Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	An Open-label, Multicenter Follow-up Study to Collect Long-term Data on Participants from Multiple Bintrafusp alfa (M7824) Clinical Studies
Study Number:	MS200647_0054
Merck Compound:	M7824
Protocol Version:	30 November 2021/Version 2.0
Merck Registered Compound Name in Japan:	Not applicable
Study Phase:	Phase III
Short Title:	Bintrafusp alfa Program Rollover Study
Acronym or Abbreviation:	CCI [redacted]
Coordinating Investigator:	PPD
Sponsor Name and Legal Registered Address:	Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US and Canada and Japan: Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 64293, Darmstadt, Germany In the US and Canada: EMD Serono Research & Development Institute, Inc. an affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, 01821, USA Local Sponsor for Sites in Japan: Merck Biopharma Co., Ltd. Japan an affiliate of Merck KGaA, Darmstadt, Germany Arco Tower, 1-8-1 Shimomeguro Meguro-ku, Tokyo 153-8926, Japan

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Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	13 May 2021
2.0	Global Amendment	30 November 2021

Protocol Version 2.0 (29-November-2021)

Overall Rationale for the Amendment

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The primary purpose of this amendment is to update the benefit/risk of the study and the management of bleeding events.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Height, Free T4 and TSH tests to be done every 6 weeks	Changes are made to align with rest of the protocol section. Free T4 and TSH test timepoints are updated to reflect only during Treatment Phase.
2.3 Benefit/Risk Assessment	Revised text to add the discontinuation of 3 randomized controlled studies	To update the benefit/risk section.
2.3.1 Risk Assessment Table 2	Editorial changes to clarify Impaired wound healing and embryofetal toxicity as an important potential risk for bintrafusp alfa	Editorial changes for clarification.
6.9 Special Precautions	The section has been merged into Section 7.1	Changes are made to align with the current protocol template.
7.1 Discontinuation of Study Intervention	Discontinuation of study intervention for participants from Study MS200647_0005 is clarified.	Discontinuation of study intervention is as specified in the parent protocol for participants from MS200647_0005.
8.3.6.2 Immune-related Adverse Evens	Immune related pneumonitis has been added For some conditions like endocrinopathies, hepatitis action to be taken on study treatment has been deleted.	The missing event has been added to complete list of irAEs. Information has been deleted to maintain consistency across protocols for the bitrafusp alfa.

Section # and Name	Description of Change	Brief Rationale
8.3.6.5 Bleeding Adverse Events	Guidance has been provided on bintrafusp alfa dose modification/interruption when Grade ≥ 3 bleeding event and rapid decrease in hemoglobin is observed during the study.	The dose modification/interruption guideline will help Investigator to ensure participants safety during the study.
8.3.7 Other Important Potential Risks	The section has been deleted as information is already presented in Section 2.3.1	Information is already presented in Section 2.3.1 Risk Assessment. Therefore, text has been deleted from Section 8.3.7.
8.4 Treatment of overdose	The definition of overdose is clarified	To clarify overdose.
11 Appendices Clinical laboratory tests	Free T4 and TSH tests are removed from the list of tests at Screening	To align with schedule of activities table as these tests to be done during Treatment Phase.
Note: Minor changes have been performed throughout the protocol to address consistency pertaining to major changes done in the protocol or to add further clarity and precision.		

Free T4 = free thyroxine; TSH = thyroid-stimulating hormone; irAEs = Immune-related adverse events

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1 Protocol Summary

1.1 Synopsis

Protocol Title: An Open-label, Multicenter Follow-up Study to Collect Long-term Data on Participants from Multiple Bintrafusp alfa (M7824) Clinical Studies

Short Title: Bintrafusp alfa Program Rollover Study

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Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate clinical safety of bintrafusp alfa in participants with solid tumors who continue treatment after completion of the primary/main analyses in parent bintrafusp alfa studies	Occurrence of AEs and treatment-related AEs, starting from baseline in parent study
Secondary	
To evaluate clinical efficacy of bintrafusp alfa based on OS	OS, starting from baseline in parent study

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Abbreviations: AE=Adverse Events; CCI CCI OS=Overall survival, RECIST=response evaluation criteria for solid tumors.

Overall Design: This is a Phase III, open-label, multicenter, rollover study designed to provide participants from parent bintrafusp alfa studies with continuous access to bintrafusp alfa, to monitor the safety and tolerability of bintrafusp alfa, and to collect long-term efficacy and safety data. Participants in a parent bintrafusp alfa study where the primary/main analysis has been completed or after discontinuation of study before primary/main analysis has been completed will be eligible for enrollment in the rollover study. Specifically, the following participants will be eligible for enrollment in this rollover study:

- Participants who are currently on active bintrafusp alfa treatment (alone as a monotherapy or following discontinuation of other combination treatment agents) in an eligible parent study without treatment interruption at the time of rollover study enrollment.
- Participants who:
  - Achieved confirmed complete response (CR), partial response (PR), or stable disease (SD) in an eligible parent study
  - Discontinued bintrafusp alfa treatment according to the parent study protocol
  - Subsequently developed disease progression
  - Are willing to re-start bintrafusp alfa treatment deemed potentially beneficial by the participants' physicians.

- Participants who:
  - Discontinued from bintrafusp alfa treatment in an eligible parent study due to an AE(s) that was subsequently well managed or resolved after stopping therapy
  - And are willing to re-start bintrafusp alfa treatment if deemed potentially beneficial by the participants' physicians and provided that the parent study protocol permits reinitiation of bintrafusp alfa if a participant discontinued treatment due to toxicity.

Note: Participants who have had AEs requiring permanent treatment discontinuation, like certain immune-related adverse events (irAEs) or certain bleeding events are excluded from participation in the rollover study.

Participants can be transferred from their respective parent bintrafusp alfa study to this rollover study once the primary/main analysis in the parent study has been completed or after discontinuation of study before primary/main analysis has been completed. Participants may also be transferred upon Sponsor decision in case the parent study is terminated for any reason as specified in the parent study protocol and there is a medical need for participants to continue to be treated with bintrafusp alfa that cannot be otherwise supplied. The final decision whether to transfer participants from the parent study rests with the Sponsor.

Brief Summary:

Brief Summary:

This study is designed to provide continuous access to treatment with bintrafusp alfa for eligible participants from ongoing bintrafusp alfa parent studies, and to collect long-term safety and efficacy data:

- Study Duration: All participants in this rollover study will be treated with bintrafusp alfa until meeting defined criteria in the initial study protocol (parent) for discontinuation, until study intervention is commercially accessible and provisioned via marketed product, or until end of study. The study also includes a 5 years survival follow-up after last dose of the study treatment.
- Treatment Duration: Treatment under the rollover protocol according to the interval and dosing schedule in the parent protocol until discontinuation.
- Treatment Frequency: 1200 mg once every 2 weeks; 2400 mg once every 2 weeks; 2400 mg once every 3 weeks. Other dose amount as specified in the participant's parent protocol: once every 2 weeks.
- Bintrafusp alfa is not available through an expanded access program.

Number of Participants: The maximum number of participants who can enter from parent studies is not limited and is dependent on the number of eligible participants from the parent studies. Based on the current status of participants in the ongoing bintrafusp alfa parent studies, it is estimated that at least 10 participants will enter this study (as of April 2021 eCRF data).

Study Intervention Groups and Duration: This is an open-label, single arm study.

