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Randomized Phase II Study of Standard Chemotherapy with Docetaxel with or without Bintrafusp Alfa in Patients with Advanced NSCLC after Progressing on a Combination of Anti-PD-1/PD-L1 Agents and Chemotherapy

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Mayo Clinic Cancer Center

Randomized Phase II Study of Standard Chemotherapy with Docetaxel with or without Bintrafusp Alfa in Patients with Advanced NSCLC after Progressing on a Combination of Anti-PD-1/PD-L1 Agents and Chemotherapy

Sponsor/Principal Investigator: Konstantinos Leventakos MD PhD
Mayo Clinic
200 First Street SW
Rochester MN 55905
507/284-2511

Co-Investigators: Dipesh Uprety MD√
Alex A Adjei MD PhD
Anja C Roden MD
Yanyan Lou MD PhD
Panayiotis (Panos) S Savvides MD PhD

Statistician: Nathan R Foster MS√

√Study contributor(s) not responsible for patient care

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Drug Availability:
Commercial Agents: docetaxel
Drug Company Supplied: bintrafusp alfa (M7824) (IND 147341)

Site Investigators & Participating sites:

Panayiotis (Panos) S Savvides MD PhD
Mayo Clinic
13400 East Shea Boulevard
Scottsdale, AZ 85259
480/301-8000

Yanyan Lou MD PhD
Mayo Clinic
4500 San Pablo Road
Jacksonville, FL 32224
904/953-2000

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Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/ interruptions/ adjustments, dose modifications, adverse events, forms completion and submission	Sharon F Solinger Quality Assurance Specialist/Data Manager Phone: 507/266-1714 E-mail: solinger.sharon@mayo.edu
Clinical coordinators (lead site first)	Amanda M Nielsen Phone: 507/538-0152 Email: nielsen.amanda@mayo.edu Sarah A Thiele or Omar M Sh Ahmed Phone: 904/953-3559 or 904/953-3974 Email: thiele.sarah@mayo.edu or shahmed.omar@mayo.edu Yojan S Shah Phone: 480/574-1077 Email: shah.yojan@mayo.edu
Forms completion and submission (lead site first)	Stephanie S Abel Phone: 507/538-3476 E-mail: abel.stephanie@mayo.edu Xxxxxxxxx Phone: E-mail: Xxxxxxxxx Phone: E-mail:
Protocol document, consent form, regulatory issues	Lynn M Flickinger MA Senior Research Protocol Specialist Phone: 507/538-7034 Email: flickinger.lynn@mayo.edu Mitchell (Mitch) G Perrizo Research Protocol Specialist Phone: 507/284-9104 Email: perrizo.mitchell@mayo.edu
Laboratory Contact	Michael A Strausbauch Laboratory Contact for Correlative Studies Phone: 507-284-8177 Email: strausbauch@mayo.edu
Pathology Coordinator	Amanda R Sand Pathology Coordinator Phone: 507/284-3559 Email: sand.amanda@mayo.edu
Serious Adverse Event Reporting	Patricia G McNamara SAE Coordinator Phone: 507/266-3028 E-mail: RSTP2CSAES@mayo.edu

*No waivers of eligibility allowed

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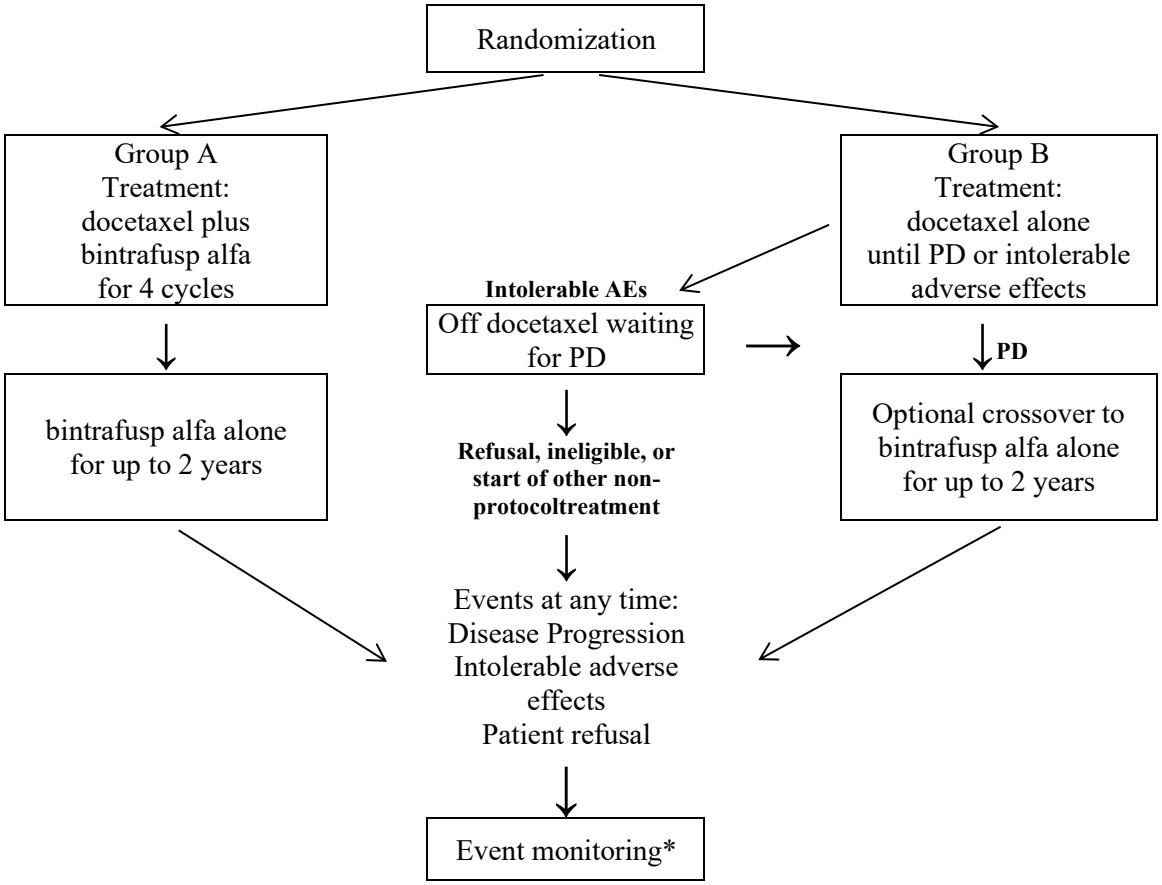
Schema



***NOTE: Survival follow-up will cease for all patients as of MCCC Amendment 3.**

Cycle = 21 days

Generic name: bintrafusp alfa (M7824) Brand name(s): n/a Mayo Abbreviation: n/a Availability: Provided by EMD Serono Inc	Generic name: Docetaxel Brand name(s): Taxotere® Mayo Abbreviation: *TATER* Availability: Commercial

SD= stable disease, PR= partial response, CR= complete response, PD= progressive disease, n/a= not available/not applicable

1.0 Background

Approximately three-fourths of patients with non-small cell lung cancer (NSCLC) have advanced disease at diagnosis (Molina JR, 2008). The majority of these patients lack actionable driver mutation. For these patients, pembrolizumab in combination with a platinum-doublet is the preferred treatment option irrespective of PD-L1 expression. This usage is based on data from two landmark phase-3 studies, namely KEYNOTE-189 and KEYNOTE-407 which showed significantly longer overall survival with the addition of pembrolizumab to platinum doublet chemotherapy than chemotherapy alone (Gandhi L, 2018 May 31) (Paz-Ares L, 2018 Nov 22). For those patients with PD-L1 ≥50%, pembrolizumab monotherapy is also a preferred option (Reck M, 2016 Nov 10). Thus, standard front-line treatment of NSCLC with advanced disease without an actionable driver mutation will either include pembrolizumab as monotherapy or in combination with a platinum-doublet. Unfortunately, most of these patients will ultimately develop disease progression. In this situation, therapeutic options outside of a clinical trial are limited to second-line docetaxel.

Autocrine and paracrine secretion of transforming growth factor β (TGFβ) in the tumor microenvironment is associated with epithelial-mesenchymal transition, a known resistance mechanism to immunotherapy in lung cancers (Xiao D, 2010). This mesenchymalization is associated with disease metastasis and progression. TGFβ isoforms are also involved in stromal modification, angiogenesis, and can directly inhibit T-cell division and NK cell function. TGFβ overexpression in the serum is associated with inferior outcomes in several malignancies.

Upregulation of TGFβ signaling-associated genes in melanoma has been associated with anti-PD1 antibody resistance in melanoma (Seidel JA, 2018); thus blocking TGFβ signaling may overcome resistance to anti-PD1/PD-L1 inhibitors.

1.1 Bintrafusp alfa (M7824)

1.11 Description

Bintrafusp alfa (MSB0011359C) is a first-in-class, intravenously administered bifunctional fusion protein that combines the soluble extracellular domain of the human transforming growth factor β (TGFβ) receptor II (RII) as a TGFβ neutralizing ‘trap’ and an anti-programmed death ligand 1 (PD-L1) antibody, into a single molecule. Specifically, the protein is a heterotetramer, consisting of the 2 immunoglobulin light chains of anti-PD-L1, and 2 heavy chains comprising the heavy chain of anti-PD-L1 genetically fused via a flexible glycine-serine linker to the extracellular domain of the human TGFβRII. The use of a bifunctional molecule targeting PD-L1 and TGFβ enables block tumor cell-intrinsic and tumor cell-extrinsic immunosuppressive pathways, respectively. Bintrafusp alfa-mediated simultaneous inhibition of the TGFβ and PD1/PD-L1 pathway may overcome treatment failure to anti-PD1/PD-L1 agents.

1.12 Non-Clinical experience

In vitro, bintrafusp alfa bound to ectopic PD-L1 overexpressed on the human embryonic kidney (HEK) 293 cell line at a similar concentration to the anti-PD-L1 agent [half-maximal effective concentration (EC_{50}) = 48 (average of three lots) and 34 ng/ml, or 0.27 and 0.24 nM, respectively]. The TGFβ trap bound to both plate-bound TGF-β1 and TGF-β3 (EC_{50} = 215.3 and 651.4 ng/ml, respectively) as well in-solution TGF-β1 at an EC_{50} of 7.1 ng/ml.

Bintrafusp alfa showed potent growth inhibition in tumor xenograft models. In EMT-6 orthoptic breast tumor mice models, bintrafusp alfa caused tumor regression in 92% (12

out of 13) of models; higher than the equimolar doses of either anti-PD-L1 (54%, 7 of 13 mice) or trap control (8%, 1 of 13 mice). In the MC38 colon cancer models, bintrafusp alfa inhibited tumor growth more strongly than either anti-PD-L1 or TGFβ trap.

1.13 Clinical experience

Bintrafusp alfa has demonstrated an acceptable safety profile to date in patients with solid tumors, including NSCLC. The pooled safety from 10 expansion cohorts from EMR200647-001 showed that most of the observed events were either in line with those expected in participants with advanced solid tumors or with similar class effects of monoclonal antibodies (mAbs) blocking the PD1/PD-L1 axis. Immune-related AEs (irAEs) and infusion-related reactions (IRRs) are identified as risks for bintrafusp alfa. In addition, skin adverse events (AEs) attributed to TGFβ are an identified risk for bintrafusp alfa, however, they have been manageable and have not led to permanent discontinuations in bintrafusp alfa. Bintrafusp alfa was evaluated at 2 dose levels (500 and 1,200 mg) in a total of 80 participants in the second-line (2L) NSCLC cohort in EMR200647-001, the safety profiles were comparable at the 2 dose levels. Bintrafusp alfa has demonstrated promising antitumor activities in Phase I studies. At the cutoff for the analysis (24 weeks after the 1st dose in the last participant, 12 March 2018), the 80 participants in the NSCLC cohort (40 participants at 500 or 1,200 mg every 2 weeks) had median follow-up of 51.1 weeks (range: 1.3 to 67.0 weeks) and had a median duration of treatment of 11.3 weeks (range: 2.0 to 66.1 weeks). Clinical activity was observed across PD-L1 expression levels and improved at higher PD-L1 tumor cell expression. Median progression-free survival (PFS) as assessed by the investigator for the 1,200 mg every 2 weeks cohort was 2.7 and 6.8 months for participants regardless of PD-L1 expression status and PD-L1 ≥1%, respectively, and was not reached for PD-L1-high patients. Responses with bintrafusp alfa were durable: median duration of response (DoR) was not reached in the 1,200 mg every 2 weeks cohort, with responses ongoing in 8/11 patients at data cutoff. However, it is unclear whether bintrafusp alfa in combination with docetaxel will be the optimal approach compared to docetaxel alone in the second-line therapy of patients with NSCLC who have progressed on a combination of anti-PD1/PD-L1 agents and chemotherapy. We hypothesize that bintrafusp alfa will overcome checkpoint inhibitor resistance by modulating the tumor microenvironment and synergize with docetaxel in the treatment of NSCLC. We propose a randomized phase II study to address this question.

