of blood will be collected at each time point.

10.4 Plasma for Cytokine and Immune-modulator Analysis

Plasma will be collected at screening or C1D1 (pre-treatment), C3D1 (on-treatment), and at the time of disease progression (post-treatment). Plasma cytokine profiling and immune-profiling will be performed to identify potential correlative markers for response and resistance.

20ml of blood will be collected at each time point.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect

For the purposes of this study, participants should be re-evaluated for response every two cycles (6 weeks).

Objective response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[19]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Target Disease 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 target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered 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.

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.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. 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 in 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. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. 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 be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be 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.

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 Fwill 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.

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 data 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 from 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.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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 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 progressions).

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

11.1.4.2 Evaluation of Non-Target Lesions

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 patient 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).

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 Evaluation of Objective Response and Best Overall Response

Objective response will be assessed by RECIST 1.1. 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 patient's best response

assignment will depend on the achievement of both measurement and confirmation criteria.

Table 8. Definition of Response for Participants with Measurable Disease

Target Lesions	Non-Target Lesions	New Lesions	Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

* 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.

11.1.5 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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.

11.1.6 Progression-Free Survival

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from starting of treatment to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Overall Survival: Overall Survival (OS) is defined as the time from treatment to death due to any cause, or censored at date last known alive.

Time to Progression: Time to Progression (TTP) is defined as the time from treatment to progression, or censored at date of last disease evaluation for those without progression reported.

11.2 Safety

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs (pulse and BP) and ECG/ECHO. These will be collected for all subjects.

11.2.1 Adverse events

AEs will be listed individually by subject. Any AE occurring before the trial treatment initiated will be included in the data listings but will not be included in the summary tables of AEs.

Any AE occurring within 90 days of discontinuation of investigational product will be included in the AE summaries. Any events in this period that occur after a subject has received further therapy for cancer (following discontinuation of M7824) will be flagged in the data listings.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Adverse events and reporting.

12.1 Data Reporting

12.1.1 Method

A customized web-based data capture system, Data Management Initiative (DMI), will be used at the study center. The CORe system will be used to register subjects. Concomitant medications will be captured in the subject's medical record only.

12.1.2 Responsibility for Data Submission

Participant institutions are responsible for submitting data and/or data forms to the study center on the study quarterly.

12.1.3 Patient Data Confidentiality

All laboratory and clinical data gathered in this protocol will be stored in a password protected database. All patient information will be handled using synonymous identifiers. Linkage to patient identity is only possible after accessing a pass-word protected database. Access to the database is only available to individuals directly involved in the study. Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design

This is an open-label, single arm phase II clinical trial to assess the efficacy of bintrafusp alfa with platinum-pemetrexed in patients with metastatic NSCLC who have progressed on prior EGFR TKI. The treatment consists of 4 cycles (every 21 days) of platinum + pemetrexed + bintrafusp alfa, followed by pemetrexed+ bintrafusp alfa maintenance at 2400mg every 3 weeks for patients who have not progressed on C5D1.

13.2 Sample Size Justification

The primary endpoints of the study are: the best objective response rate within 6 months and progression-free survival at 18 weeks, after initiation of treatment.

The study will be considered positive if at least one the primary endpoints were met.

The ORR under the null hypothesis is assumed to be 30%. After treatment start, we expect that the best ORR increases to 50% within 6 months. The median PFS for EGFR-mutant NSCLC patients who receive chemotherapy is around 4.2-4.4 months. Therefore, 18-week PFS rate is estimated to be 50%. We expect an increase in 18-week PFS rate to 70%.

We simultaneously monitor two co-primary efficacy endpoints using the Bayesian optimal phase 2 (BOP2) design (Zhou, Lee and Yuan, 2017). Specifically, let n denote the interim sample size and N denote the maximum sample size. Let Y_1 (ORR) and Y_2 (18-week PFS) denote the two binary co-primary endpoints, with $Y_1 = 1$ and $Y_2 = 1$ indicating that patients experienced favorable treatment responses in the two respective endpoints. We assume that the joint distribution of (Y_1, Y_2) follows a multinomial distribution with 4 elementary outcomes: (Y_1, Y_2) = (1, 1), (1, 0), (0, 1) and (0, 0). Let $\mathbf{p} = (P_{11}, P_{10}, P_{01}, P_{00})$ denote the probabilities of observing the four outcomes, and let $p_1 = Pr(Y_1 = 1)$, $p_2 = Pr(Y_2 = 1)$, and $p_3 = Pr(Y_1 = 1, Y_2 = 1)$.