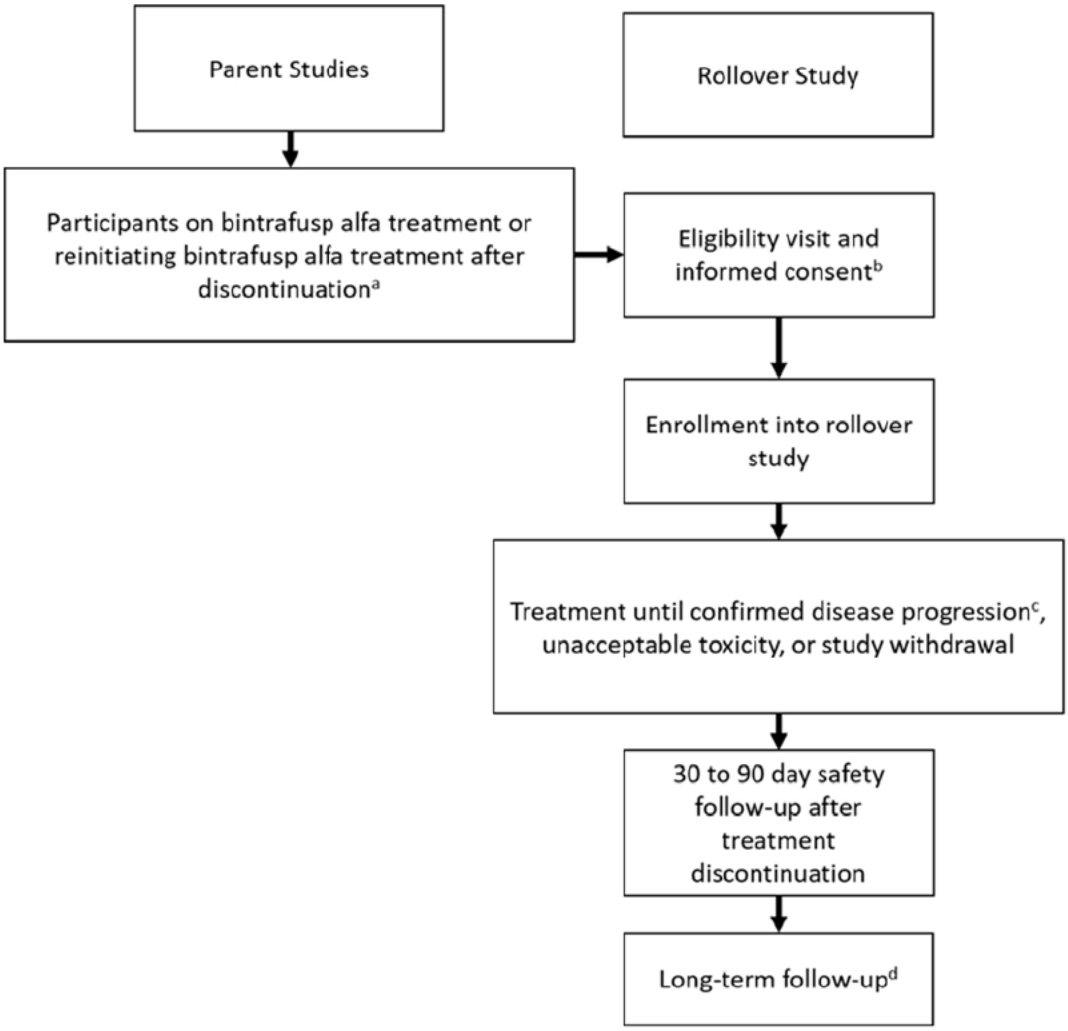
The study includes:

- Treatment with bintrafusp alfa until disease progression per RECIST v1.1, clinical deterioration, unacceptable toxicity, or any other criterion for withdrawal from study intervention or study is fulfilled.
- In the case of progressive disease, treatment may continue if the participant's performance status (PS) has remained at least stable in the opinion of the Investigator, the participant will benefit from continued treatment, in the opinion of the Investigator and if other criteria are fulfilled as outlined in the protocol.
- Participants who have experienced a confirmed CR should continue treatment for a maximum of 24 months after confirmation of response (at the discretion of the Investigator). If the Investigator believes that a participant with confirmed CR may benefit from treatment beyond 24 months, it may be permissible to continue treatment after discussion with the Medical Monitor and the Sponsor's Medical Responsible.
- Participants with SD or PR who are receiving bintrafusp alfa should continue treatment until meeting criteria for discontinuation.

- Safety Follow-up will continue until 90 days after the last dose of bintrafusp alfa. The 90-day Safety Follow-up is allowed to be conducted via telephone calls unless there is medical necessity requiring a clinical visit.
- Long-term Follow-up should be performed every 12 weeks after the Safety Follow-up according to the Schedule of Activities. Long-term Follow-up should be performed telephone calls unless there is medical necessity requiring a clinical visit
- Survival Follow-up will continue until a maximum of 5 years after the last participant receives the last dose of bintrafusp alfa. This duration may be shortened at the discretion of the Sponsor for any given indication.

Involvement of Special Committee(s): No

1.2 Schema



[a]Participants in eligible parent studies who discontinued treatment due to confirmed CR, PR, or SD, subsequently developed disease progression or due to an AE(s) that is subsequently well managed or resolved after stopping therapy are eligible for enrollment in order to reinitiate treatment with bintrafusp alfa in the rollover study, as permitted by the parent study protocol.

[b] Informed consent may be obtained during the last scheduled treatment visit of the parent study, provided that the participant is on active treatment in the parent study at the time of the visit. Informed consent will be obtained during Eligibility Visit of the rollover study from participants who discontinued treatment due to confirmed CR, PR, or SD, subsequently developed disease progression or due to an AE(s) in eligible parent studies.

[c] In the case of progressive disease, treatment may continue if the participant's performance status (PS) has remained at least stable in the opinion of the Investigator, the participant will benefit from continued treatment, in the opinion of the Investigator and if other criteria are fulfilled as outlined in the protocol (see Section 7.1.2).

[d] Overall survival and post-treatment anticancer therapies data collection will continue for all participants. For participants without disease progression at the time of rollover or treatment discontinuation, tumor assessment data collection will continue until PD or until 30 days after end of treatment with bintrafusp alfa, whichever is later. For details on reinitiating course of treatment refer to Section 6.7

1.3 Schedule of Activities

The Schedule of Activities is presented in Table 1.

Table 1 Schedule of Activities

Assessments and Procedures	Eligibility Visit	Treatment Phase	End of Treatment	Safety Follow-up		Long-term Follow-up	Notes
	Day -28 to -1	Day 1 Until Discontinuation of Treatment (± 3 days); See Notes	See Notes	Visit 30 Days After Last Treatment (± 5 days)	Phone Call 90 Days After Last Treatment (± 5 days)	Phone Call Every 12 weeks (± 2 weeks)	Treatment Phase: Participants entering this rollover study on active treatment with bintrafusp alfa in a parent study should begin Day 1 treatment under the rollover protocol according to the interval and dosing schedule in the parent protocol. End of Treatment: Visit should be held within 30 days of last treatment for participants discontinuing due to AEs. For all others, visit should be held within 7 days of last treatment or prior to any new antineoplastic therapy, whichever is earlier.
Informed Consent	X						If the participant is on active treatment in the parent study, informed consent can be obtained during the last scheduled treatment visit of the parent study. Informed consent will be obtained during Eligibility Visit of the Rollover study from participants who discontinued due to confirmed CR, PR, or SD, subsequently developed disease progression or due to an AE(s) in eligible parent studies.
Inclusion/ Exclusion Criteria	X						
Enrollment	X						Enrollment (if eligible) after fulfilling Inclusion/Exclusion Criteria (see Section 5.1 and Section 5.2).
Physical Exam		According to SOC and institutional guidelines					
Vital Signs							
ECOG PS							

Assessments and Procedures	Eligibility Visit	Treatment Phase	End of Treatment	Safety Follow-up		Long-term Follow-up	Notes
	Day -28 to -1	Day 1 Until Discontinuation of Treatment (± 3 days); See Notes	See Notes	Visit 30 Days After Last Treatment (± 5 days)	Phone Call 90 Days After Last Treatment (± 5 days)	Phone Call Every 12 weeks (± 2 weeks)	Treatment Phase: Participants entering this rollover study on active treatment with bintrafusp alfa in a parent study should begin Day 1 treatment under the rollover protocol according to the interval and dosing schedule in the parent protocol. End of Treatment: Visit should be held within 30 days of last treatment for participants discontinuing due to AEs. For all others, visit should be held within 7 days of last treatment or prior to any new antineoplastic therapy, whichever is earlier.
Pregnancy test		Day 1 of every other cycle		X			The β-hCG pregnancy test should be determined from either a urine or serum sample according to local practice.
Skin assessment	X	Every 6 weeks	X	X			See Section 8.3.6.3.
Weight		Participants on mg/kg dosing: Day 1 of each cycle; Participants on flat dose: according to SOC					Cycle length determined based upon treatment cycle duration from parent protocol. For participants continuing to receive bintrafusp alfa doses based on their weight (mg/kg dosing), body weight should be determined prior to bintrafusp alfa administration.
Height	X						
ECG		According to SOC and institutional guidelines					
Hematology							See Section 8.2.4 and Appendix 6 for further details. Blood samples must be drawn prior to dosing and results of selected laboratory tests (see Appendix 6) must be reviewed within 3 days prior to dosing.
Biochemistry							
Urinalysis							
Free T4 and TSH		Every 6 weeks		X			