1.14 Justification for dose

The dose for bintrafusp alfa in this study is 2,400 mg administered as an intravenous infusion once every 3 weeks.

Per the current investigator's brochure (IB) (M7824 Investigator's Brochure, 2019) integration of all available Phase I data and modeling and simulations support the selection of 1200 mg as the recommended phase two dose (RP2D) for every two-week (q2w) dosing of bintrafusp alfa. Since most chemotherapies are administered q3w, the same dosing interval for bintrafusp alfa is preferred for convenience and compliance. Therefore, 2400 mg once every three weeks (q3w) is the RP2D for q3w dosing of bintrafusp alfa in combination with chemotherapies (for details see IB).

1.2 Docetaxel

Docetaxel is a semisynthetic taxane that binds to β tubulin and stabilizes microtubules, thus leading to cell cycle arrest and apoptosis. Docetaxel is approved in a variety of human malignancies such as breast cancer, gastro-esophageal cancers, prostate cancers

and non-small cell lung cancers. In the TAX-320 trial, docetaxel improved response rate, duration of response and one year survival when compared to vinorelbine or ifosfamide in platinum-refractory NSCLC (Fossella FV, 2000). Two doses of docetaxel were examined – 75 mg/m^2 and 100 mg/m^2. While both doses were equally effective, the lower dose was better tolerated. The TAX-317 trial showed that docetaxel improved survival over best supportive care by 2.9 months (7.5m vs 4.6m; RR 0.56, 95% CI 0.35-0.88) (Shepherd FA, 2000). Based on the above trial results, docetaxel at 75 mg/m^2 was approved as second-line therapy in platinum-refractory metastatic non-small cell lung cancer. To date, this dose remains the preferred second line treatment for patients progressing on the combination of platinum-based chemotherapy and pembrolizumab.

There is increasing evidence that responses to chemotherapy are accentuated if administered following immune checkpoint inhibitors. A recent study showed that response to single agent chemotherapy was significantly higher after immunotherapy than when compared with pre-immunotherapeutic historical control and almost equaled the ORR to first-line chemotherapy. The ORR to chemotherapy (50% patients had docetaxel) after immunotherapy (68% patients had nivolumab) was 39% compared to 37% ORR to first line chemotherapy. Historically, in the TAX 320 trial, docetaxel 75 mg/m^2 had a response rate of 6.7%. It is postulated that immunotherapy sensitizes tumors to subsequent chemotherapeutic agents. The exact mechanisms leading to this effect are not clearly understood. We aim to explore the synergy of an immunotherapy and docetaxel when combined with a checkpoint inhibitor and a microenvironment modulating TGFβ trap.

1.3 Trial Design

This is a phase II trial of bintrafusp alfa in combination with standard therapy in the treatment of adult patients with non-small cell lung cancer (NSCLC) that has progressed on combination chemotherapy and anti-PD-L1 immuno-therapy. Treatment will be administered as

1) Docetaxel with bintrafusp alfa for 4 cycles, followed by bintrafusp alfa alone for up to 2 years.

OR

2) Docetaxel alone until docetaxel is permanently discontinued due to disease progression or intolerable adverse events.

When a patient discontinues docetaxel alone, the patient may be offered optional crossover to bintrafusp alfa alone when disease progression is diagnosed, as long as all eligibility criteria for crossover are met.

NOTE: If patient on docetaxel-alone discontinues docetaxel due to intolerable adverse events, patient will be monitored every 6 weeks until disease progression.

NOTE: If patient on docetaxel-alone does not meet criteria for crossover at the time of disease progression, then patient will go off study per Section 13.0, and may be treated per institutional standard of care.

More than 650 patients have been treated with single-agent bintrafusp alfa. The toxicity profile is similar to those described for other PD1/PD-L1 inhibitors.

Bintrafusp alfa is in a phase II/III trial combined with chemotherapy: cisplatin/etoposide or paclitaxel/carboplatin and radiation therapy for NSCLC (NCT03840902). Over 20 patients have been evaluated to date, and the combination is well-tolerated. There is no reason to expect any significant safety concerns with a combination of bintrafusp alfa and docetaxel based on these chemo/radiation combination data.

In addition, there is an ongoing international multicenter study of chemotherapy + M7824 (NCT03840915). One arm is a combination of docetaxel + M7824 arm (75 mg/m^2 + 2400 mg). There will be adequate safety data for us to adjust our drug doses by the time this present study is open for accrual, in the unlikely circumstance that concerning toxicities are found.

1.4 Correlative Research

The following samples for biomarker research are required and will be collected from all participants in this study: Tumor samples obtained by endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies, and surgical specimens that are <6 months old and adequate for biomarker analysis are mandatory at Baseline to evaluate the association of PD-L1 protein expression as well as other immune or tumor cell markers with the observed clinical responses. Biopsies obtained by fine needle aspiration are not acceptable. Fresh biopsies are mandatory at W4D1 (prior to Cycle 2).

Tumor mutational burden (TMB) status in tumor tissue may be also evaluated to determine the correlation with clinical outcome. In addition, tumor samples may be analyzed for genetic variants of biomarkers which could play a role in the biology of the drug targets, the tumor or the tumor microenvironment including, but not limited to, specific gene mutations, genome-wide analysis for RNA, or protein biomarkers to evaluate their association with observed clinical responses.

Optional collection of tissue procured outside of specified procedures, as part of routine care, at the discretion of Investigator (e.g., skin biopsies or tumors obtained as part of unscheduled interventions) may be analyzed for genetic variants of biomarkers thought to play a role in the biology of the drug targets, the tumor, or the tumor microenvironment, including, but not limited to, specific gene mutations, genome-wide analysis for RNA, or protein biomarkers to evaluate their association with observed clinical responses.

Blood and tumor samples will be tested for 1) PD-L1 expression in tumor at Baseline assessed with IHC to evaluate the association of PD-L1 expression at Baseline with efficacy; and 2) TMB status in plasma ctDNA and in tumor tissue as well as level of ctDNA in plasma to evaluate the correlation with clinical outcome.

In addition, tumor samples may be analyzed for genetic variants of biomarkers which could play a role in the biology of the drug targets, the tumor or the tumor microenvironment including, but not limited to, specific gene mutations, genome-wide analysis for RNA, or protein biomarkers to evaluate their association with observed clinical responses.

1) Biopsies will be performed at study entry and after one cycle of treatment to explore biomarkers related to inhibition of TGFβ and PD-L1.
2) Peripheral blood will be collected at study entry and prespecified time points to explore biomarkers related to inhibition of TGFβ and PD-L1.
3) Peripheral blood will also be collected at study entry and prespecified time points for understanding the immune status of patients in response to therapy using mass cytometry.

2.0 Goals

2.1 Primary Goal

To compare the progression-free survival (PFS) of bintrafusp alfa in combination with docetaxel vs docetaxel alone.

2.2 Secondary Goals

2.21 To evaluate overall survival of bintrafusp alfa in combination with docetaxel vs docetaxel alone.

2.22 To evaluate overall response rates of bintrafusp alfa in combination with docetaxel vs docetaxel alone.

2.23 To evaluate duration of response of bintrafusp alfa in combination with docetaxel vs docetaxel alone.

2.24 To evaluate the safety of bintrafusp alfa in combination with docetaxel vs docetaxel alone.

2.3 Correlative Research

2.31 To evaluate PD-L1, TGFβ, and TMB as potential predictive markers of clinical response in tumor biopsies and in plasma.

2.32 To evaluate biomarkers associated with inhibition of TGF β and PD-L1

2.33 To evaluate the changes in immune system using mass cytometry in response to TGF β and PD-L1 inhibition.

3.0 Patient Eligibility

3.1 Randomization – Inclusion Criteria

3.11 Age ≥18 years

3.12 Histological confirmation of non-small cell lung cancer (NSCLC) with advanced disease.

3.13 Prior treatment required:
- Anti-PD1/PD-L1 agent in combination with platinum-based chemotherapy

3.14 Measurable disease as defined in Section 11.0.
NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease; Disease that is measurable by physical examination only is not eligible.

3.15 ECOG Performance Status (PS) 0 or 1 (Appendix I).

3.16 The following laboratory values obtained ≤14 days prior to registration:
- Hemoglobin ≥9.0 g/dL
- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥100,000/mm^3
- Total bilirubin ≤ULN
- Alanine aminotransferase (ALT/SGPT) and aspartate transaminase (AST/SGOT) ≤1.5 × ULN
- Alkaline phosphatase ≤2.5 × ULN
- PT/INR/aPTT ≤1.5 × ULN
  OR if patient is receiving anticoagulant therapy INR or aPTT is within target range of therapy
- Calculated creatinine clearance ≥30 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\dfrac{\textbf{(140 - age)(weight in kg)}}{(72)(\text{serum creatinine in mg/dL})}$

Creatinine clearance for females = $\dfrac{\textbf{(140 - age)(weight in kg)(0.85)}}{(72)(\text{serum creatinine in mg/dL})}$

3.17 Negative pregnancy test done ≤7 days prior to registration, for persons of childbearing potential only.

NOTE: If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3.18 Willing to use birth control as follows:

3.181 If able to become pregnant: Willing to use birth control during treatment and for 6 months after last dose of docetaxel and/or bintrafusp alfa, whichever is later.

3.182 If able to father a child: Willing to use birth control with partners able to become pregnant during treatment and for 3 months after last dose of docetaxel and/or bintrafusp alfa, whichever is later.

3.19a Provide written informed consent.

3.19b Willingness to provide mandatory blood specimens for correlative research (see Section 14.0).

3.19c Willingness to provide mandatory tissue specimens for correlative research (see Section 17.0).

3.19d Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.2 Randomization - Exclusion Criteria

3.21 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant persons
- Nursing persons
- Persons of childbearing potential who are unwilling to employ adequate contraception

3.22 Any of the following prior therapies:

- Surgery ≤4 weeks prior to registration
- Chemotherapy ≤4 weeks prior to registration
- Received single agent anti-PD1/PD-L1 as first line therapy for metastatic disease

3.23 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.24 Uncontrolled intercurrent illness including, but not limited to:

- ongoing or active infection
- symptomatic congestive heart failure
- unstable angina pectoris
- cardiac arrhythmia
- or psychiatric illness/social situations that would limit compliance with study requirements.

3.25 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.26 Other active malignancy ≤5 years prior to registration.
EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix.
NOTE: If there is a history of prior malignancy, they must not be receiving other specific treatment for their cancer.

3.27 History of myocardial infarction ≤6 months, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

3.28 Known primary central nervous system (CNS) malignancy or symptomatic CNS metastases are excluded, with the following exceptions:

3.281 Patients with asymptomatic *un*treated CNS disease may be enrolled, provided all of the following criteria are met:

- Evaluable or measurable disease outside the CNS

- No metastases to brain stem, midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)
- No history of intracranial hemorrhage or spinal cord hemorrhage
- No ongoing requirement for dexamethasone for CNS disease; patients on a stable dose of anticonvulsants are permitted.
- No neurosurgical resection or brain biopsy ≤28 days prior to registration

3.282 Patients with asymptomatic treated CNS metastases may be enrolled, provided all the criteria listed above are met as well as the following:

- Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
- No stereotactic radiation or whole-brain radiation ≤28 days prior to registration
- Screening CNS radiographic study ≥4 weeks from completion of radiotherapy and ≥2 weeks from discontinuation of corticosteroids

3.29a History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

3.29b History or current evidence of bleeding disorder, including bleeding diathesis, i.e., any hemorrhage/bleeding event of CTCAE Grade ≥2 in ≤28 days prior to registration.

3.29c Taking oral prednisone of ≥10 mg daily or equivalent.

3.29d Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease.

Notes:

- Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible.
- Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA

3.29e History or risk of autoimmune disease, including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis.

Notes:

- Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible.
- Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen are eligible.
- Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
  - Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations

- Rash must cover less than 10% of body surface area (BSA)
- Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)
- No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

3.29f Known active human immunodeficiency virus (HIV) infection (defined as patients who are not on anti-retroviral treatment and have detectable viral load and CD4+ <500/ml).
NOTE: HIV-positive patients who are well controlled on anti-retroviral therapy are allowed to enroll.

3.29g History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan.
Note: History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

3.29h Severe infections ≤4 weeks prior to registration, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia.

3.29i History of peripheral neuropathy ≥Grade 2.

3.29j Known hypersensitivity to docetaxel or polysorbate 80.

3.3 Crossover Eligibility

Crossover is allowed for patients in the docetaxel alone arm upon disease progression.