The treatment is deemed as unacceptable if $p_1 \leq 0.3$ and $p_2 \leq 0.5$, i.e., the treatment is not promising in both co-primary endpoints. Thus, we will stop enrolling patients and claim the treatment is not promising if

$$Pr(p_1 > 0.3|data) < \lambda(\frac{n}{N})^{\alpha},$$

AND

$$Pr(p_2 > 0.5|data) < \lambda\left(\frac{n}{N}\right)^{\alpha},$$

where λ=0.95 and α=0.86 are design parameters optimized to maximize the probability of correctly concluding an efficacious treatment as acceptable when $p_1 = 0.5$, $p_2 = 0.7$ and $p_3 = 0.4$, while controlling that the probability of incorrectly claiming an inefficacious treatment, with $p_1 = 0.3$, $p_2 = 0.5$ and $p_3 = 0.2$, as acceptable is less than 10%. This optimization is performed assuming a vague Dirichlet prior $Dir(0.2,0.1,0.3,0.4)$ for $\mathbf{p}$. The prior is chosen such that it corresponds to a prior effective sample size of 1 patient, and the prior estimates of p_1 and p_2 match the cutoff values specified above. The above decision rule leads to the following optimal stopping boundaries:

Table 2.1: Optimized stopping boundaries

# patients treated	Stop if # ORR <=	AND # PFS <=
15	4	7
20	6	10
25	8	13
30	11	17
35	15	22

Based on Table 1, we perform the interim analysis when the number of enrolled patients reaches 15, 20, 25, 30. When the total number of patients reaches the maximum sample size of 35, we conclude that the treatment is acceptable if the number of patients with best objective response is greater than 15, or the number of progression-free patients by 18 weeks is greater than 22; otherwise we conclude that the treatment is unacceptable. The go/no-go criteria in Table 1 are non-binding. To account for a 12.5% inevaluable rate, we will enroll a total of 40 patients.

Below are the operating characteristics of the design based on 10000 simulations using the BOP2 web application V1.3.7.0, which is available at http://www.trialdesign.org.

Table 2.2: Operating characteristics

Pr(ORR)	Pr(PFS)	Pr(ORR & PFS)	Early stopping (%)	Claim promising (%)	Sample size
0.3	0.5	0.20	73.18	7.00	24.9
0.5	0.7	0.40	2.60	91.36	34.7
0.5	0.6	0.35	7.61	80.02	34.1
0.4	0.7	0.32	6.31	82.08	34.3
0.3	0.7	0.25	9.91	76.65	33.8
0.5	0.5	0.30	12.23	74.54	33.5

13.3 Definition of Analysis Sets

13.3.1 Per protocol analysis set:

The per protocol analysis set will consist of all patients who received at least one dose of bintrafusp alfa with platinum-pemetrexed and for whom post dose data are available. This set will be used for efficacy and safety analyses.

13.3.2 Safety analysis set:

The safety analysis set will consist of all patients who received at least one dose of bintrafusp alfa with platinum-pemetrexed and for whom post dose data are available. Safety data will be summarized using the safety analysis set, according to the treatment received.

13.3.3 Evaluable efficacy analysis set:

The evaluable analysis set will consist of patients who received bintrafusp alfa with platinum-pemetrexed treatment, who had measurable disease, appropriate restaging scans for response evaluation and adequate follow-up. This set will be used for all efficacy analyses.

13.4 Analysis Plan

Summary statistics will be provided for continuous variables and frequency tables and percentages will be used to summarize categorical variables. The distribution of time-to-event endpoints will be estimated using the method of Kaplan and Meier. Best objective response rate within 6 months and progression-free survival rate at 18 weeks will be provided together with 95% confidence intervals. Adverse event data will be summarized by type, severity grade, and attribution. Cox proportional hazards regression analysis or logistic regression will be used to correlate the time-to-event endpoints such as PFS or OS and binary endpoints such as objective response with medical demographical variables and/or biomarkers or changes in biomarkers.

The Investigator is responsible for completing an efficacy/safety summary report and submitting to the IND Office Medical Affairs and Safety Group, for review and approval.

The first analysis will be done after the first 15 evaluable subjects complete 2 cycles of therapy and then every 5 evaluable subjects after completing 2 cycles. On every submission, survival data of previously reported patients will need to be updated.
A copy of the summary report should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome

data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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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.