Assessments and Procedures	Eligibility Visit	Treatment Phase	End of Treatment	Safety Follow-up		Long-term Follow-up	Notes
	Day -28 to -1	**Day 1 Until Discontinuation of Treatment (± 3 days); See Notes**	**See Notes**	**Visit 30 Days After Last Treatment (± 5 days)**	**Phone Call 90 Days After Last Treatment (± 5 days)**	**Phone Call Every 12 weeks (± 2 weeks)**	Treatment Phase: Participants entering this rollover study on active treatment with bintrafusp alfa in a parent study should begin Day 1 treatment under the rollover protocol according to the interval and dosing schedule in the parent protocol. End of Treatment: Visit should be held within 30 days of last treatment for participants discontinuing due to AEs. For all others, visit should be held within 7 days of last treatment or prior to any new antineoplastic therapy, whichever is earlier.
Viral serology (HIV)	As clinically indicated in participants with a history of HIV infection						See Appendix 6 for details. Not required for all participants. Only applicable for participants with a history of HIV. Participants must be adequately consented per local regulations for any HIV-related testing.
Viral serology (HBV and HCV)	As clinically indicated in participants with a history of HBV or HCV infection						See Appendix 6 for details.
Tumor evaluation/staging	X	Until PD or until 30 days after end of treatment with bintrafusp alfa, whichever is later, OR according to SOC and institutional guidelines					For participants reinitiating bintrafusp alfa treatment at study entry (or reinitiating treatment after treatment discontinuation in the rollover study; see Section 7.1.2), a rebaseline scan must be performed prior to treatment. For participants entering this rollover study on active treatment with bintrafusp alfa, the baseline assessment from the parent study will be used for progression determination (see Section 8.1.1) and therefore imaging is not required during the Eligibility Visit. Tumor response assessments by CT scan or MRI will be performed according to site SOC/institutional guidelines (see Section 8.1.1). For treatment beyond disease progression, see Section 7.1.2. The tumor response assessments will be performed according to RECIST v1.1

Assessments and Procedures	Eligibility Visit	Treatment Phase	End of Treatment	Safety Follow-up		Long-term Follow-up	Notes
	Day -28 to -1	Day 1 Until Discontinuation of Treatment (± 3 days); See Notes	See Notes	Visit 30 Days After Last Treatment (± 5 days)	Phone Call 90 Days After Last Treatment (± 5 days)	Phone Call Every 12 weeks (± 2 weeks)	Treatment Phase: Participants entering this rollover study on active treatment with bintrafusp alfa in a parent study should begin Day 1 treatment under the rollover protocol according to the interval and dosing schedule in the parent protocol. End of Treatment: Visit should be held within 30 days of last treatment for participants discontinuing due to AEs. For all others, visit should be held within 7 days of last treatment or prior to any new antineoplastic therapy, whichever is earlier.
OS and post-treatment anticancer therapies				X	X	X	Survival information (including assessment of any further anticancer therapy) will be collected every 12 weeks (± 2 weeks) up to the end of the study (see Section 4.4).
Premedication (optional) and study intervention administration		Day 1 of each cycle					See Section 6.5.2 and Section 8.3.6 for premedication information Participants on bintrafusp alfa will continue treatment until disease progression, unacceptable toxicity, or study withdrawal (see Section 7). Cycle length determined based upon treatment cycle duration from the parent protocol.
Documentation of AEs	X	X	X	X	X		See Section 8.3 and Appendix 4 for safety recording and reporting. The Safety Follow-up and Long-term Follow-up visits may be conducted by telephone calls as necessary, unless there is a medical necessity requiring a clinical visit.
Concomitant medications	X	X	X	X			

AE = adverse event; β-hCG = beta-human chorionic gonadotropin; CR=complete response, CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; OS = overall survival; PD = progressive disease; PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease, SOC = standard of care; Free T4 = free thyroxine; TSH = thyroid-stimulating hormone.

2 Introduction

Bintrafusp alfa (M7824) is an innovative first-in-class bifunctional fusion protein composed of the extracellular domain of the human transforming growth factor β (TGFβ) receptor II (TGFβRII or TGFβ Trap) covalently linked via a flexible linker to the C-terminus of each heavy chain of an immunoglobulin G1 (IgG1) antibody blocking programmed death-ligand 1 (anti-PD-L1). Bintrafusp alfa is currently in clinical development with multiple ongoing Phase I to III clinical studies, in which bintrafusp alfa is being investigated as a monotherapy or in combination with other anticancer treatments in participants with different types of malignancies.

Detailed information on the chemistry, pharmacology, efficacy, and safety of bintrafusp alfa is in the Investigator's Brochure (IB).

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2.2 Background

Bintrafusp alfa is being developed as an immuno-oncology agent for treatment in a number of tumor types, including non-small cell lung cancer (NSCLC), biliary tract cancer (BTC), cervical cancer, and triple-negative breast cancer (TNBC). Bintrafusp alfa is designed to simultaneously target 2 pathways that have independent and complementary immunosuppressive functions in the tumor microenvironment. Programmed-death ligand 1 (PD-L1) signaling plays a key role in the immunosuppressive network that dampens T-cell activity and TGFβ functions as an autocrine or paracrine signal within the local tumor microenvironment, where it promotes tumor progression.

The novel design of bintrafusp alfa, which binds all 3 isoforms of TGFβ and simultaneously inhibits the anti-PD-L1 pathway in the tumor microenvironment, may be more effective than agents targeting PD-L1 and TGFβ separately. Nonclinical experiments conducted by the Sponsor (Lan 2018) demonstrated that bintrafusp alfa strongly enhances antitumor activity and prolongs survival in mouse tumor models above the effect of either an anti-PD-L1 control antibody or the TGFβ Trap control alone (at the same molarity as bintrafusp alfa).

The overall safety profile of bintrafusp alfa at 1,200 mg every 2 weeks as a monotherapy in close to 700 participants with various cancer types is manageable; no new safety signals emerged in the 2 Phase I studies (EMR200647-001 and MS200647-0008) compared with therapies targeting PD-L1 or TGFβ. Albeit limited experience to date, the safety profile in participants treated at a dose level of 2400 mg every 3 weeks appears to be consistent with the safety profile in patients treated at lower doses.

In addition, currently available safety data on bintrafusp alfa in combination with chemotherapy indicated no increased risks compared to what can be expected from current experience with chemotherapy and bintrafusp alfa alone.

2.3 Benefit/Risk Assessment

Bintrafusp alfa, a first-in-class bifunctional fusion protein that targets the tumor microenvironment where it blocks both the cell intrinsic programmed cell death protein 1 (PD-1)/PD-L1 interaction and the immunosuppressive TGFβ, is hypothesized to be more effective than agents that target only a single pathway. With the clinical activity of bintrafusp alfa observed in a number of tumor types, including NSCLC, biliary tract cancer, cervical cancer, and TNBC, together with the safety profile that appears to be manageable given the advanced disease of the studied populations, the benefit/risk evaluation is considered favorable to conduct this rollover study. The emerging safety profile of bintrafusp alfa across tumor types is manageable and consistent with other therapies targeting either PD-L1 (Brahmer 2012, D'Angelo 2018 and Kelly 2018) or TGFβ pathways (mainly referencing Phase I fresolimumab clinical study; Morris 2014). The risks of bintrafusp alfa are classified as presented in Table 2.

The data review outcome from the 3 randomized controlled studies in NSCLC and BTC (MS200647_0037 [NCT03631706], MS200647_0055 [NCT04066491] and MS200647_0005 [NCT03840902]), which have been discontinued in the course of 2021, appears to indicate, consistently across 2 indications, either poorer observed hazard ratios for progression free survival (PFS) and OS in the experimental arms with bintrafusp alfa or low likelihood for bintrafusp alfa to add benefits compared to standard of care. No new safety signal has been identified. The data review also showed that cases of early progression and death (i.e., within 60 days after start of treatment) were observed more frequently with bintrafusp alfa: 16 patients (10.6%) versus 9 patients (5.9%) in NSCLC Stage IV first line (bintrafusp versus pembrolizumab, MS200647_0037); 11 patients (7.5%) versus 2 patients (1.3%) in BTC first line (bintrafusp in combination with chemotherapy versus placebo plus chemotherapy, MS200647-0055); immature data with 3 patients (4.1%) versus 2 patients (2.6%) in NSCLC Stage III (bintrafusp plus concurrent chemoradiation followed by bintrafusp maintenance versus chemoradiation followed by durvalumab, MS200647-0005). Early deaths were due to progressive disease, signs and symptoms of progressive disease, or known treatment toxicities.

Two types of participants will be eligible for this study: participants on treatment with bintrafusp alfa in an eligible parent study after the primary/main analysis has been completed, and participants who have discontinued treatment in an eligible parent study and are reinitiating treatment in this rollover study (provided that the parent protocol allows reinitiation of treatment). Participants continuing treatment in the rollover study and demonstrating benefit from the active treatment will be transferred from the parent study to this rollover study. Participants reinitiating treatment in the rollover study have previously demonstrated benefit from bintrafusp alfa and reinitiation is deemed a reasonable option that may provide clinical benefit. Based on the available nonclinical and clinical data to date, inclusion in the rollover study, as specified in this protocol, is considered justifiable for both groups.