3.31 Documented disease progression ≤28 days prior to crossover registration.

3.32 No contratindications to bintrafusp alfa at the time of crossover registration.

3.33 Patient and physician agree to try crossover treatment with bintrafusp alfa.

3.34 Provide written informed consent.

4.0 Test Schedule

4.1 Test schedule

Tests and procedures	≤14 days prior to registration	Active Monitoring Phase							
		Prior to Treatment on C1D1	End of Cycle 1 prior to C2D1	Day 8 during docetaxel[1]	Prior to subsequent cycle/ treatment (≥Cycle 2)	End of every other cycle[2]	End of treatment[3]	Crossover: Prior to each cycle	Safety followup[4]
Window				±3 days	±7 days		±7 days	±7 days	
History and exam, Wt, PS	X				X		X	X	X
Adverse event assessment	X				X		X	X	X
Height	X								
Pregnancy test[5]		X							
Hematology group: CBC /w 5 part diff	X			X[6]	X		X	X	X
Coagulation (PT/INR/aPTT as applicable)	X								
Chemistry group[7]	X				X		X	X	X
TSH[8]	X								
Tumor measurement[9]	X					X	X	X[10]	
ECG	X[11]								
Research biopsy[12R]		X	X						
Mandatory research blood specimens[13,R]		X				X	X		
Mandatory research tissue specimens[14,R]		X	X						

Cycle = 21 days; R=Research funded (see Section 19.0)

[1] Only needed for first four cycles of docetaxel
[2] End of Cycle 2, 4, 6, etc. NOTE: Maintain imaging schedule for patients on docetaxel alone after docetaxel is stopped due to AEs if prior to PD.
[3] End of treatment with docetaxel (prior to crossover) for patients on docetaxel alone; or end of all study treatment for patients on combination
[4] Single visit approximately 30 days ±5 days after last dose of bintrafusp alfa (due to timing, this visit may coincide with EOT visit)
[5] For persons of childbearing potential only. Baseline must be done ≤7 days prior to registration. Subsequent testing should be done as needed for clinical care.
[6] Blood draw one week after docetaxel is given – may be done locally and results transmitted to Mayo Clinic
[7] Albumin, alk phos, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium
[8] Baseline TSH testing is required; then monitor clinically if symptomatic
[9] Standard clinical imaging should be used. Contrast-enhanced CT/MRI is acceptable as a baseline scan if done≤28 days prior to C1D1. Subsequent visit window of ≤7 days is allowed. Tumor measurements are repeated prior to every odd cycle starting with Cycle 3. Once patient has achieved CR or SD, frequency may be reduced per clinical guidelines. Documentation (radiologic) must be provided for patients removed from study for progressive disease.
[10] Most recent imaging while on study should be ≤28 days prior to crossover. Continue prior to every odd cycle per footnote above.
[11] 12-lead ECG at screening only; may be repeated at any time if clinically indicated
[12] Consultation with Interventional Radiology is required prior to scheduling research **lung** biopsy (not needed for liver, lymph node, abdomen)
[13] Blood samples are collected per Section 14.0. Kits are required for sites outside of Rochester, MN.
[14] Tissue specimens are collected per Section 17.0.

4.2 Survival Follow-up/Event Monitoring

NOTE: Survival follow-up will cease for all patients as of MCCC Amendment 3.

	Survival Follow-up				
	q. 3 months until PD	At PD	After PD q. 3 months	Death	New Primary
Survival Follow-up	X	X	X	X	At each occurrence

1. If a patient is still alive 5 years after registration, no further follow-up is required.

5.0 Stratification Factors

5.1 Primary PD during Chemo+Anti-PDx: Yes vs. No

5.2 Acquired resistance PD after SD as best response during Chemo+Anti-PDx: Yes vs. No

5.3 Acquired resistance PD after PR/CR during Chemo+Anti-PDx: Yes vs. No

5.4 Diagnosis: Squamous cell carcinoma vs non-squamous cell carcinoma

6.0 Registration/Randomization Procedures

6.1 Registration (Step 1)

To register a patient, access the Mayo Clinic Research Registration Application at www.registration.mayo.edu. The Research Registration Application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, contact the Mayo Clinic Research Site Management Office at (507) 284-2753 or ResearchSiteManagement@mayo.edu between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Access and training instructions for the Research Registration Application are available on the Office of Clinical Trials web page (https://www.mayo.edu/research/centers-programs/center-clinical-translational-science/offices/office-of-clinical-trials/research-registration-application) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the Mayo Clinic Research Site Management Office (507) 284-2753. If the patient was fully registered, the Research Site Management Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

6.2 Verification of materials

Prior to accepting the registration, the Research Registration Application will verify the following:

- IRB approval at the registering institution

- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.3 Documentation of IRB approval

Documentation of IRB approval must be on file in the Research Site Management Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Mayo Clinic Research Site Management Office (fax: 507-284-0885). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Research Site Management Office is no longer necessary.

6.4 Correlative Research

6.41 Mandatory

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19c, 3.19d, 14.0, 17.0*)*.

6.5 Banking of data and specimens

At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research on cancer at Mayo Clinic.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for Mayo Clinic to give his/her sample(s) to researchers at other institutions.

6.6 Treatment on protocol

Treatment on this protocol must commence at Mayo Clinic under the supervision of a medical oncologist.

6.7 Treatment start

Treatment cannot begin prior to registration and must begin ≤14 days after registration.

6.8 Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.9a Baseline symptoms

All required baseline symptoms (see Section 10.6) must be documented and graded.

6.9c Study drug

Study drug is available on site.

6.9f Study Conduct

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

6.9g Randomization Procedures

6.9g1 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.9g2 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups.
{Reference: Pocock SJ, Simon R. Sequential Treatment Assignment with Balancing for Prognostic Factors in the Controlled Clinical Trial. Biometrics 31(1):103-115, 1975 Mar}

- Bintrafusp alfa and docetaxel
- Docetaxel alone

6.9h Crossover for Patients on Docetaxel Alone Arm after Progression

If the patient was on the docetaxel alone arm at the time of disease progression, then the patient can be offered the opportunity to crossover to treatment with bintrafusp alfa.

Eligibility is determined by the treating physician and the patient. Patient must be reconsented and may be enrolled in the crossover through the remote registration application.

To register a patient, access the Mayo Clinic Research Registration Application at www.registration.mayo.edu. The Research Registration Application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, call the Research Site Management Office at (507) 284-2753 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

7.0 Protocol Treatment

7.1 Treatment Schedule

Use actual weight or estimated dry weight if fluid retention

7.11 Suggested pretreatment medication tables

7.111 Suggested pretreatment for docetaxel (please follow institutional guidelines)

Agent	Dose	Route	Day (include +/-buffer)
Dexamethasone (DXM)	10-20 mg	IV*	Per institutional guidelines (prior to docetaxel)

*Research test results may be affected by oral DXM if given prior to research sample collection

7.112 Optional pretreatment for bintrafusp alfa

Agent	Dose	Route	Day (include +/-buffer)
Acetaminophen	500-650mg	Oral	1 of each cycle PRN
Diphenhydramine	25mg	Oral	1 of each cycle PRN

7.12 Treatment medication table

Note: Docetaxel <u>in combination</u> with bintrafusp alfa should be given for four cycles. Docetaxel <u>alone</u> should be given until disease progression or intolerable adverse events.

Group	**Agent**	**Dose Level**	**Route**	**Day**	**ReRx**
A	Bintrafusp alfa	2400 mg	IVPB	1	Q3w for up to 2 years
	Docetaxel	75 mg/m^2	IVPB	1	Q3w for 4 cycles
OR					
B	Docetaxel	75 mg/m^2	IVPB	1	Q3w

IVPB = intravenous piggyback; Q3w = once every 3 weeks

7.13 Treatment medication table: Crossover for up to 2 years

Patients assigned to docetaxel alone may crossover ≤28 days after scan showing progressive disease.

Agent	**Dose Level**	**Route**	**Day**	**ReRx**
Bintrafusp alfa	2400 mg	IVPB	1	Q3w

IVPB = intravenous piggyback; Q3w = once every 3 weeks

7.2 Bintrafusp alfa

7.21 Bintrafusp alfa

Bintrafusp alfa is an intravenous medication administered once every three weeks for up to 2 years (35 doses).

7.22 Timing of drug administration

Bintrafusp alfa will be administered as a 1 hour infusion (-10 minutes/+20 minutes, i.e., 50-80 minutes).

After bintrafusp alfa, docetaxel at the dose of 75 mg/m^2 should be administered as an intravenous infusion over approximately one hour.

7.3 Docetaxel

Docetaxel is administered according to institutional standards for four cycles only in combination with bintrafusp alfa; and until disease progression or intolerable adverse events when given alone.

If patient on docetaxel alone discontinues docetaxel for intolerable adverse events, the patient should continue to be monitored every 6 weeks until disease progression (PD). At time of PD, patient may be offered option to crossover to bintrafusp alfa alone (see Section 7.4).

7.4 Crossover for patients on docetaxel alone

Patients on docetaxel alone may crossover once disease progression is diagnosed. Patients should crossover within 28 days after the scan showing progressive disease. Crossover patients may be treated with bintrafusp alfa for up to 2 years.

NOTE: If patient on docetaxel-alone does not meet criteria for crossover at the time of disease progression, then patient will go off study per Section 13.2, and may be offered other treatment per institutional standard of care.

7.5 Return to consenting institution

For this protocol, the patient must return to the consenting institution for evaluation at least every 21 days during treatment (Active Monitoring Phase).

7.6 Treatment by local medical doctor (LMD)

Treatment by a local medical doctor (LMD) is not allowed.

Blood draws (CBC with differential) one week after docetaxel dose may be done locally and submitted to Mayo Clinic. (This check is only needed while patient is being treated with docetaxel.)

8.0 Dosage Modification Based on Adverse Events

Follow the modifications in these tables for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

Providers may hold, delay, or reduce (in line with Section 8.1) doses, even in the absence of a requirement to do so in this section per clinical judgement to maximize patient safety. For example, if the patient's AE is Grade 2, and the tables do not indicate a change in action, if the provider determines that the patient's Grade 2 AE is severe enough to warrant a change in the patient's clinical care (i.e., for medically significant or intolerable Grade 2 AE despite appropriate (maximal) supportive care), then the provider may make that change, as long as the reason for the change is discussed with the PI, and documented in the medical record.

→ ***ALERT:*** ***ADR reporting may be required for some adverse events (See Section 10.0)*** ←

8.1 Dose Levels

(Based on Adverse Events in Tables 8.*2* and 8.3)

Dose Level	Bintrafusp alfa	Docetaxel
1*	2400 mg	75 mg /m^2
-1	NA	60 mg/m^2
-2	NA	50 mg//m^2

*Dose level 1 refers to the starting dose.

Bintrafusp alfa dose is always 2400 mg. It may be held or discontinued but dose reduction is not allowed. If bintrafusp alfa is discontinued, docetaxel should be continued for a minimum of 4 cycles or until disease progression or unacceptable toxicity, whichever is first.

Docetaxel will not be re-escalated once reduced. If dose reduction for docetaxel beyond Dose Level -2 is required or if docetaxel is held for more than 6 weeks (from the date of last docetaxel treatment), docetaxel should be discontinued. In that case, bintrafusp alfa should be continued until disease progression or unacceptable toxicity.

NOTE: If either of docetaxel or bintrafusp alfa is discontinued, the patient can continue on the other drug, unless specified otherwise in the dose modification tables. If both are discontinued, the patient will go to survival follow-up (Section 4.2).

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the two dose-reduction steps (levels –1 and –2) will be at the discretion of the treating physician, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data.

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) current version 5.0* unless otherwise specified*** ← ←

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

8.2 Dose Modifications for Bintrafusp Alfa Guidelines

There will be no dose reduction for bintrafusp alfa in this study. Patients may temporarily suspend study treatment for up to 6 weeks beyond the last infusion if study drug-related toxicity requiring dose suspension is experienced. If bintrafusp alfa is held because of AEs for >6 weeks beyond the last date of infusion, the patient will be discontinued from bintrafusp alfa and will be followed for safety and efficacy as specified in this protocol.

If a patient must be tapered off steroids used to treat AEs, bintrafusp alfa may be held for ≤6 weeks from last infusion until steroids are discontinued or reduced to a prednisone dose (or dose equivalent) of 10 mg/day. The acceptable length of interruption will be at the discretion of the investigator.

Dose interruptions for reasons other than toxicity, such as surgical procedures or medical events, may be allowed. The reason for interruption should be documented. The acceptable length of interruption is less than 6 weeks and should be discussed with lead investigator.

Any adverse event associated or possibly associated with bintrafusp alfa treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. Although most immune- related adverse events (irAEs) observed with immuno-modulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of bintrafusp alfa may not have an immediate therapeutic effect, and there is no available antidote for bintrafusp alfa. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents. The investigator should consider the benefit-risk balance prior to further administration of bintrafusp alfa. In patients who have met the criteria for permanent discontinuation, resumption of bintrafusp alfa may be considered if the patient is deriving clinical benefit and has fully recovered from the immune-related event.