Of note, participants that are reinitiating after discontinuing their prior course of bintrafusp alfa treatment due to an adverse event (AE) are required to have that AE completely resolved or well

controlled, and the decision to reinitiate must be discussed with the Medical Monitor prior to enrollment to determine the suitability of the participant. This discussion should confirm the status of the AE and confirm that the likelihood of recurrence/worsening of the AE that led to the prior discontinuation is low. The outcome of the discussion will provide an opportunity to weigh the risk against prior benefit demonstrated while on treatment and assess the benefit-risk for individual participants prior to enrollment.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of bintrafusp alfa may be found in Section 2.3.1 and the current IB.

Based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

2.3.1 Risk Assessment

The important identified and potential risks, as well the identified risk of infusion-related reaction (IRRs) were analyzed in depth based on a pooled dataset of N = 765 participants who received bintrafusp alfa monotherapy at 12,00 mg once every 2 weeks.

Table 2 Bintrafusp alfa - Identified and Potential Risks with Mitigation Strategies

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Bintrafusp alfa		
Important Identified Risks:		
Immune-related adverse events[a] (IrAEs): • Immune-related pneumonitis • Immune-related hepatitis • Immune-related colitis • Immune-related nephritis and renal dysfunction • Immune-related endocrinopathies: thyroid disorders, adrenal insufficiency, Type 1 diabetes mellitus, pituitary disorders • Immune-related rash • Other immune-related events (myositis, myocarditis, encephalitis)	In general, immune-related adverse events (irAEs) are known class effects of anti-PD-1/anti-PD-L1 anticancer immunotherapies (Postow 2018) and have been carefully monitored in the bintrafusp alfa clinical studies. irAEs of different nature have occurred in patients receiving bintrafusp alfa in the pooled monotherapy studies and these irAEs have been classified as important identified risks.	Management of irAEs and instructions for study treatment discontinuation or interruption in case of irAEs is described in Section 8.3.6.2. Regular laboratory tests on parameters indicative for autoimmune disorders, such as thyroid stimulating hormone (TSH), will be performed as detailed in the Schedule of Activities (see Table 1).

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Human transforming growth factor β (TGFβ) inhibition mediated skin reactions[a]	TGFβ inhibition mediated skin reactions are important identified risks because neutralization of TGFβ by bintrafusp alfa may induce the development of skin lesions such as hyperkeratosis, keratoacanthoma, cutaneous squamous cell carcinoma (Lacouture 2015). Such skin lesions have indeed been observed in the clinical studies with bintrafusp alfa, but not in patients treated with the anti-PD L1 antibody avelumab. Thus, it is plausible that skin tumors observed in patients treated with bintrafusp alfa may be related to the TGFβ signal pathway inhibition.	Monitoring will include skin assessments as defined in the Schedule of Activities (see Table 1). Management of TGFβ inhibition mediated skin reactions is described in Section 8.3.6.3.
Anemia	Anemia is considered an important identified risk. Toxicological findings with bintrafusp alfa in cynomolgus monkey indicated a decrease in hemoglobin, red blood cell count, and hematocrit. This decrease was fully reversible or showed trend towards recovery after treatment discontinuation. These nonclinical findings were also observed in clinical studies. The mechanism for the effect remains to be fully elucidated, however, the occurrence of hemorrhages may contribute to the observed effect.	Management of anemia is described in Section 8.3.6.4.
Bleeding adverse events	Bleeding adverse events are considered important identified risk. Participants treated with bintrafusp alfa were commonly reported with mild to moderate mucosal adverse events such as epistaxis, hemoptysis, gingival bleeding and hematuria, and in lower frequencies, with Grade ≥ 3 hemorrhages including tumor bleeding. Other TGFβ inhibitors like fresolimumab are also known to be associated with bleeding (Morris 2014; Vincenti 2017). No bleeding events were observed during the nonclinical studies with bintrafusp alfa.	Management of bleeding adverse events is described in Section 8.3.6.5.
Identified Risks		
Infusion-related reactions	Infusion-related reactions (IRRs) are known class effects of monoclonal antibodies including anti PD-L1 antibodies and have been observed in the clinical studies with bintrafusp alfa. However, the frequency and severity of IRRs was relatively low, and no premedication is required to prevent the occurrence of IRRs. Therefore, IRRs are classified as identified (non-important) risk.	Special precautions and management of IRRs and immediate hypersensitivity reactions are described in Section 8.3.6.1.
Important Potential Risks		

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Immune-related adverse events (irAEs) • Guillain-Barré syndrome • Uveitis • Pancreatitis • Myasthenia gravis/myasthenic syndrome	irAEs like Guillain-Barré syndrome, uveitis, pancreatitis and myasthenia gravis/myasthenic syndrome have not been observed for bintrafusp alfa in the pooled monotherapy studies and are therefore considered as important potential risks, as these are known risks of the therapeutic drug class of anti-PD-1/anti-PD-L1 antibodies including avelumab.	Management of irAEs and instructions for study treatment discontinuation or interruption in case of irAEs is described in Section 8.3.6.2.
Impaired wound healing	Impaired wound healing is considered as an important potential risk (a theoretical risk based on literature findings) for bintrafusp alfa, given the role of TGFβ in wound healing, repair of skin and other tissue injuries (Pakyari 2013).	Management should be discussed with the Medical Monitor for participants requiring surgery on study. It is recommended to hold study intervention for approximately 4 weeks post major surgery for observation. Postoperative wound healing will be closely monitored.
Embryofetal toxicity	Embryofetal toxicity is a known risk of anti-PD-1/anti-PD-L1 antibodies, and therefore considered as important potential risk for bintrafusp alfa. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue.	An appropriate contraception warning is provided as part of the inclusion criteria. Participants with pregnancy or in lactation are prohibited from enrolling in bintrafusp alfa clinical trials and adequate contraceptive measures are recommended during the study to minimize or eliminate the potential risk to the developing fetus.

for any serious events, an SAE Report Form has to be used (see Section 8.3.4).

2.3.2 Benefit Assessment

Participants who will be enrolled in the rollover study to continue bintrafusp alfa treatment have been receiving bintrafusp alfa for a prolonged period of time in the parent study without toxicities requiring permanent treatment discontinuation, while experiencing clinical benefit from the treatment.

The clinical activity of bintrafusp alfa is further summarized in the IB.

2.3.3 Overall Benefit/Risk Conclusion

Participants enrolled in parent protocols with bintrafusp alfa treatment underwent benefit/risk assessments and, by means of their eligibility to participate in this rollover study, have an expected overall positive benefit from continuation or reinitiation of bintrafusp alfa treatment. Given the observed clinical activity of bintrafusp alfa in patients with a number of tumor types and the manageable safety profile observed in more than 700 participants in the Phase I and Phase II studies, the benefit/risk assessment is considered favorable to conduct this study.

3 Objectives and Endpoints

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate clinical safety of bintrafusp alfa in participants with solid tumors who continue treatment after completion of the primary/main analyses in parent bintrafusp alfa studies	Occurrence of AEs and treatment-related AEs, starting from baseline in parent study
Secondary	
To evaluate clinical efficacy of bintrafusp alfa based on OS	OS, starting from baseline in parent study
CCI	

AE = adverse event CCI ; OS = overall survival; CCI ;
RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1.