Patients can be re-challenged with bintrafusp alfa ONLY after careful consideration of benefit- risk balance and medical judgment by the trial Principal Investigator. Bintrafusp alfa may NOT be resumed if the patient experiences any of the following events, regardless of benefit:

- Grade 3 or 4 pneumonitis
- AST or ALT >5×ULN or total bilirubin >3×ULN
- Grade 4 diarrhea or colitis
- Grade 4 hypophysitis
- Any grade myasthenic syndrome/myasthenia gravis, Guillain-Barré, or meningoencephalitis
- Grade 3 or 4 ocular inflammatory toxicity
- Grade 4 or any grade of recurrent pancreatitis
- Grade 3 or 4 infusion-related reactions
- Grade 4 rash

The table below presents dose modification guidelines of bintrafusp alfa for immune related adverse events. For recommendations to hold bintrafusp alfa and begin corticosteroid treatment, use the following guidance for tapering the corticosteroid and resuming bintrafusp alfa therapy after resolution of the event:

- Corticosteroids must be tapered over ≥1 month to <10 mg/day oral prednisone or equivalent before bintrafusp alfa can be resumed.

- Bintrafusp alfa may be held for a period of time of 6 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent.

Use the following to describe actions in the Action column:

- **Omit** = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time.
- **Hold/Delay** = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- **Discontinue** = The specified drug(s) are totally stopped.

8.3 Dose Modifications for Bintrafusp Alfa Day 1 of Subsequent Cycles

CTCAE System/Organ/Class (SOC)	Adverse Event	Grade	Dose Adjustment and Management Recommendations
Endocrine disorders	Adrenal insufficiency	Grade 2+ (symptomatic)	Hold bintrafusp alfa. Resume bintrafusp alfa if event resolves to Grade 1 or better and patient is stable on replacement therapy (if required) within 6 weeks. Permanently discontinue bintrafusp alfa and contact Study Chair if event does not resolve to Grade 1 or better or patient is not stable on replacement therapy within 6 weeks.
	Hyperthyroidism	Grade 1 (asymptomatic)	TSH ≥0.1 mU/L and <0.5 mU/L: Continue bintrafusp alfa. (See Section 9.5 for supportive care guidelines) TSH <0.1 mU/L: Follow guidelines for symptomatic hyperthyroidism
		Grade 2+ (symptomatic)	Hold bintrafusp alfa. (See Section 9.5 for supportive care guidelines) Resume bintrafusp alfa when symptoms are controlled and thyroid function is improving Permanently discontinue bintrafusp alfa and contact Study Chair for life-threatening immune-related hyperthyroidism
Endocrine disorders	Hypothyroidism	Grade 1 (asymptomatic)	Continue bintrafusp alfa. (See Section 9.5 for supportive care guidelines)

CTCAE System/Organ/Class (SOC)	Adverse Event	Grade	Dose Adjustment and Management Recommendations
Endocrine disorders	Hypothyroidism (continued)	Grades 2+ (symptomatic)	Hold bintrafusp alfa (See Section 9.5 for supportive care guidelines) Restart bintrafusp alfa when symptoms are controlled and thyroid function is improving
Gastrointestinal disorders	Diarrhea or Entercolitis	Any grade	Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. (See Section 9.4 for supportive care guidelines)
		Grade 1	Continue bintrafusp alfa. Initiate symptomatic treatment. (See Section 9.4 for supportive care guidelines)
		Grade 2	Hold bintrafusp alfa. (See Section 9.4 for supportive care guidelines) If event resolves to Grade 1 or better within 6 weeks, taper corticosteroids and resume bintrafusp alfa according to the guidelines above. Permanently discontinue bintrafusp alfa and contact Study Chair if event does not resolve to ≤Grade 1 within 6 weeks. Resumption of bintrafusp alfa may be considered in patients who are deriving benefit and have fully recovered from the immune- related event.
Gastrointestinal disorders	Diarrhea or Entercolitis	Grade 3	Hold bintrafusp alfa (See Section 9.4 for supportive care guidelines) If event resolves to ≤Grade 1 within 6 weeks, taper corticosteroids and resume bintrafusp alfa according to the guidelines above. Permanently discontinue bintrafusp alfa and contact Study Chair if event does not resolve to ≤Grade 1 within 6 weeks. Resumption of bintrafusp alfa may be considered in patients who are deriving benefit and have fully recovered from the immune- related event

CTCAE System/Organ/Class (SOC)	Adverse Event	Grade	Dose Adjustment and Management Recommendations
Gastrointestinal disorders	Diarrhea or Enterocolitis (continued)	Grade 4	Permanently discontinue bintrafusp alfa. Patient may not resume treatment, regardless of benefit. (See Section 9.4 for supportive care guidelines)
Hepatobiliary disorders	Hepatic Failure	≥Grade 3	Permanently discontinue bintrafusp alfa and contact Study Chair. Patient may not resume treatment, regardless of benefit.
Immune system disorders	Anaphylaxis	≥Grade 3	If hypersensitivity reaction occurs, participant should be treated according to the best available medical practice Permanently discontinue bintrafusp alfa Patient should go to Event Monitoring
Infections and infestations	Encephalitis infection or Meningitis	All grades	Permanently discontinue bintrafusp alfa and contact Study Chair. Patient may not resume treatment, regardless of benefit. (See Section 9.6 for supportive care guidelines)
Injury, poisoning or procedural complications	Infusion related reaction	Grade 1	Increased monitoring of vital signs as medically indicated Consider interrupting or slow the rate of infusion, and use premedication for subsequent doses
		Grade 2	Stop infusion Increased monitoring of vital signs as medically indicated If symptoms resolve quickly or decrease to Grade 1, resume infusion at 50% of original rate with close monitoring of any worsening otherwise dosing held until resolution of symptoms with mandated pre-medication for the next schedule At the next infusion, H2 blockers (e.g., famotidine or ranitidine) may be considered as clinically indicated. Participants with a second Grade ≥2 IRR on the reduced-rate infusion with the suggested medication, the infusion should be stopped, and if clinically indicated the participant should be removed from study intervention

CTCAE System/Organ/Class (SOC)	Adverse Event	Grade	Dose Adjustment and Management Recommendations
Injury, poisoning or procedural complications	Infusion related reaction	Grade 3 or Grade 4	Stop infusion immediately and disconnect tubing from the participant Take additional appropriate medical measures and close monitoring until deemed medically stable by attending Investigator Participants must be immediately withdrawn and must NOT receive any further infusions
Investigations	Lipase increased or Serum amylase increased	Grade 1 (>ULN - 1.5 x ULN)	Continue bintrafusp alfa. (See Section 9.7 for supportive care guidelines)
		Grade 2 (>1.5 - 2.0 x ULN)	Continue bintrafusp alfa. (See Section 9.7 for supportive care guidelines)
		Grade 3 (>2.0 - 5.0 x ULN) or Grade 4 (>5.0 x ULN)	Hold bintrafusp alfa. (See Section 9.7 for supportive care guidelines) Resume bintrafusp alfa if event resolves to Grade 1 or better within 6 weeks. Permanently discontinue bintrafusp alfa and contact Study Chair if event does not resolve to Grade 1 or better within 6 weeks. For recurrent events associated with pancreatitis symptoms, permanently discontinue bintrafusp alfa and contact Study Chair. Treatment for recurrent events not associated with pancreatitis symptoms may be resumed after consultation with the trial Study Chair.
Metabolism and nutrition disorders	Hyperglycemia	Grade 1 or 2	Continue bintrafusp alfa. (See Section 9.8 for supportive care guidelines)
	Hypoglycemia	Grade 3 or 4	Hold bintrafusp alfa. (See Section 9.8 for supportive care guidelines) Resume bintrafusp alfa when symptoms resolve and glucose levels are stable.

CTCAE System/Organ/Class (SOC)	Adverse Event	Grade	Dose Adjustment and Management Recommendations
Musculoskeletal and connective tissue disorders	Arthritis	Grade 3	Hold bintrafusp alfa. Evaluate for alternative etiologies. Initiate treatment per institutional guidelines. Resume bintrafusp alfa if event resolves to Grade 1 or better within 6 weeks. Permanently discontinue bintrafusp alfa and contact Study Chair if event does not resolve to Grade 1 or better within 6 weeks.
Nervous system disorders	Peripheral motor neuropathy OR Peripheral sensory neuropathy	Grade 1	Continue bintrafusp alfa. Evaluate for alternative etiologies.
		Grade 2	Hold bintrafusp alfa. Evaluate for alternative etiologies. Initiate treatment per institutional guidelines. Resume bintrafusp alfa if event resolves to Grade 1 or better within 6 weeks. Permanently discontinue bintrafusp alfa and contact Study Chair if event does not resolve to Grade 1 or better within 6 weeks.
		Grade 3 or 4	Permanently discontinue bintrafusp alfa and contact Study Chair. Initiate treatment per institutional guidelines.
Renal and urinary disorders	Acute kidney injury	Grade 3 or 4	Permanently discontinue bintrafusp alfa and contact Study Chair. Initiate treatment per institutional guidelines.
Respiratory, thoracic and	All pulmonary events (such as Cough, Pneumonitis, Bronchospasm, Pulmonary edema, or any other respiratory tract AE)	All grades	(See Section 9.9a for supportive care guidelines)
		Grade 1	Continue bintrafusp alfa and monitor closely. (See Section 9.9a for supportive care guidelines) For recurrent pneumonitis, treat as a Grade 3 or 4 event.
		Grade 2	Hold bintrafusp alfa. (See Section 9.9a for supportive care guidelines) Permanently discontinue bintrafusp alfa

CTCAE System/Organ/Class (SOC)	Adverse Event	Grade	Dose Adjustment and Management Recommendations
			and contact Principal Investigator if event does not resolve to Grade 1 or better within 6 weeks. For recurrent events, treat as a Grade 3 or 4 event.
Respiratory, thoracic and mediastinal disorders	All pulmonary events (continued)	Grade 3 or 4	Permanently discontinue bintrafusp alfa and contact Study Chair. For Grade 3, patient may only resume treatment after consultation with the trial PI (Study Chair) For Grade 4, patient may not resume treatment, regardless of benefit. (See Section 9.9a for supportive care guidelines)
Skin and subcutaneous tissue disorders	Rash maculo-papular or Purpura	Grade 1	Continue bintrafusp alfa. (See Section 9.9b for supportive care guidelines)
		Grade 2 lasting >7 days	Hold bintrafusp alfa until resolution to ≤Grade 1. (See Section 9.9b for supportive care guidelines)
		Grade 3	Hold bintrafusp alfa. (See Section 9.9b for supportive care guidelines) Restart bintrafusp alfa if event resolves to Grade 1 or better within 6 weeks. Permanently discontinue bintrafusp alfa and consult Study Chair if event does not resolve to Grade 1 or better within 6 weeks.
		Grade 4	Permanently discontinue bintrafusp alfa and contact Study Chair. Patient may not resume treatment, regardless of benefit.

8.4 Dose Modifications for Docetaxel

Docetaxel administration should follow institutional guidelines. The information below may serve as a guideline.

8.41 Initiation of new cycle for docetaxel

Instruction for initiation of a new cycle of therapy or restarting therapy after interruption during a cycle for adverse events. A new cycle of treatment may begin on the scheduled Day 1 of a new cycle if:

Neutrophil Count		Platelet Count	Docetaxel
≥1,500/μL	AND	≥100,000/μL	100%
<1500/μL	OR	<100,000/μL	Hold

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of therapy will be held until the adverse event has resolved as described above. If dose is held for longer than 1 week, resume with docetaxel at one lower level.

If any drug dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle.

If any drug dosing was held for the remainder of the previous cycle or if the new cycle is held due to known cytopenia newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction. If a new cycle of therapy cannot be restarted within 6 weeks due to non-resolution of drug related adverse events, the patient will be removed from protocol therapy and will go to survival follow-up.

For febrile neutropenia during any cycle, defined at ANC <500/μL and temperature ≥38°C (100.4°F), docetaxel should be decreased one dose level for all subsequent cycles.

8.42 Dose Modification of Docetaxel for Hepatic Dysfunction

Parameter		Other Parameters	Action for Docetaxel
Bili ≤ULN	AND	AST >1.5 - 5.0 × ULN	Decrease by one dose level
Bili >ULN			Hold
Alk phos >2.5 × ULN	AND	AST and/or ALT>1.5 × ULN	Hold

8.43 Dose Modification for Neurotoxicity

For Grade 3 or 4 neurotoxicity, hold docetaxel until the adverse event resolves to Grade 2 or less and then resume therapy at one lower dose level. If symptoms worsen or persist despite dose reduction, hold docetaxel until adverse event resolves to Grade 2 or less and then resume therapy at one more lower dose level. If therapy is held for more than 6 weeks (from date of last docetaxel treatment) or symptoms persist despite 2 dose reductions, discontinue docetaxel.