4 Study Design

4.1 Overall Design

Study Design	Open-label, single arm, rollover
Control Method	None
Single or Multicenter	Multicenter
Control Group	Not applicable
Study Population Type	Patients with solid tumor; see Sections 5.1 and 5.2. Participants can be transferred from their respective parent bintrafusp alfa study to this rollover study once the primary/main analysis in the parent study has been completed or after discontinuation of study before primary/main analysis has been completed. Participants may also be transferred upon Sponsor decision in case the parent study is terminated for any reason as specified in the parent study protocol and there is a medical need for participants to continue to be treated with bintrafusp alfa that cannot be otherwise supplied. The final decision whether to transfer participants from the parent study rests with the Sponsor. A full list of bintrafusp alfa clinical studies from which participants may be potentially enrolled after completion of the primary analysis or after discontinuation of study before primary/main analysis is provided in Appendix 10.
Level and Method of Blinding	Open-label
Bias Minimalization Method(s)	Not applicable

Study Intervention Assignment Method	For participants who are continuing treatment with bintrafusp alfa and were previously assigned to a bintrafusp alfa dose based on body weight (i.e., a mg/kg dose) in a parent protocol, the Sponsor recommends switching to a flat dose of bintrafusp alfa 1200 mg every 2 weeks as they enroll in the rollover study, after consultation with the Sponsor Medical Lead. However, participants still on active treatment in their respective parent study may, if considered appropriate by the Investigator, opt to continue treatment at their ongoing dose level as they enter this rollover study, with treatment as follows: • Bintrafusp alfa administered on Day 1 of a 2-week cycle at the dose specified based upon the participant's parent protocol and treatment assignment. OR • Bintrafusp alfa administered on Day 1 of a 3-week cycle at a dose of 2400 mg. Participants who are entering the rollover study after discontinuation of treatment in a parent study will reinitiate bintrafusp alfa as a monotherapy following the same treatment schedule as specified in their original parent protocol. These participants will reinitiate treatment as either: • Bintrafusp alfa administered on Day 1 of a 2-week cycle at a dose of either 1200 or 2400 mg OR • Bintrafusp alfa administered on Day 1 of a 3-week cycle at a dose of 2400 mg. Restarting treatment as a combination will not be allowed
Involvement of Special Committee(s):	No.
Total Duration of Study Participation per Participant	All participants in this rollover study will be treated with bintrafusp alfa until meeting criteria for discontinuation (see Section 7.1), until study intervention is commercially accessible and provisioned via marketed product, or until end of study (see Section 4.4). The study also includes a 5 years survival follow-up after last dose of the study treatment.
Provisions for Study Extension or Entry into Rollover Studies	This is a rollover study and it is designed to provide continuous access to treatment with bintrafusp alfa for eligible participants from ongoing bintrafusp alfa parent studies, and to collect long-term safety and efficacy data.
Adaptive Aspects of Study Design	Not applicable

4.2 Scientific Rationale for Study Design

Although not yet approved in any country, bintrafusp alfa has demonstrated meaningful clinical activity across various tumor types and treatment settings. In recent years checkpoint inhibitors have been increasingly used in clinical practice based on superior efficacy and manageable safety profile. Regardless of the tumor type or previous anticancer treatments, responses with bintrafusp alfa appear durable in nature, including ongoing responses > 1 year in several of the cohorts in parent studies. Overall, many responses were still ongoing at the time of database lock of parent studies.

Enrollment in this study will provide continuous access to bintrafusp alfa treatment for participants from parent studies who may experience long-term clinical benefit. Collection of safety data for these participants will provide valuable information to physicians regarding the safety of prolonged treatment with bintrafusp alfa. Participants to be enrolled in this study have been on active bintrafusp alfa treatment without major toxicities requiring treatment discontinuation; therefore, from a long-term perspective it is considered appropriate to continue collection of treatment-related AEs.

CCI

Overall survival is the most reliable efficacy endpoint in oncology studies to demonstrate treatment benefit in cancer subjects. Long-term OS data collection will be continued for participants in this study to further support clinical development of bintrafusp alfa.

4.2.1 Participant Input into Design

Not applicable.

4.3 Justification for Dose

In this rollover study, the doses and treatment schedules for bintrafusp alfa (administered as an intravenous [IV] infusion) were selected based on those used in the parent studies and include the following:

- On Day 1 of a 2-week cycle at either a) the flat dose of 1200 mg or b) the dose specified based upon the participant's parent protocol and treatment assignment.
- On Day 1 of a 3-week cycle at a flat dose of 2400 mg.

For participants who are continuing treatment with bintrafusp alfa and were previously assigned to a bintrafusp alfa dose based on body weight (i.e., a mg/kg dose) in a parent protocol, the Sponsor recommends switching to a flat dose of bintrafusp alfa 1200 mg every 2 weeks as they enroll in the rollover study, in consultation with the Sponsor Medical Lead. However, participants still on active treatment in their respective parent study may, if considered

appropriate by the Investigator, opt to continue treatment at their ongoing dose level as they enter this rollover study.

Participants who are entering the rollover study after discontinuation of treatment in a parent study will restart bintrafusp alfa as a monotherapy at either 1200 mg or 2400 mg following the same treatment schedule as specified in their original parent protocol.

These doses for bintrafusp alfa were selected based on safety/tolerability, pharmacokinetics (PK), pharmacodynamics (PD-L1 target occupancy in peripheral blood mononuclear cell and TGFβ plasma concentrations), and efficacy data in the parent studies, as well as population PK and exposure-response modeling and simulations.

The 1200 mg every 2 weeks dose selection was based on the recommended Phase II dose for bintrafusp alfa, and the 2400 mg every 3 weeks dose selection was based on modeling and simulation data indicating this dose maintains target efficacious $C_{trough,ss}$ of bintrafusp alfa. Additionally, assessment of potential PK interactions and overlapping toxicities with chemotherapies was conducted to support 2400 mg every 3 weeks dose of bintrafusp alfa in the parent combination studies. Since most chemotherapies are administered every 3 weeks, the same dosing interval for bintrafusp alfa was preferred for convenience and compliance in the parent combination studies.

Refer to the IB for additional details and data for dose justification.

4.4 End of Study Definition

A participant has completed the study if he/she has completed all study parts, including the last visit or the last scheduled procedure shown in Section 1.3.

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the study and when there are no other eligible parent studies ongoing from which participants could enroll in this rollover study.

The survival follow-up will continue until up to a maximum of 5 years after the last participant receives the last dose of bintrafusp alfa. This duration may be shortened at the discretion of the Sponsor for any given indication.

The Sponsor may terminate the study at any time once access to study intervention for participants still benefiting is provisioned via marketed product or another mechanism of access as appropriate. See also Appendix 2 for study and site closure.

5 Study Population

The criteria in Sections 5.1 and 5.2 are designed to enroll only participants, who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions are considered when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative (where allowed by local laws and regulations) has provided written informed consent, as indicated in Appendix 2 Study Governance.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Category	Criterion
Age	1. Are ≥ 18 years of age at the time of signing the informed consent. In Japan, if a participant is at least 18 but < 20 years of age, written informed consent from his/her parent or guardian will be required in addition to the participant's written consent.
Type of Participant and Disease Characteristics	2. Are participants currently enrolled in an eligible bintrafusp alfa parent study (see Appendix 10) where the primary/main analysis has been completed or after discontinuation of study before primary/main analysis has been completed and who: • Are currently on active bintrafusp alfa treatment (alone as a monotherapy or following discontinuation of other combination treatment agents) in the parent study and without treatment interruption at the time of rollover study enrollment, OR. • Experienced a confirmed CR, PR, or SD in an eligible parent study, discontinued bintrafusp alfa treatment according to the parent study protocol, and subsequently developed disease progression and are willing to re-start bintrafusp alfa treatment deemed potentially beneficial by the participants' physicians OR • Discontinued from bintrafusp alfa treatment in an eligible parent study due to an AE(s) that was subsequently well controlled or completely resolved after stopping therapy, provided that the parent study protocol permits reinitiation of bintrafusp alfa if a participant discontinued treatment due to toxicity and these participants are willing to re-start bintrafusp alfa treatment deemed potentially beneficial by the participants' physicians. Participants who have had AEs requiring permanent treatment discontinuation, like certain irAEs or certain bleeding events (see Sections 6.8 and 2.3.1 for details) are excluded from participation in this Rollover study. Note: Prior to treatment reinitiation, the Investigator, in consultation with the study Medical Monitor as needed, must confirm that the benefit of reinitiating treatment outweighs any risk involved, including that which led to the prior treatment discontinuation. For participants with only SD at the time of discontinuation, the Investigator should confirm that no other reasonable treatment options are available. • Have completed End of treatment (EoT) assessment of a parent study.

Category	Criterion
Sex and Contraception/Barrier Requirements	3. The allowed sex/sexes for the study: • Male • Female The investigator confirms that each participant agrees to use appropriate contraception and barriers, if applicable. The contraception, barrier, and pregnancy testing requirements are below. For female participants of childbearing potential or for male participants who have female partners of childbearing potential, the following applies: Participants on active treatment must agree to continue to use highly effective contraception (i.e., methods with a failure rate of less than 1% per year; see Appendix 3) for both male and female participants if the risk of conception exists (Note: The effects of the study intervention on the developing human fetus are unknown (refer to Section 2.3.1); thus, women of childbearing potential and men must agree to use highly effective contraception as stipulated in national or local guidelines). Highly effective contraception must be used 28 days prior to the first study intervention administration, for the duration of study intervention, and at least for 2 months (for female participants) or 4 months (for male participants) after stopping study intervention. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, the treating physician should be informed immediately.
Informed Consent	4. Capable of giving signed informed consent, as indicated in Appendix 2, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Category	Criterion
Medical Conditions	1. Pregnancy or currently in lactation
	2. Known hypersensitivity to any of the study intervention ingredients.
Prior/Concomitant Therapy	3. For participants reinitiating treatment with bintrafusp alfa at study entry: have received any systemic anticancer therapies/treatments since discontinuing bintrafusp alfa treatment. 4. Concurrent treatment with prohibited drugs (see Section 6.5.3)
Prior/Concurrent Clinical Study Experience	5. Participant has withdrawn consent from the parent study for any reason
Other Exclusions	6. Any other reason that, in the opinion of the Investigator, precludes the participant from participating in the study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

There are no dietary restrictions.

5.4 Screen Failures

The Investigator will maintain an eligibility log to record details of all participants, to confirm eligibility, and if applicable, record reasons for exclusion.

6 Study Intervention(s)

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Study Intervention(s) Administration

Bintrafusp alfa will be administered as a monotherapy in this rollover study (see Table 4).

Table 4 Study Intervention

Intervention Name	Bintrafusp alfa
Type	Drug
Dose Formulation[a]	Sterile concentrate solution for infusion
Unit Dose Strength(s)	10 mg/mL in single-use glass vials (600 mg provided per vial)
Dose Amount	• 1200 mg • 2400 mg • Other dose amount as specified in the participant's parent protocol
Frequency	• 1200 mg: once every 2 weeks • 2400 mg: once every 2 weeks • 2400 mg: once every 3 weeks • Other dose amount as specified in the participant's parent protocol: once every 2 weeks
Route of Administration	Intravenous infusion
Dosing Instructions	• Flat dose of 1200 mg administered over 1 hour (-10/+20 minutes, i.e., over 50 to 80 minutes) once every 2 weeks. • Flat dose of 2400 mg administered over a minimum of 1 hour (-10/+20 minutes) and up to 2 hours (-10/+20 minutes) once every 3 weeks. • Flat dose of 2400 mg administered over a minimum of 1 hour (-10/+20 minutes) and up to 2 hours (-10/+20 minutes) once every 2 weeks • Other dose amount, as specified in the participant's parent protocol, administered over 1 hour (-10/+20 minutes, i.e., over 50 to 80 minutes) once every 2 weeks.
Use	Experimental
Sourcing	Provided centrally by the Sponsor
Packaging and Labeling	Study Intervention will be provided in vial. Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study intervention(s), the Investigator or designee will confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the Pharmacy Manual.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) will be stored in a secure, environmentally controlled, and monitored (manual or automated) area, per the labeled storage conditions, and with access limited to the Investigator and authorized site staff.

- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused study intervention(s).
  - Dates, quantities, batch numbers, vial numbers, expiry dates, formulations for study interventions prepared at the site, and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) will not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- Destruction of used and unused study intervention(s) should be performed at the site if allowed by local law only after Sponsor authorization. If that is not possible, the Sponsor/designee will be responsible for the destruction process.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Pharmacy Manual
- Bintrafusp alfa should be stored in a refrigerator (2°C to 8°C) until use. Bintrafusp alfa must not be frozen and should be stored in the original packaging.
- Additional instructions for the preparation, handling, storage, and disposal of bintrafusp alfa will be provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Sites will be required to discontinue participants in the parent study Interactive Web Response System (IWRS) before contacting the rollover study IWRS for enrollment. The rollover study IWRS will assign new unique patient identifiers number to participants in chronological order at the time of informed consent signature for parent study participants continuing in the rollover study.

6.3.2 Blinding

Blinding Method

This is an open-label, single-arm study; thus, study intervention is not blinded to participants or Investigators.

Assignment Method Retention

Not applicable, as this is an open-label study and blinding will not be used.

6.3.3 Emergency Unblinding

Not applicable.

6.4 Study Intervention Compliance

In this study, participants will receive study intervention at the study site. When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

A record of the number of bintrafusp alfa vials dispensed to and taken by each participant will be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

Noncompliance is defined as a participant missing > 1 consecutive infusion of study intervention for nonmedical reasons and barring any extenuating circumstances in the opinion of the Investigator. Extenuating circumstances should be documented, and when possible, discussed with the Sponsor in advance. If > 1 infusion is missed and the interval between the subsequent infusion and the last administered treatment is longer than 6 weeks for nonmedical reasons, the criterion of insufficient compliance is met as well.

Consequences of noncompliance may lead to discontinuation of study interventions as described in Section 7.1. In case of overdose, see Section 8.4.

6.5 Concomitant Therapy

Record in the CRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Any additional concomitant therapy that becomes necessary during the study and any change to concomitant drugs must be recorded in the corresponding section of the electronic eCRF, noting the name, dose, duration, and indication of each drug.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.5.1 Rescue Medicine

Not applicable

6.5.2 Permitted Medicines

The only permitted medications are the following:

1. Any medications (other than prohibited in Section 6.5.3) that are considered necessary for the participants' welfare and will not interfere with the study intervention may be given at the Investigator's discretion.

2. Other drugs to be used for non-steroid premedication (antihistamine and acetaminophen) for the treatment of anaphylactic reactions, IRRs, and severe hypersensitivity reactions/flu-like symptoms and irAEs (see Section 8.3.6). Note that premedication should be administered prior to bintrafusp alfa dosing and should be based upon clinical judgment and presence and severity of prior infusion reactions

3. Blood transfusions and erythroid growth factors are permitted as clinically indicated.

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

6.5.3 Prohibited Medicines

The following treatments must not be administered within 14 days before the start of study intervention or throughout the duration of study intervention. If the administration of a nonpermitted concomitant drug becomes necessary during the study, the participant will be withdrawn from study intervention (the Sponsor may be contacted to discuss whether the study intervention must be discontinued).

- Immunotherapy, immunosuppressive drugs (e.g., chemotherapy or systemic corticosteroids), or other experimental pharmaceutical products are prohibited (prior administration of bintrafusp alfa in an eligible parent study within 14 days before enrollment in this rollover study is allowed). Exceptions are allowed for short-term treatment of allergic reactions or for the treatment of irAEs, specifically:
- Short term administration of systemic steroid (i.e., for allergic reactions, for prophylaxis and management of radiographic contrast allergy or the management of irAEs and other AEs) is allowed.
- Steroids with no or minimal systemic effect (topical, intranasal, intro-ocular, inhalation) are allowed.
- Hormone replacement with corticosteroids for adrenal insufficiency is allowed if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or equivalent prednisone per day.
- Prophylactic use of corticosteroids for IRRs is prohibited.

- Concomitant local or regional treatment (radio/chemo-embolization) is prohibited.
- Other systemic anti-cancer therapy.
- Live vaccines are prohibited. Administration of inactivated vaccines (e.g., inactivated influenza vaccines) or approved SARS-COV-2 vaccines is allowed.
- Any traditional Chinese medication used as anticancer treatment (regardless of the type of cancer) is prohibited. Traditional Chinese medication for indications other than anticancer treatment, such as supportive care, may be administered at the discretion of the Investigator.
- Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin).

Medications other than those specifically excluded in this study (see above) may be administered for the management of symptoms associated with the administration of bintrafusp alfa as required. These might include analgesics, anti-nausea medications, antihistamines, diuretics, antianxiety medications, and medication for pain management, including narcotic agents.

6.5.4 Other Interventions

Palliative organ-sparing radiotherapy may be administered only for specific clinical indications during the study treatment period. The assessment of progressive disease (PD) will be made according to RECIST v1.1 and not based on the necessity for palliative radiotherapy.

6.6 Dose Selection and Modification

The doses and treatment schedules for bintrafusp alfa in this study were selected based on those used in the parent studies (see Section 4.1, Section 4.3, and Section 6.1 for details).

For participants who are continuing treatment with bintrafusp alfa and were previously assigned to a bintrafusp alfa dose based on body weight (i.e., a mg/kg dose) in a parent protocol, the Sponsor recommends switching to a flat dose of bintrafusp alfa 1200 mg every 2 weeks as they enroll in the rollover study, in consultation with the Sponsor Medical Lead. Otherwise, dose modification of bintrafusp alfa is not allowed except for management of bleeding AEs.

Modifications of the infusion rate due to IRRs are described in Section 7.1.

Doses cannot be delayed beyond the treatment window (± 3 days). Participants must skip the dose if the treatment window is missed. Every attempt should be made to perform applicable assessments in Table 1 for any missed visits. Complete the next visit following the SoA (see Table 1).

6.7 Reinitiation Criteria

For participants who discontinue bintrafusp alfa treatment during this rollover study, one reinitiating course of treatment at the same dose and schedule is allowed at the discretion of the Investigator and with agreement of the Study Medical Responsible:

- Participants who enter into this rollover study on active treatment will be eligible for one reinitiating course of treatment during this rollover study, regardless of whether or not they reinitiated treatment in a parent study.
- Participants who reinitiate treatment with bintrafusp alfa at study entry into this rollover study will be eligible for one more reinitiation (second reinitiation) if treatment is discontinued during this rollover study.