8.44 Dose Modification for Gastrointestinal Toxicity

For Grade ≥3 mucositis, diarrhea, nausea or vomiting, omit docetaxel. Resume at 1 lower dose level when symptoms resolve to Grade 1 or less.

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Volume 33, No 28 (October 1), 2015: pp. 3199-3212 (WBC growth factors) AND Journal of Clinical Oncology, Volume 28, No 33 (November 20), 2010: pp. 4955-5010 (darbepoetin/epoetin).

9.3 Antiemetics

Antiemetics may be used at the discretion of the attending physician.

9.4 Diarrhea or Enterocolitis

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased CRP, f count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

9.41 Grade 1

Endoscopy is recommended if symptoms persist for ≥7 days
Monitor closely

9.42 Grade 2

Initiate symptomatic treatment.
Patient referral to GI specialist is recommended.
For recurrent events or events that persist >5 days, initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent.

9.43 Grade 3

Refer patient to GI specialist for evaluation and confirmatory biopsy.
Initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
If event resolves to Grade 1 or better within 12 weeks, taper corticosteroids and resume bintrafusp alfa according to guidelines in Section 8.0.

9.44 Grade 4

Refer patient to GI specialist for evaluation and confirmation biopsy.
Initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or

equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

9.5 Endocrine Disorders

9.51 Adrenal insufficiency

Refer patient to endocrinologist.
Perform appropriate imaging.
Initiate treatment with hydrocortisone. .

9.52 Hyperthyroidism

For asymptomatic (Grade 1) (TSH ≥0.1 mU/L and <0.5 mU/L):
Monitor TSH every 4 weeks.

For asymptomatic (Grade 1) (TSH <0.1 mU/L) or symptomatic (Grade 2+):
Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.
Consider patient referral to endocrinologist.

9.53 Hypothyroidism

For Grade 1:
Start thyroid-replacement hormone.
Monitor TSH weekly.

For Grade 2+:
Start thyroid-replacement hormone.
Consider referral to an endocrinologist.
Monitor TSH weekly.

9.6 Encephalitis infection or Meningitis

Refer patient to neurologist.
Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.
If event resolves to Grade 1 or better, taper corticosteroids over ≥28 days.
If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.

9.7 Immune-related Pancreatitis or Lipase increased and/or Serum amylase increased

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with administration of other immunomodulatory agents. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for obstruction, as well as serum amylase and lipase tests. See the guidelines for “Amylase and/or lipase increase” and “Immune- related pancreatitis” elsewhere in this document, as needed.

9.71 Grade 1

Monitor amylase and lipase prior to dosing bintrafusp alfa (approximately every 3 weeks)

9.72 Grade 2

Monitor amylase and lipase weekly

9.73 Grade 3 or 4

Refer patient to gastrointestinal (GI) specialist.
Monitor amylase and lipase every other day.
If no improvement, consider treatment with 1-2 mg/kg/day oral prednisone or equivalent.

9.8 Hyperglycemia (all grades)

Initiate treatment with insulin if needed.
Monitor for glucose control.

9.9a Pulmonary events

For all pulmonary events (such as, but NOT limited to: Cough, Pneumonitis, Bronchospasm, Pulmonary edema, or any other respiratory tract AE)

Evaluate thoroughly for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease (COPD), or pulmonary hypertension.

9.9a1 Grade 1

Re-evaluate on serial imaging.
Consider patient referral to a pulmonary specialist.

9.9a2 Grade 2

Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or bronchoscopic alveolar lavage (BAL).

Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. Resume bintrafusp alfa if event resolves to Grade 1 or better within 12 weeks (consult tapering guideline above).

9.9a3 Grade 3 or 4

Bronchoscopy or BAL is recommended.
Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent.

If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.

If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

9.9b Skin and subcutaneous tissue disorders: Rash maculo-papular or Purpura

9.9b1 Grade 1

Consider topical steroids and/or other symptomatic therapy (e.g., antihistamines)

9.9b2 Grade 2

Consider dermatologist referral.
Administer topical corticosteroids.
Consider higher potency topical corticosteroids if event does not improve.

9.9b3 Grade 3 or higher

Refer patient to dermatologist.
Administer oral prednisone 10 mg or equivalent.
If the event does not improve within 48-72 hours, increase dose to1–2 mg/kg/day or equivalent.

9.9b4 Persistent and/or severe rash or pruritus

A dermatologist should evaluate the event.
A biopsy should be performed unless contraindicated.

9.9c Hepatoxicity

Right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should be evaluated for potential hepatotoxicity.

10.0 Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form:http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 AND attach Pregnancy Reporting http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf	Send to EMD Serono: ICSR_CT_GPS@merckgroup.com Will automatically be sent to CANCERCROSAFETYIN@mayo.edu and RSTP2CSAES@mayo.edu Non Mayo sites – complete and forward to RSTP2CSAES@mayo.edu
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form:http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 AND attach MedWatch 3500A: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf	Send to EMD Serono: ICSR_CT_GPS@merckgroup.com Will automatically be sent to CANCERCROSAFETYIN@mayo.edu and RSTP2CSAES@mayo.edu

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0 A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

a. Identify the grade and severity of the event using the CTCAE version 5.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.
NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination) Arm

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting.**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for **investigational** agents/interventions.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report, unless hospitalization is required. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch 3500A for Health Professionals (complete all three pages of the form).

  http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

10.32 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

*Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

CTCAE System/Organ/Class (SOC)	**Adverse Event/ Symptoms**	CTCAE Grade at which the event **will not** be expeditedly reported[1]
Blood and lymphatic system disorders	Anemia	≤Grade 3
Investigations	Lymphocyte count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
	White blood cell count decreased	≤Grade 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for IND Agents

10.41 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

NOTE: Refer to Section 10.32 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND and/or MCCC Compliance will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 for investigational agents or commercial/investigational agents on the same arm.

For commercial agents (for commercial agent(s) on its own arm):

Attach the MedWatch 3500A form to the Mayo Expedited Event Report form https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda

Submit to EMD Serono via fax/email to the following:
Fax No.: +49 6151 72 6914
Email address: ICSR_CT_GPS@merckgroup.com

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously

reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the appropriate documentation and use the Mayo Clinic Cancer Center Expedited Event Report form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56, to submit to CANCERCROSAFETYIN@mayo.edu. The Mayo Clinic Compliance Unit will review and process the submission to the Mayo Clinic IRB and work with the IND Coordinator for submission to FDA.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Disease progression"** under the system organ class (SOC) "General disorders and administrative site condition." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND will be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)

- Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 Baseline and Adverse Events Evaluations

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.
Grading is per CTCAE v5.0 **unless** alternate grading is indicated in the table below:

CTCAE System/Organ/Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic system disorders	Anemia	X	X
Endocrine disorders	Hypothyroidism	X	
Gastrointestinal disorders	# of stools at baseline	X	
	Diarrhea		X
Injury, poisoning and procedural complications	Infusion-related reaction		X
Investigations	Alanine aminotransferase increased	X	X
	Aspartate aminotransferase increased	X	X
	Blood bilirubin in creased	X	X
	Creatinine increased	X	X
Skin and subcutaneous tissue disorders	Purpura	X	X
	Rash maculopapular	X	X

10.62 All other AEs

Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly

treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.8 EMD Serono Additional Event Reporting Instructions

The exchange of AEs between the sponsor and EMD Serono will be outlined in the ISS agreement.

11.0 Treatment Evaluation/Measurement of Effect

NOTE: This study uses protocol irRECIST for measurement of treatment effect. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised immune related Response Evaluation Criteria in Solid Tumors (irRECIST) guidelines. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the irRECIST guideline.

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response or progressive disease.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease.

11.22 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non- measurable as well.

NOTE: '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 patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal

fractions of centimeters) using a ruler or calipers.

- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow- up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- 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. The lesions should be measured on the same pulse sequence. 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.
- 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 scans are preferable.
- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.33 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained at least 4 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see Section 11.44).
- In case of progressive disease (PD), confirmatory scan must be obtained at least 4 weeks following initial documentation of PD. In case confirmatory scan shows progression, first scan date should be used as the date of progression.
- 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.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non-targetlesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 Measurement

All target lesions and target lymph nodes followed by CT/MRI/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

Complete Response (irCR):	All of the following must be true: a. Disappearance of all target lesions. b. Each target lymph node must have reduction in short axis to <1.0 cm.
Partial Response (irPR):	At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).
Progressive Disease (irPD):	At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD. Death or immunotherapy discontinuation due to clinical progression is considered as confirmation of progression
Stable Disease (irSD):	Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.
New Lesion:	The presence of a new lesion does not define progression. The measurements of the new lesion(s) are included in the sum of all measurements.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

Complete Response (CR):	All of the following must be true: a. Disappearance of all non-target lesions. b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
Non-CR/Non-PD:	Persistence of one or more non-target lesions or non-target lymph nodes.

Progression (PD):	At least one of the following must be true: a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up. b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.) c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

12.0 Descriptive Factors

12.1 Smoking status: Current vs Past vs Never

12.2 Diagnosis: Squamous cell carcinoma vs non-squamous cell carcinoma

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Continuation of treatment

Patients who are CR, PR, or SD will continue treatment per protocol, up to 2 years.

13.2 Progressive disease (PD)

Patients on docetaxel alone who develop PD while receiving therapy may crossover to treatment with bintrafusp alfa, if they meet eligibility criteria, otherwise they will go off protocol treatment and go to the event monitoring phase per Section 4.0.

Patients who develop PD while receiving bintrafusp alfa therapy alone will go to the survival follow-up/event monitoring phase.

13.3 Off protocol treatment

Patients in the docetaxel alone arm who go off protocol treatment for reasons other than PD will be monitored on study every 6 weeks for disease progression, and may be offered crossover to the treatment arm at the time of PD.
NOTE: If the patient does not meet eligibility for crossover or does not go to crossover treatment for other reasons, they will go off protocol treatment and go to event monitoring. These patients should be treated with alternative chemotherapy (off protocol) if their clinical status is good enough to allow further therapy.

Patients in the combination arm who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 4.0.

Patients in either group who start non-protocol anti-cancer treatment will be considered “off protocol treatment” and go to event monitoring.

13.4 CNS PD

Patients who develop PD in the CNS only should receive local therapy and continue treatment on study after completion of local therapy.

13.5 Non-CNS PD

Patients in the combination arm who develop non-CNS PD at any time should go to event monitoring. These patients should be treated with alternative chemotherapy (off protocol) if their clinical status is good enough to allow further therapy.

Patients in the docetaxel alone arm who develop non-CNS PD at any time may be eligible for crossover to treatment arm per physician discretion.
NOTE: If the patient does not meet eligibility for crossover or does not go to crossover treatment for other reasons, they will go off protocol treatment and go to event monitoring. These patients should be treated with alternative chemotherapy (off protocol) if their clinical status is good enough to allow further therapy.

13.6 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.

- If the patient never received treatment, on-study material must be submitted.

13.7 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.

13.8 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

Research (Section for more information)	Specimen Purpose (check all that apply)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline (≥2 hours prior to tx on C1D1)	End of Cycles 2 and 4[15]	End of treatment for any reason[16]	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Immune profiling	☒ Correlative	Mandatory	PBMC	Heparin (green)	10 mL	X	X	X	No	Ship refrigerated
Circulating tumor DNA (ctDNA)	☒ Correlative	Mandatory	Whole blood	Streck	10 mL (2)	X	X	X	No	Ship ambient
Banking: DNA, plasma, buffy coat	☒ Banking	Mandatory	Whole blood	K2 EDTA	10 mL (1)	X			No	Ship refrigerated

PBMC= peripheral blood mononuclear cells

[15] Samples should be obtained at time of imaging at end of Cycle 2, then end of Cycle 4.
[16] End of docetaxel (prior to crossover) for patients on docetaxel alone; or end of all study treatment for patients on combination

14.2 Collection and Processing

14.21 Sample collection should be restricted to Monday – Thursday. However, if the subject can only be seen on a Friday, please contact the Biospecimen Resource Manager for additional instructions (see protocol resource pages for contact information).

14.22 Specimen tube(s) must be labeled with the protocol number, study patient ID number, and the time and date of the blood draw.

14.23 Blood/blood products must be collected and shipped according to specific instructions provided in the kit and the table above.

14.21 Immune profiling

Using the kit provided by BAP, AZ and FL sites will ship whole blood refrigerated overnight to BAP at Mayo Clinic in Rochester, MN for future processing in the Immune Monitoring Core.

14.22 Banking

Using the kit provided by BAP, AZ and FL sites will ship whole blood ambient overnight to Mayo Clinic in Rochester, MN.

Send to:

BAP Freezer
Stabile SL-39
150 Third Street SW
Rochester, MN 55902

Phone: 507/538-0602

14.3 Shipping and Handling

14.31 **Kits will be used for this study** for sites outside of Rochester, MN.

14.311 Kits will be supplied by the Biospecimen Accessioning and Processing Shared Resource (BAP).

14.312 The kit contains supplies and instructions for collecting, processing and shipping specimens.

14.313 Participating institutions may obtain kits by faxing the Supply Order Form to the number listed on the form. Because we are charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. **Supply Order Forms must be filled in completely and legibly for quick processing.**

14.314 Kits will be sent via Fed Ex® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.**

14.315 Kits will not be sent via rush delivery service unless the participating institution provides their own Fed Ex® account number or alternate billing number for express mail. **Cost for rush delivery of kits will not be covered by the study.**

14.316 All specimens must be collected and shipped Monday – Thursday ONLY.

14.32 Shipping Specimens

14.321 Mayo Clinic Rochester samples will be routed through BAP for lab pickup.

14.322 All other sites will use kits as described in Section 14.31, shipped to BAP Mayo Clinic in Rochester

14.33 Verify that ALL sections of the Blood Specimen Submission Form (see Forms Packet), BAP Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly. Enter information from the Blood Specimen Submission Form into the remote data entry system within 7 days after specimen collection (see Forms Packet).

14.34 Specimens collected in the Streck cfDNA tubes should be shipped at ambient temperature on the same day they are drawn.

14.35 Samples should be shipped to BAP Freezer Mondays – Thursdays (with arrival Tue-Fri) according to kit instructions. Samples should not be sent on weekends or just prior to federal holidays. (If samples can only be shipped on Fridays, please contact the Biospecimen Resource Manager for additional instructions.)

14.36 Handling Specimens (once received in destination laboratory)

NOTE: BAP Shared Resource will process the specimens including prepping PBMCs for immune profiling (Immune Monitoring Core – Jolaine Hines/Kevin Pavelko PhD)

14.361 PBMC Handling and Isolation
Patient donors will provide 10 mL of whole blood drawn into a green top heparin tube. The whole blood sample will be layered over Ficoll-Paque for enrichment of peripheral blood mononuclear cells (PBMC). After centrifugation of the sample at 1500g, the enriched PBMC cells are washed with RPMI media. After washing with PBS cells are counted and prepared for cryopreservation. Cells are resuspended in cryopreservation media (10% DMSO in RPMI supplemented with fetal bovine serum and a penicillin streptomycin glutamine cocktail). Controlled rate freezing methods are then used to freeze the samples prior to storage in liquid nitrogen.

14.362 Sample Thawing and Preparation for Mass Cytometry
Cells will be thawed and resuspended in complete media (RPMI supplemented with fetal bovine serum) containing 2.5 units/mL of Benzonase Nuclease (Sigma-Aldrich). After washing, cells are rested for 1 hour in complete media at 37°C before staining. After resting $4x10^6$ cells are resuspended in 1 mL of CSB. FcR-block will be added to block non-specific staining due to Fc receptor antibody interactions. Each sample will then be incubated for 5 minutes with 0.5 μm Cisplatin solution in PBS. Cells are then transferred to the 5 mL tubes containing the dry antibody pellet cocktail (Table 1). Samples are then incubated at room temperature for 30 minutes. After washing twice with CSB, samples are then fixed with 2% PFA in PBS. After fixation and wash, samples are resuspended in 30 nM intercalation solution and incubated overnight at 4°C. On the following morning cells are washed with PBS and pooled prior to resuspension in a 1:10 solution of

calibration beads and cell acquisition solution at a concentration of $0.5x10^6$ cells/mL. Prior to data acquisition samples were filtered through a 35 µm blue cap tube (Falcon).

14.363 Mass Cytometry and Data Acquisition
The prepared samples are loaded onto a Helios CyTOF® system (Fluidigm) using an attached autosampler and cellular events are acquired at a rate of 200-400 events per second. Data are collected as .FCS files using the Cytof software (Version 6.7.1014). After acquisition intrafile signal drift is normalized to the acquired calibration bead signal using the Cytof software. File cleanup and analysis will be performed using the Pathsetter software (Verity Software House) cleanup protocol.

14.37 Double spun, platelet poor plasma will be derived from the Streck cfDNA BCT tubes using established laboratory processes, and stored at ≤-65ºC by BAP.

14.38 For banking: DNA will be extracted from whole blood, and white blood cells and plasma will be derived from remaining blood from the EDTA tubes, divided into aliquots, and stored at ≤-65ºC by BAP according to patient consent information.

14.39a As part of ongoing research at the Mayo Clinic, we will retain residual whole blood, white blood cells, CTCs, DNA, and plasma for future research studies, according to patient consent information. Samples will be stored until specific analyses are identified and may be used for exploratory biomarker analyses, validation studies, or potential diagnostic development. As protocols are developed, they will be presented for IRB review and approval.

14.4 Background and Methodology

Each potential biomarker (ctDNA amounts, tumor mutation profile and TMB) will be evaluated versus the observed clinical responses.

14.41 Immune Profiling

14.411 Mass Cytometry (CyTOF)
Maxpar ® Direct Immune Profiling System provides a comprehensive evaluation and analysis tool for assessing the abundance and phenotypic characteristics of peripheral mononuclear cells (PBMC). This system is designed using industry-proven antibody clones that can analyze 37 immune cell types from PBMC or whole blood with an optimized 30-marker panel (see table in appendix II)

Whole blood (10 ml) is collected in a heparinized green top tube. PBMC are isolated from whole blood samples using Ficoll-Hypaque at the Biospecimens Accessioning and Processing laboratory (BAP) prior to cryopreservation. Cryopreserved samples are sent in batches to the Mayo Clinic Immune Monitoring Core for analysis by mass cytometry. A concentration of $6 X 10^7$ viable cells/mL is prepared from the cryopreserved sample in Maxpar Cell Staining Buffer (Fluidigm). Fc receptors are blocked by adding Human TruStain FcX (BioLegend) to 4X10 ^6 cells in 50 µL followed by incubation for 10 minutes at room temperature. PBMC are added directly to the ready to assay tubes containing 30 lyophilized metal-conjugated antibodies. After a 45-minute incubation, the cells are washed, and then fixed in 2%

paraformaldehyde. The fixed cells are spun to a pellet, fixative is removed, followed by resuspension in 1 mL of the 125 nM cell-ID Intercalator-Ir (Fluidigm) and incubated overnight at 4°C. Following the overnight incubation, PBMC are resuspended in MaxPar Cell Acquisition Solution (Fluidigm) at 0.5x10 ^6 cells/mL with 0.1X EQ™ Four Element Calibration Beads (Fluidigm). 300,000 events are acquired per sample at an acquisition rate of 250–500 events/second using the Fluidigm Helios mass cytometry platform. Data will be normalized for intra-sample signal drift using EQ™ Four Element Calibration Beads as a calibrator with the CyTOF Software v.6.7.1016. FCS files generated by the Helios are analyzed by Maxpar Pathsetter, an automated analysis system based on GemStoneTM 2.0.41 (Verity Software House, Topsham, ME). The results are reported as numbers of cells exhibiting distinct phenotypes. See Appendix II.

14.412 Tumor mutation profile and tumor mutation burden (TMB)
Samples will be tested for TMB status in plasma as well as level of ctDNA in plasma to evaluate the correlation with clinical outcome.

15.0 Drug Information

15.1 B**intrafusp Alfa** (M7824, MSB0011359C)

15.11 Background

Bintrafusp alfa is an innovative first-in-class bifunctional fusion protein composed of the extracellular domain of the human transforming growth factor β receptor II (TGFβRII or TGFβ Trap) covalently linked via a flexible linker to the C-terminus of each heavy chain of an immunoglobulin (IgG1) antibody blocking programmed death-ligand 1 (anti-PD-L1).

15.12 Formulation

Bintrafusp alfa drug product is provided as a sterile liquid formulation.

The bintrafusp alfa concentrate for solution for infusion (liquid formulation) is packaged at a 10 mg/mL concentration in USP / Ph. Eur. Type I 50R or 20R vials which are filled with drug product solution to allow an extractable volume of 60 mL (600 mg/60 mL) or 20 mL (200mg/20mL)

15.13 Preparation, Storage, and Stability

Bintrafusp alfa must be stored at 2°C to 8°C until use. The storage condition is based on data from ongoing long-term stability studies.

For the preparation of bintrafusp alfa, use the following supplies:

Ancillary supplies

Item	**Acronym of approved materials**
IV bags	Main material: PE, PP, EVA, LDPE bags that are DEHP free and latex free
Infusion set	PUR, PVC, PP, PS, LDPE, PC, PB
Port	Titanium
Catheter	PUR, PVC, PP, PS, LDPE, PB
Adaptor	PUR, PVC, PP, PS, LDPE, silicone
Filter	Membrane material: PES, PSU, Nylon Tubing and connections: PUR, PVC, PP,PS, LDPE
Needle	Steel, preferably 18G needles
Syringe	PP
PE = Polyethylene, PP=Polypropylene, EVA=Ethylene Vinyl Acetate, LDPE=Low Density Poly Ethylene, DEHP = Di(2-ethylhexyl)phthalate, PUR=Polyurethane, PVC=Polyvinylchloride, PS=Polystyrene, PC=Polycarbonate, PB=Polybutadiene	

Allow each vial to equilibrate to room temperature (15-25°C) for a minimum of 30 minutes; and may be used up to 24 hours after equilibration start. A vial that is removed from the refrigerator for equilibration at room temperature may not be stored again at 2-8°C for re-use.

Gently invert the bintrafusp alfa vial(s) several times before use. Do not shake or agitate vigorously. Remove the desired volume of bintrafusp alfa, preferably with a 18G needle, and dilute in 0.9% sodium chloride to a total volume of 250 mL or 500 mL in an empty viaflex bag. The final concentration must be 0.5 mg/mL to 9.6 mg/mL. Gently invert the prepared IV bag 10 times to mix. Do not shake or

agitate the final preparation vigorously. Prime the tubing with and 0.2 micron PES-inline filter with bintrafusp alfa.

The prepared bintrafusp alfa infusion should be kept at room temperature (15-25°C) and used immediately after preparation. In case the prepared infusion cannot be administered immediately after preparation, the acceptable holding time is: no more than 4 hours at room temperature (15-25°C) under aseptic conditions, including infusion time, or no more than 72 hours under refrigerated conditions (2-8°C), including infusion time. Do not freeze or shake the diluted solution. No other drugs should be added to the infusion containers containing bintrafusp alfa.

15.14 Administration

Administer over 60 minutes -10/+20 minutes by intravenous infusion with a 0.2 micron PES-inline filter. A constant infusion rate is achieved by using a microprocessor-controlled infusion pump.

It is recommended (but not mandatory) that immediately following the bintrafusp alfa infusion, using the same tubing, 25-100 mL normal saline are flushed and infused at the same rate to clear the infusion set of residual drug.

15.15 Pharmacokinetic information

The PK profile of bintrafusp alfa is in general typical for a human antibody, with a low clearance and volume of distribution. Its apparent elimination $t_{1/2}$ is approximately 7 days, which is shorter than that for a typical human antibody. The mean volume of distribution at steady state (Vss) was calculated to be 3.72 L. No time-dependent changes in clearance were observed for any tumor type in the population. Based on the PK profile after the first dose of bintrafusp alfa evaluated by NCA , bintrafusp alfa exposures (C_{max}, AUC, and C_{trough}) increased in approximately dose-proportional manner at doses >3 mg/kg.

15.16 Potential drug interactions

Bintrafusp alfa is not expected to have DDI potential because it is primarily metabolized through catabolic pathways, does not cause significant cytokine modulation in vivo or systemic inflammation based on available cytokine data, and does not cause modulation (increase) of 4β-hydroxycholesterol (an endogenous marker of CYP3A4/5 activity) levels based on available exploratory analyses. The expected low risk of DDI for bintrafusp alfa is consistent with lack of reported DDI risk for other anti-TGFβ or anti-PD-L1 antibodies or targeted inhibitors that are in clinical development. Therefore, a dedicated DDI study to investigate the in vivo effects of bintrafusp alfa is not planned. Additionally, preliminary analysis of QT data from 19 participants from study EMR200647-001 dose escalation cohorts up to a dose of bintrafusp alfa 20 mg/kg and a nonclinical safety study revealed no identified proarrhythmic risk.