The following participants are eligible for reinitiation:

- Participants who are experiencing a CR, a PR, or SD at the time of treatment discontinuation in the rollover study, and then subsequently develop disease progression after stopping therapy, but prior to the end of the study.
- Participants who discontinue from treatment in the rollover study due to an AE that is subsequently well managed or resolved, as assessed by the Investigator, prior to the end of the study.

The participant should reinitiate treatment at the treatment phase visit where they left off according to the SoA (see Section 1.3). Participants who reinitiate treatment should stay on study and should be treated and monitored according the SoA for the rest of the study.

Prior to reinitiation, the Investigator will need to confirm that the benefit of reinitiating treatment outweighs any risk involved, such as that which led to initial treatment discontinuation. For participants with only SD at the time of discontinuation, the Investigator should confirm that no other reasonable treatment options are available. In addition, to be eligible for reinitiation, the participant must not have previously withdrawn consent for this study and should have been followed up with regular eCRF documented evaluation scans up to reinitiation of treatment.

A rebaseline scan must be performed prior to reinitiation of study intervention. Additionally, relevant safety laboratory assessments, including both full hematology and full chemistry results within 2 weeks, must be available and verified. The clinical Investigator will determine whether additional evaluation and work-up are required on a case-by-case basis.

6.8 Study Intervention after the End of the Study

After a participant has completed the study, has withdrawn consent, or has been withdrawn early, no further treatment is foreseen within the scope of this protocol. If required and in accordance with the study site's SOC, symptom-guided appropriate treatment may be administered per the generally accepted medical practice and depending on the participant's individual medical needs.

On withdrawal from the study, participants may receive care they and their physicians agree upon.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Duration of study intervention/criteria for treatment discontinuation will follow guidelines stated in the respective parent protocols.

Participants from all studies except for Study MS200647_0005:

Participants (except those from Study MS200647_0005) who have experienced a confirmed CR should continue treatment for a maximum of 24 months after confirmation of response (at the discretion of the Investigator). If the Investigator believes that a participant with confirmed CR may benefit from treatment beyond 24 months, it may be permissible to continue treatment after discussion with the Medical Monitor and the Sponsor's Medical Responsible.

Participants with SD or PR who are receiving bintrafusp alfa should continue treatment until meeting criteria for discontinuation.

Participants from Study MS200647_0005:

For participants from Study MS200647_0005, study intervention will continue until unacceptable toxicity, confirmed PD assessed by Investigator (unless participant meets the criteria for study intervention beyond progression), or for up to 26 doses in total across both the MS200647_0005 parent and MS200647_0054 rollover studies since the completion of cCRT doses in the MS200647_0005 parent study, whichever occurs first.

All Participants:

Participants may be discontinued from study intervention for any of the following reasons, one reinitiating course of treatment may be allowed (see Section 6.7):

- A participant may discontinue from the study intervention at any time at his/her own request (i.e., withdrawal of consent), and without giving a reason.
- Occurrence of an exclusion criterion that is clinically relevant and affects the participant's safety, OR if discontinuation is considered necessary by the Investigator and/or Sponsor.
- A participant may be discontinued at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons (e.g., disruption of operations due to natural disasters, interruption of laboratory or facility accreditation, participant moving to another country, resignation of key staff). (See Sections 7.1 and Section 8.3.6 for TEAEs and AESIs that require treatment discontinuation).
- PD per RECIST v1.1, with the exception that participants receiving treatment may continue post PD if the participant's Eastern Cooperative Oncology Group Performance Status (ECOG PS) has remained at least stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment (See Section 7.1.2).
- Unacceptable toxicity

- Drug must not be given to a known pregnant participant (see to Appendix 3)
- Use of a prohibited concomitant drug, as defined in Section 6.5.3 if discontinuation is considered necessary by Investigator/Sponsor.

Any treatment-emergent AE, especially of Grade 4 or recurrent event of Grade 3, that is assessed as related to bintrafusp alfa may require treatment interruption or permanent discontinuation of bintrafusp alfa treatment.

Grade 4 treatment-related TEAEs: Any Grade 4 treatment-related TEAEs require permanent treatment discontinuation, except:

a. Endocrinopathies that have been controlled by hormone replacement,

b. Isolated laboratory values out of normal range that do not have any clinical correlation. Discuss with Medical Monitor regarding work-up, management, and treatment continuation versus hold versus discontinuation for isolated Grade 4 laboratory abnormalities,

c. If an alternative explanation is identified for Grade 4 non tumor bleeding.

Grade 3 treatment-related TEAEs: Participants with any recurrent Grade 3 treatment-related TEAEs should be permanently discontinued. **Exceptions** may be considered for the following after discussion with Medical Monitor (see also relevant management guidance sections):

a. Transient Grade 3 flu-like symptoms or fever that is controlled with medical management.

b. Transient Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1 or baseline.

c. Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumors.

d. Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis.

e. Grade 3 hemoglobin (Hgb) decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor use.

f. Increases ECOG PS ≥ 3 that resolves to ≤ 2 by Day 1 of the next infusion (i.e., infusions should not be given if the ECOG PS is ≥ 3 on the day of treatment and should be delayed until ECOG PS ≤ 2).

g. Keratoacanthoma (KA) and cutaneous squamous cell carcinoma (cSCC).

h. Grade 3 non tumor bleeding requiring intervention or hospitalization if alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic event, etc.).

If persistent Grade 3 treatment-related AEs (excluding endocrinopathies controlled with hormone replacement therapy) either do not resolve or improve to Grade 1 within 12 weeks after last dose of study intervention, treatment must be permanently discontinued. If a Grade 2

treatment-related TEAE improves to Grade ≤ 1 or completely resolves by the day before the next infusion, study intervention may be continued.

Grade 2 treatment-related TEAE

If a Grade 2 treatment-related TEAE does not improve to Grade 1 or completely resolve by the day before the next infusion, but it is manageable and/or not clinically relevant, the Medical Monitor should be consulted to assess if it is clinically reasonable to administer the following infusion. In any case, if ≥ 2 doses are missed due to AE, the Medical Monitor should be consulted.

Immune-related AEs, IRRs, anemia, TGFβ inhibition mediated skin reactions, and bleeding AEs

Permanent study intervention discontinuation may be recommended, so the relevant section must be reviewed:

- For suspected irAEs, general guidance and management are provided in Section 8.3.6.2. Recommended guidance and management for specific irAEs as per published guidelines is provided in the current National Comprehensive Cancer Network (NCCN) guideline available at http://www.nccn.org.
- IRR and hypersensitivity reaction management guidance are presented in Section 8.3.6.1.
- Anemia management guidance is presented in Section 8.3.6.4.
- TGFβ inhibition mediated skin reactions management guidance is provided in Section 8.3.6.3.
- For guidance and management of bleeding AEs, see Section 8.3.6.5.

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for the End of Treatment and Safety Follow-up. The Schedule of activity (see Table 1) indicates data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

In case of discontinuation from the study intervention:

- The day of End of Treatment will correspond to the day of withdrawal (or within 7 days) for further details refer to Table 1.
- An attempt should be made to perform all assessments scheduled for the End of Treatment visit if possible. If not possible, the most clinically relevant assessments and appropriate eCRFs for the End of Treatment visit should be prioritized as feasible.
- Participants will be asked to continue Safety and Survival Follow-up, which includes the collection of data on survival and subsequent anticancer therapy.
- If the participant is enrolled into a new study or any new therapy post-withdrawal from study intervention, the Safety Follow-up visit should be scheduled prior to the start of the new treatment irrespective of the 30-day Safety Follow-up period.
- Liver Injury:

The Investigator will consider discontinuation of study intervention for abnormal liver function if the Investigator believes that it is in best interest of the participant.

- Cardiac changes (e.g., QTc):

  If a clinically significant finding is identified (including changes from baseline in QT interval corrected using Bazett's formula [QTcB] or Fridericia's formula [QTcF] after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the electrocardiogram (ECG) printed at the time of collection will be documented. Any new clinically relevant finding is reported as an AE.

7.1.1 Temporary Discontinuation

See Sections 7.1 and 8.3.6 for guidance on temporary discontinuation from study intervention.

7.1.2 Treatment Beyond Progression

7.1.2.1 Treatment Beyond Disease Progression

Participants will receive bintrafusp alfa as outlined in the SoA (see Table 1) until disease progression. Bintrafusp alfa treatment may continue post the initial determination of disease progression according to RECIST v1.1 as long as the following criteria are met:

- No new unacceptable treatment or disease-related toxicity
- Tolerance of study interventions
- At least stable ECOG PS
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system metastases).