15.17 Known potential adverse events

Most Common Treatment Emergent Adverse Events (TEAEs) by System/Organ/Class (SOC) and Preferred Term (PT) (≥10% of participants)

Blood and lymphatic system disorders:
Anaemia

Gastrointestinal disorders:
Constipation

Nausea
Abdominal pain
Diarrhoea
Vomiting

General disorders and administration site conditions
Fatigue
Pyrexia
Asthenia
Oedema peripheral

Investigations
Aspartate aminotransferase increased

Metabolism and nutrition disorders
Decreased appetite

Nervous system disorders
Headache

Respiratory, thoracic and mediastinal disorders
Dyspnoea
Cough
Epistaxis

Skin and subcutaneous tissue disorders
Pruritus
Rash

Most Common Treatment-Related TEAEs by SOC and PT (≥5% of participants)

Blood and lymphatic system disorders
Anaemia

Endocrine disorders
Hypothyroidism

Gastrointestinal disorders
Diarrhoea
Nausea

General disorders and administration site conditions
Asthenia
Fatigue

Metabolism and nutrition disorders
Decreased appetite
Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Keratoacanthoma

Skin and subcutaneous tissue disorders
Pruritus
Rash maculo-papular
Rash

15.18 Drug procurement

EMD Serono Research and Development Institute, Inc. will supply the bintrafusp alfa to each enrolling site.

15.19 Nursing guidelines

15.191 Infusion must include a 0.2 micron PES- inline filter and after infusion, line must be flushed with 25-100 ml of NS to finish clearing the line.

15.192 Monitor LFTs.

15.193 Patients may experience gastrointestinal side effects including but not limited to: constipation, diarrhea, and nausea. Treat symptomatically and monitor for effectiveness.

15.194 Pancreatic enzyme elevations have been noted. Monitor patients for signs of pancreatitis, including but not limited to: postprandial pain, generalized abdominal pain, steatorrhea, nausea, and vomiting. Instruct patient to report these to the study team immediately.

15.195 Rash has been reported and is generally maculo-papular in nature.

15.196 Monitor electrolytes, as hyponatremia, and hypokalemia have been reported.

15.2 Docetaxel (Taxotere®, TATER) Commercial Supply

15.21 Background

Antineoplastic Agent, Antimicrotubular, Taxane derivative. Docetaxel promotes the assembly of microtubules from tubulin dimers, and inhibits the depolymerization of tubulin which stabilizes microtubules in the cell. This results in inhibition of DNA, RNA, and protein synthesis. Most activity occurs during the M phase of the cell cycle.

15.22 Formulation

Docetaxel is now available as a one-vial formulation in two concentrations: 10 mg/mL and 20 mg/mL. The older formulation included 2 vials which consisted of a concentrated docetaxel vial and a diluent vial, resulting in a reconstituted concentration of 10 mg/mL. Admixture errors could occur due to the concentration difference between the new formulations of 10 mg/mL and 20 mg/mL and the old formulation (10 mg/mL). Do not use the two-vial formulation with the one-vial formulation for the same admixture product.

15.23 Preparation, storage, and stability

Storage conditions: Store the packaged docetaxel between 2 and 25°C (36 and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

One-vial formulation: Note: One-vial formulation is available in two concentrations: 10 mg/mL and 20 mg/mL. Further reconstitution with diluent is not required. Further dilute for infusion in 250-500 mL of NS or D_5W in a non-DEHP container (e.g., glass, polypropylene, polyolefin) to a final concentration of 0.3-0.74 mg/mL. Gently rotate to mix thoroughly. Solutions prepared from the one-vial formulation and diluted for infusion should be used within 4 hours of preparation (infusion should be completed within 4 hours).

15.24 Administration

Administer IV infusion over 1-hour through nonsorbing polyethylene lined (non-DEHP) tubing; in-line filter is not necessary. **Note:** Premedication with dexamethasone 8 – 10 mg orally twice daily for 3-5 days, beginning the day before docetaxel administration is recommended to decrease the incidence and severity of fluid retention and prevent hypersensitivity reactions and pulmonary/peripheral edema. When administered as sequential infusions, taxane derivatives should be administered before platinum derivatives (cisplatin, carboplatin) to limit myelosuppression and to enhance efficacy. Infusion should be completed within 4 hours of final preparation.

15.25 Pharmacokinetic information

Docetaxel exhibits linear pharmacokinetics at the recommended dosage range.
Distribution: Extensive extravascular distribution and/or tissue binding; $V_{d:}$ 80-90 L/m^2, V_{dss}: 113 L (mean steady state)
Protein binding: ~94% to 97%
Metabolism: Hepatic; oxidation via CYP3A4 to metabolites
Half-life elimination: Terminal: ~11 hours
Excretion: Feces (~75%, <8% as unchanged drug); Urine (~6%)

15.26 Potential Drug Interactions

Cytochrome P450 Effect: Substrate (major) of CYP3A4; **Inhibits** CYP3A4 (weak).

Increased Effect/Toxicity: CYP3A4 inhibitors may increase the levels/effects of docetaxel. Concomitant use of docetaxel with a potent CYP3A4 inhibitor should be avoided. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, a 50% reduction in docetaxel dose should be considered along with close monitoring for docetaxel toxicity. Refer to the package insert or LexiComp[1] for example inhibitors. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin) are administered before taxane derivatives (docetaxel, paclitaxel). Taxane derivatives may enhance the adverse/toxic effect of anthracyclines.

Decreased Effect: CYP3A4 inducers may decrease the levels/effects of paclitaxel. Refer to the package insert or LexiComp[1] for example inducers.

Ethanol/Herb/Nutraceutical Interactions: Avoid ethanol (due to GI irritation). Avoid St John's wort (may decrease docetaxel levels).

Immunosuppressants: (ex: denosumab, pimecrolimus, tacrolimus, etc.) docetaxel may enhance the adverse/toxic effect of immunosuppressants (risk for serious infections may increase)

Myleosuppressived Agents: increased risk of agranulocytosis and/or pancytopenia (ex: clozapine, dipyrone)

BCG: Immunosuppressants may diminish the therapeutic effect of BCG

Treatment with Docetaxel Products May Cause Symptoms of Alcohol Intoxication June 2014

The FDA is warning health care providers and patients that docetaxel injection products contain ethanol, which may cause patients to experience symptoms of alcohol intoxication during and after treatment. The FDA is revising the labels of all docetaxel drug products to warn about this risk. Health care providers should consider the alcohol content of docetaxel products when prescribing or administering the drug to patients, particularly in those whom alcohol intake should be avoided or minimized and when using it in conjunction with other medications.Patients should avoid driving, operating machinery, or performing other activities that are dangerous for one to two hours after docetaxel infusion.

15.27 Known potential adverse events

Consult the package insert for the most current and complete information. Percentages reported for docetaxel Monotherapy; frequency may vary depending on diagnosis, dose, liver function, prior treatment, and premedication. The incidence of adverse events was usually higher in patients with elevated liver function tests.

Common known potential adverse events, >10%:

Cardiovascular: Fluid retention

Central nervous system: Neurosensory events including neuropathy, fever, neuromotor events.

Dermatologic: Alopecia, cutaneous events, nail disorder

Gastrointestinal: Stomatitis, diarrhea, nausea, vomiting
Hematologic: Neutropenia, leukopenia, anemia, thrombocytopenia, febrile neutropenia
Hepatic: Transaminases increased
Neuromuscular & skeletal: Weakness, myalgia
Respiratory: Pulmonary events
Miscellaneous: Infection, hypersensitivity

Less common known potential adverse events, 1% - 10%:
Cardiovascular: Left ventricular ejection fraction decreased, hypotension
Central nervous system: Peripheral motor neuropathy
Dermatologic: Rash/erythema
Gastrointestinal: Taste perversion
Hepatic: Bilirubin increased, alkaline phosphatase increased
Local: Infusion-site reactions including hyperpigmentation, inflammation, redness, dryness, phlebitis, extravasation, swelling of the vein
Neuromuscular and skeletal: Arthralgia
Ocular: Epiphora associated with canalicular stenosis

Rare known potential adverse events, <1% (Limited to important or life-threatening):
Acute myeloid leukemia, acute respiratory distress syndrome, anaphylactic shock, angina, ascites, atrial fibrillation, atrial flutter, bleeding episodes, bronchospasm, cardiac tamponade, chest pain, chest tightness, colitis, conjunctivitis, constipation, cutaneous lupus erythematosus, deep vein thrombosis, dehydration, disseminated intravascular coagulation, drug fever, duodenal ulcer, Dyspnea, dysrhythmia, ECG abnormalities, erythema multiforme, esophagitis, gastrointestinal hemorrhage, gastrointestinal obstruction, gastrointestinal perforation, hand and foot syndrome, hearing loss, heart failure, hepatitis, hypertension, ileus, intestinal pneumonia, ischemic colitis, lacrimal duct obstruction, loss of consciousness (transient), MI, multiorgan failure, Myelodysplastic syndrome, neutropenic enterocolitis, ototoxicity, pleural effusion, pruritus, pulmonary edema, pulmonary embolism, pulmonary fibrosis, radiation pneumonitis, radiation recall, renal insufficiency, seizure, sepsis, sinus tachycardia, Stevens-Johnson syndrome, syncope, toxic epidermal necrolysis, tachycardia, thrombophlebitis, unstable angina, visual disturbances (transient)

15.28 Drug procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 Nursing Guidelines

15.291 Monitor CBC closely, as neutropenia, and thrombocytopenia are common and may be life threatening, and dose limiting. Instruct patient to report any signs or symptoms of infection, any unusual bruising, or bleeding.

15.292 Administer antiemetics as ordered. Evaluate for their effectiveness.

15.293 Monitor for signs/symptoms of hypersensitivity reactions that may include chills, rigors, dyspnea, bronchospasms, etc. Stop infusion immediately and administer proper emergency treatment.

15.294 Because of the risk of anaphylaxis and development of edema, instruct patient that is imperative to take steroid premedications as ordered.

15,295 Instruct patient on proper oral care, as mucositis may occur.

15.296 Advise patient about alopecia.

15.297 Monitor liver function tests.

15.298 Drug is a vesicant. Monitor infusion site frequently for signs of irritation or infiltration. Drug extravasation causes acute streaking, burning pain, and discoloration at the site. Skin may be reddened for several weeks and occasionally blister and/or peel. Reactions are usually reversible over time. Because of this central venous access may be necessary. Discuss with MD if patient has poor peripheral venous access. If docetaxel concentrate or diluted solution comes into contact with skin, wash with soapy water immediately. If it comes into contact with mucosa, wash with warm water immediately.

15.299a Instruct patient to report any signs of peripheral neuropathy to the health care team (pain, numbness, tingling).

15.299b Monitor for signs and symptoms of fluid retention, weight gain, ascites and CHF.

15.299c Instruct patient about possible facial flushing, rash, and skin and nail changes. Monitor for signs and symptoms of hand/foot syndrome. However premedication with steroids can minimize this side effect. Discuss with MD possible ways to manage itching and skin changes that may occur up to a week after docetaxel administration. Advise patients that nails may crack, peel, or fall off all together. This may be a chronic toxicity. Instruct patient to keep nails clean, short and to avoid wearing nail polish or artificial nails.

15.299d In case of overdose, patient should be hospitalized and vital signs monitored. Patient should receive therapeutic G-CSF ASAP after discovery of the overdose.

16.0 Statistical Considerations and Methodology

16.1 Primary Endpoint and Analysis

This randomized Phase II trial will compare the progression-free survival (PFS) of bintrafusp alfa in combination with docetaxel vs. docetaxel alone in patients with advanced NSCLC in the 2nd line setting. Prior studies have shown that the median PFS is generally around 3.8 months for docetaxel alone (Horn L, 2017). It is hoped that the combination of bintrafusp alfa and docetaxel can increase the median PFS rate to at least 7.3 months, which corresponds to a hazard ratio of around 0.52 for comparing PFS between the arms. Prior phase I data suggests that the experimental arm can reach a median PFS of around 7.3 months (ongoing phase I study [EMR200647-001; https://clinicaltrials.gov/ct2/show/NCT02517398] demonstrated a median PFS of 6.8 months for bintrafusp alfa, where the bintrafusp alfa dose was only half the dose that will be used in this study). In addition to PFS, this trial will also compare the overall survival (OS), confirmed response rates, duration of response, and adverse event rates between the treatment arms. In addition, exploratory translational studies will be done as well.

The primary endpoint for this study will compare PFS between bintrafusp alfa combined with docetaxel vs. docetaxel alone in patients with advanced NSCLC. PFS is defined as the time from randomization to the first of either disease progression or death from any cause, where disease progression will be determined based on irRECIST criteria and will be documented at each enrolling site with no central review planned.

16.11 Final Analysis

The primary goal is to compare bintrafusp alfa plus docetaxel vs. docetaxel alone, where the alternative hypothesis is that bintrafusp alfa combined with docetaxel has improved PFS compared to docetaxel alone. We will enter 33 evaluable patients to each arm of the study using a 1:1 randomization scheme (66 evaluable patients in total), unless the study is stopped early at the time of the interim futility analysis (see below). The null hypothesis is that the hazard ratio (HR) ≥1. The alternative hypothesis is that the HR <1. With 66 evaluable patients (33 per arm) and an alpha of 5% (1-sided), we have 80% power to detect a hazard ratio of 0.52 or less, assuming an accrual rate of 3 patients per month. The primary analysis of PFS will be a comparison of the Kaplan-Meier curves for docetaxel + bintrafusp alfa vs. docetaxel alone using a one-sided log-rank test. This analysis will take place after an approximate 27 month accrual period, and after 60 total events have occurred across both arms combined (which should happen after about 12 months of follow-up in all evaluable patients). All patients who meet the eligibility criteria, sign the consent form, and are randomized will be considered evaluable for this endpoint. **To account for possible drop-outs, ineligibles, cancellations, etc., we plan to randomize a total of 80 patients (40 per arm).** Cross-over to bintrafusp alfa will be allowed after progression or intolerable effects on docetaxel alone treatment arm. (Patients already on bintrafusp alfa, will be allowed to continue.)

16.12 Interim Futility Analysis

The interim futility analysis will happen after 30 events are observed across both arms combined. The interim futility boundary was selected using EAST software. We selected a Rho family "Beta" spending function with rho parameter "equal" 2.42. To reject the alternative hypothesis at the interim analysis (i.e., reject

docetaxel + bintrafusp alfa as promising), the HR will need to be >1 for docetaxel + bintrafusp alfa vs. docetaxel alone, which corresponds to a 1-sided p-value greater than 0.50. If the HR is less than or equal to 1 (1-sided p <=0.50), the study will continue to full accrual and the final analysis will be conducted as discussed above.

16.2 Secondary Endpoints and Analysis

The following endpoints will be compared between the two arms: overall survival (OS), confirmed response rates, duration of response, and adverse event rates.

16.21 Overall Survival

Overall survival (OS) is defined as the time from study entry to death from any cause. OS will be estimated using the Kaplan-Meier method, where the log-rank test will be used to compare the 2 treatment arms.

16.22 Confirmed Response Rate

A patient will be classified as a confirmed response per the irRECIST criteria, if they have a partial or complete response for 2 consecutive evaluations at least 4 weeks apart. The proportion of patients with a confirmed response will be calculated and compared between the 2 arms using a Chi-square or Fisher's Exact test.

16.23 Duration of Response

The duration of confirmed responses will be assessed using the Kaplan-Meier method, where the duration of confirmed response will be defined as the time from the first documented date of response (CR or PR) to the date at which progression is first documented. Duration of response will be estimated using the Kaplan-Meier method, where the log-rank test will be used to compare the 2 treatment arms.

16.24 Adverse events

The maximum grade for each type of adverse event will be summarized using CTCAE version 5.0. The frequency and percentage of Grade 3+ adverse events will be compared between the 2 treatment arms. Comparisons between arms will be made by using either the Chi-square or Fisher's Exact test.

16.25 Crossover patients exploratory analysis

In the crossover group that receives bintrafusp alfa alone after disease progression on docetaxel alone, we will assess both the response rate and progression-free survival as an exploratory analysis.

16.3 Translational endpoints

The goals of the translational studies are to evaluate PD-L1 and TGFβ as potential predictive markers of clinical response in tumor biopsies, to evaluate mutation types and numbers (TMB) in plasma or in tumor tissue, assess the association between TMB and clinical outcome, and to evaluate genes or gene signatures as a potential predictive biomarkers of clinical response in tumor biopsies. Due to the limited sample size, these analyses will be hypothesis generating and descriptive in nature. Descriptive statistics will be summarized and the blood and tissue marker data will be correlated with clinical endpoints (response, duration of response, OS, PFS, etc.). For time-to-event data, the Kaplan-Meier method, log-rank tests, and Cox proportional hazards models will be used.

For categorical data, we'll use the Fisher's exact or Chi-square test. For marker data used to predict binary outcomes (i.e. response vs. no response), we'll use Logistic regression models.

16.4 Total Sample Size and study duration

A maximum of 66 evaluable patients (33 per arm) will be accrued onto this randomized phase II study unless the study is closed early for excessive toxicity or lack of efficacy. To account for possible drop-outs, ineligibles, cancellations, etc., we plan to randomize a total of 80 patients (40 per arm). The expected accrual rate is about 3 patients per month. With this accrual rate, we expect to finish accrual within about 27 months, assuming we accrue 80 total patients. We anticipate that the study will take approximately 42 months to complete. This allows a 12-month follow-up for the final patient enrolled, along with data entry, data clean-up, and analysis.

16.5 Data & Safety Monitoring

16.51 Safety review

The principal investigator(s) and the study statistician will review the study monthly to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least biannually, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rules

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below. Accrual may be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (ie, an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy the following in each arm separately:

- If 4 or more of the first 10 patients (or 40% or more of all patients after 10 are accrued) experience a Grade 4 non-laboratory AE.
- If 2 or more experience a Grade 5 AE at any time.

After consideration by the study team (study chair, statistician, etc.), a decision will be made as to whether accrual can be resumed.

16.6 Subset Analyses for Minorities

16.61 Study availability

This study will be available to all eligible patients, regardless of gender, race or ethnic origin.

16.62 Statistical analysis by subset

There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will

look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.63 Regional population

The geographical region served by MCCC has a population which includes approximately 3% minorities. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	3	3	6
Not Hispanic or Latino	37	37	74
Ethnic Category: Total of all subjects	**40**	**40**	**80**
Racial Category			
American Indian or Alaskan Native	1	0	1
Asian	0	1	1
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	38	38	76
Racial Category: Total of all subjects	**40**	**40**	**80**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa.

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Research Study (Section for more information)	Specimen Purpose (check all that apply)	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	Baseline – after Registration and prior to treatment on C1D1[17]	End of Cycle 1 Prior to Cycle 2[18]	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
PD-L1	☒ Correlative	Mandatory	FFPE	1 cores	X	X	No	Ambient
DNA seq (TMB)	☒ Correlative	Mandatory	FFPE	10 slides	X	X	No	Ambient
RNA seq (TGFβ)	☒ Correlative	Mandatory	FFPE	2 cores	X	X	No	Ambient
Future research	☒ Banking	Mandatory	FFPE	1 core	X	X	No	Ambient

[17] Baseline samples must be from fresh biopsy. If biopsy is attempted and tissue is not obtained the patient is still eligible.
[18] Mandatory fresh biopsy required at end of Cycle 1, prior to treatment on Cycle 2, Day 1.

17.2 Diagnostic Slides from Original and /or Recurrent Tissue

If fresh biopsy tissue is not available after biopsy is attempted (per Section 17.311 below), study pathologist will request blocks from Tissue Registry to determine best option for study use. Pathologist will request a minimum of 4 slides including one H&E cut at 4 microns. These slides will be used for PD-L1, and, if sufficient tissue is available, RNA and/or DNA sequencing per Section 17.1.

17.3 Correlative Tissue Collection

17.31 Biopsies for research tissue collection

NOTE: Consultation with Interventional Radiology is required prior to scheduling **lung** biopsy (not needed for liver, lymph node, or abdominal/ retroperitoneal)

17.311 Baseline biopsy

Fresh biopsy is mandatory at Baseline (prior to treatment on Cycle 1, Day 1). If biopsy is attempted and tissue is not obtained for any reason, the patient is still eligible provided previously obtained tissue is available.

If fresh biopsy at baseline is unsuccessful, tumor samples obtained by endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies, and surgical specimens that are <6 months old and adequate for biomarker analysis are mandatory to evaluate the association of PD-L1 protein expression as well as other immune or tumor cell markers with the observed clinical responses. Biopsies obtained by fine needle aspiration are not acceptable.

17.312 Biopsy at End of Cycle 1 (prior to C2D1)

Fresh biopsies are mandatory prior to Cycle 2, Day 1, unless deemed unfeasible by the investigator or interventional radiologist.

17.31 Tissue kits will <u>not</u> be provided for this protocol.

17.32 Paraffin Embedded Tissue

17.321 Rochester

Tissue sections can be picked up from Interventional Radiology by the study coordinator for routing.

Coordinator will route tissue samples for formalin fixing/paraffin embedding (block creation and one H&E per block).

Once blocks and slides are created, coordinator will route to Study Pathologist (Dr Anja Roden) for review with MC1821 Tissue Specimen Submission Form so all blocks can be noted on form.

Once pathologist has reviewed blocks/slides can be sent to the Pathology Coordinator Office at NW Clinic via General Service.

Be sure to include the pathology report and the completed MC1821 Specimen Submission Tissue Form with patient ID/protocol #, collection date, tissue submitted, and a contact person for questions

17.322 Arizona and Florida

FFPE blocks will be created at the time of the research biopsy with one block per core and one H&E per block.

AZ and FL will ship FFPE tissue blocks with accompanying H&E to Rochester, MN, at the address below and include the completed MC1821 Specimen Submission Tissue Form with patient ID/protocol #, collection date, list of tissue blocks submitted, and a contact person for questions.
NOTE: Please include room temperature cool pack if weather conditions are hot in either shipping or receiving location.

Send blocks/slides and forms to:
Pathology Coordinators Operations Office
Attn: PC office (Amanda Sand/MC 1821)
RO-FF-3-24-CC/NW Clinic
200 First Street SW
Rochester, MN 55905
Telephone: 507/284-3559

17.323 Pathology Coordinator in Rochester will accession.

17.324 All tissue will be stored in Rochester until the end of the study.

17.33 Frozen Tissue - NONE

17.4 Background and Methodology

17.41 PD-L1

PD-L1 will be processed through Mayo Clinical Laboratory in Rochester, MN using best available clone at the time the assay is being run. Current expectation is to use 22C3.

17.43 DNA sequencing (TMB)

At the end of the study, tissue samples will be processed for DNA seq per best available methods at that time.

17.42 RNA sequencing (TGFβ)

At the end of the study, tissue samples will be processed for RNA seq per best available methods at that time

17.44 Banking for future research

As part of ongoing research at the Mayo Clinic, we will retain tissue for future research studies, according to patient consent information. Samples will be stored until specific analyses are identified and may be used for exploratory biomarker analyses, validation studies, or potential diagnostic development. As protocols are developed, they will be presented for IRB review and approval.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Survival Follow-up

See Section 4.

18.3 CRF completion

This study will use Medidata Rave® for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on the organization roster at the enrolling site.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for diagnosis and progression prior to study entry as well as for evidence of response to study therapy and progression after study therapy. These documents should be submitted within 14 days of registration (for prior to study entry materials) or within 14 days after the visit at which response or progression is determined.

18.6 Overdue lists

A list of overdue forms and outstanding queries will be available in Rave through the Rave Task Summary. In addition to this, the Overdue Materials report is available on the Cancer Center Systems homepage.

19.0 Budget

19.1 Costs charged to patient

Routine clinical care including the cost of docetaxel and its administration.

19.2 Tests to be research funded

Research testing on blood and tissue specimens

Research biopsy prior to treatment and at end of Cycle 1 (prior to Cycle 2, Day 1)

19.3 Other budget concerns:

EMD-Serono will provide Mayo Clinic with funding to support the costs of running this study.

EMD-Serono will provide study drug, bintrafusp alfa, for use in this study

20.0 References

EMD Serono Research and Development Institute Inc. (2019, April 10). M7824 Investigator's Brochure. *Version 5.0*. Billerica, MA, USA: EMD Serono Research and Development Institute Inc.

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Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

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

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix II Peripheral Blood Mononuclear Cells (PBMC) Panel for Cytof Analysis

Mayo Immune Monitoring Core, Guggenheim 5-27

No.	Species	Clone	Metal	Target
1	Human	HI30	089Y	CD45
2	Human	G034E3	141Pr	CD196/CCR6
3	Human	6H6	143Nd	CD123/IL-3R
4	Human	HIB19	144Nd	CD19
5	Human	RPA-T8	145Nd	CD4
6	Human	RPA-T8	146Nd	CD8a
7	Human	Bu15	147Sm	CD11c
8	Human	3G8	148Nd	CD16
9	Human	UCHL1	149Sm	CD45RO
10	Human	HI100	150Nd	CD45RA
11	Human	HP_3G10	151Eu	CD161
12	Human	L291H4	152Sm	CD194/CCR4
13	Human	BC96	153Eu	CD25/IL-2R
14	Human	O323	154Sm	CD27
15	Human	HCD57	155Gd	CD57
16	Human	G025H7	156Gd	CD183/CXCR3
17	Human	J252D4	158Gd	CD185/CXCR5
18	Human	CD28.2	160Gd	CD28
19	Human	HB-7	161Dy	CD38
20	Human	NCAM16.2	163Dy	CD56/NCAM
21	Human	B1	164Dy	TCRgd
22	Human	BM16	166Er	CD294
23	Human	G043H7	167Er	CD197/CCR7
24	Human	63D3	168Er	CD14
25	Human	UCHT1	170Er	CD3
26	Human	2H7	171Yb	CD20
27	Human	G10F5	172Yb	CD66b
28	Human	LN3	173Yb	HLA-DR
29	Human	IA6-2	174Yb	IgD
30	Human	A019D5	176Yb	CD127/IL-7Ra