A radiographic assessment should be performed within 4 to 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with bintrafusp alfa.

7.1.2.2 Continuation of Study Intervention After Local Treatment of Disease Progression

If disease progression is due to brain metastasis, participants may continue study interventions after the local treatment of the brain lesions provided that the above criteria are met in addition to the following:

- Tumor assessment showing disease progression has been performed and was documented according to RECIST v1.1. prior to the procedure.
- Brain metastases have been treated locally and are clinically stable for at least 2 weeks prior to reinitiation of study interventions.

- There are no ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable).
- Participants must be either off steroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).
- Benefit-risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator.

In addition, if disease progression is mainly due to a metastatic lesion which in the opinion of the Investigator may be surgically removed or benefit from radiotherapy, participants may continue study interventions after the local treatment of such a lesion provided that:

- Tumor assessment showing disease progression has been performed and was documented according to RECIST v1.1. prior to the procedure.
- It has been at least 2 weeks and the participant has fully recovered from the surgery.
- Benefit-risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may discontinue from the study at any time, at his/her own request or at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of discontinuing from the study, if possible, a discontinuation visit will be conducted, as listed in the SoA (see Table 1). The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed. In any case, the appropriate End of Treatment eCRF visit must be completed. In case of withdrawal, subjects will be asked to continue safety and survival follow-up, which includes the collection of data on survival and subsequent anticancer therapy. After completion of the Follow-up period or after the End of Treatment visit, whatever is applicable, the appropriate eCRF section for Trial Termination must be completed.
- If the participant revokes consent for the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- A participant has the right at any time to request destruction of any biological samples taken. The investigator will document this in the site study records and the eCRF and inform the Sponsor. The samples will be destroyed.
- The Investigator will secure the safety of the study participants and make every attempt to collect data. If a participant fails to attend the scheduled study assessments, the Investigator must determine the reasons and the circumstances as completely and as accurately as possible.

7.3 Lost to Follow-Up

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

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

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee will make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner or caretaker (where allowed by local regulations) for information. These contact attempts will be documented in the participant's medical record.
- If the participant continues to be unreachable, he/she will be deemed as "lost to follow-up".

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA (see Table 1).
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All eligibility evaluations will be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain an eligibility log to record details of all participants, to confirm eligibility, and if applicable, record reasons for exclusion.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2 Study Governance.
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- No more than 15 mL of blood may be drawn in a 24-hour period, and no more than 30 mL of blood in a 4-week period.

8.1 Efficacy Assessments and Procedures

The following secondary efficacy endpoint will be assessed:

- OS, defined as the time (in months) starting from the baseline date of the parent study to the date of death due to any cause. For participants alive at the time of data analysis or who are lost to follow-up, OS will be censored at the last recorded date that the participant is known to be alive.

8.1.1 Tumor Assessments

For participants continuing on bintrafusp alfa treatment, tumor response assessment will be conducted, at a frequency according to site SOC/institutional guidelines, by computed tomography (CT) scan or magnetic resonance imaging (MRI) for the same anatomical regions as in the parent study. Baseline/nadir tumor assessments from the parent studies (performed before the first dose of bintrafusp alfa) will be used for response or progression determination according to RECIST v1.1 (see Appendix 11). In general, all lesions detected at the parent study baseline should be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits, if possible, however the frequency of assessments should follow site SOC/institutional guidelines.

For participants reinitiating treatment with bintrafusp alfa at entry into this rollover study (or reinitiating treatment after treatment discontinuation in the rollover study; see Section 6.7), new baseline tumor assessments will be used to estimate tumor burden and for comparison with subsequent measurements. Lesions detected at the parent study baseline should be followed, in addition to any new lesions identified in the rebaseline assessment. As a general guidance, it is preferable not to select new target lesions, and follow any new lesions presenting at the start of this continuation study as non-target lesions. Any new lesions in other anatomic areas, especially but not limited to the brain, should be imaged using institutional standard imaging for following disease in that region.

The tumor response assessments will be performed at a frequency according to site SOC/institutional guidelines (e.g., every 6 months or 12 weeks), calculated from the last assessment performed in the parent study (see Table 1), until PD is assessed by the Investigator according to RECIST v1.1, or until 30 days after the end of treatment with bintrafusp alfa, whichever occurs later, including for participants who discontinued treatment prior to disease

progression, as well as for participants who reinitiate bintrafusp alfa treatment upon entry into this rollover study after development of PD in a parent study.

Treatment decisions will be made by the Investigator based on the Investigator's assessment of tumor status. Tumor lesions will be categorized in target and non-target lesions as described in RECIST v1.1 (see Appendix 11).

Results for these evaluations will be recorded with as much specificity as possible so that pre- and post-treatment results will provide the best opportunity for evaluating tumor response and/or progression.

8.1.2 Follow-up

For participants without PD according to RECIST v1.1 at treatment discontinuation, sites will be asked to continue collection of all available tumor assessments performed according to SOC until determination of disease progression. Subsequent anticancer treatment should be documented after discontinuation of study intervention.

Participants will be followed up every 12 weeks (± 2 weeks) for survival and assessment of subsequent anticancer therapy. The survival follow-up will continue until a maximum of 5 years after the last participant receives the last dose of bintrafusp alfa (see Section 4.4). Under some circumstances, participants may not be followed for the entire duration of survival follow-up in this study (see also Section 7.3 and Appendix 11). The Sponsor may terminate the study at any time once access to study intervention for participants still benefiting is provisioned via marketed product or another mechanism of access as appropriate.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, ECGs, and laboratory tests. The baseline status and medical history of the participant is assessed at the baseline of the respective parent study.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1.

The safety assessments will be performed according to the SoA (Table 1). Periodic evaluations of the study data will be conducted by the study team to ensure safety and the validity and scientific merit of the study (see Section 8.2).

Ongoing events at the 12-week Safety Follow-up visit should continue to be monitored and documented until resolution or resolution with sequelae. All SAEs ongoing at the End of Treatment visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of

the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

If a liver function test is elevated in a Hepatitis B virus (HBV) or Hepatitis C virus (HCV) positive participant, HBV DNA or HCV ribonucleic acid (RNA) must be monitored to exclude the possibility of reactivation of viral hepatitis. In case of viral reactivation, follow the HBV and HCV management guidelines.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators will pay special attention to clinical signs related to previous serious illnesses.

General status, such as asthenia or appetite, should be evaluated at Baseline. Pre-existing symptoms of underlying conditions and/or signs of infection should be investigated as clinically indicated. Abnormal findings are to be reassessed at subsequent visits.

8.2.2 Vital Signs

- Height (at screening visit only) and weight on screening and per SoA on subsequent study visits as described in Table 1 will be measured and recorded.
- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed per SoA as described in Table 1.
- Blood pressure and pulse measurements will be assessed in semi supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements will be recorded in semi supine position by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and measured with an automated device. Manual techniques will be used only if an automated device is not available.
- Blood oxygen saturation (SpO_2) will be measured with a pulse oximeter and recorded in the eCRF.

8.2.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (Table 1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.2.4 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 6 at the time points listed in the SoA (Table 1). All samples will be clearly identified.

- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- The tests will be performed by the local laboratory.

The Sponsor will receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study will be forwarded to the Sponsor or designated organization.

The Investigator will review each laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports will be filed with the source documents.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and a SAE are in Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting.

The Investigator and any qualified designees (e.g., Sub-Investigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up AEs that are serious or that caused the participant to discontinue the study intervention as specified in Section 8.3.3.

Requests for follow-up will usually be made via the Study Monitor, although in exceptional circumstances the global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

- All AEs will be collected from the signing of the ICF until 90 days as specified in the SoA.
- All SAEs will be collected from the signing of the ICF until 90 days of last dose of the study treatment at the time points specified in the SoA (Table 1). Beyond this reporting period, any new unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.
- Investigators are not obligated to actively solicit AEs or SAEs after the end of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 4.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AESIs (as defined in Section 8.3), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to Follow-up (as defined in Section 7.3). Reasonable attempts to obtain this information will be made and documented. It is also the Investigator's responsibility to ensure that any necessary additional therapeutic measures and Follow-up procedures are performed. Further information on Follow-up procedures is in Appendix 4.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE (particularly life-threatening and deaths) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Individual Case Safety Reports will be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

An Investigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g., Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will review and then file it along with the IB in the Investigator's Site File and will notify the IRB/IEC, if appropriate according to local requirements.

In this global clinical multicenter study, the Sponsor is in the best position to determine an unanticipated problem (as defined in US Regulations 21 CFR 312.66). The Sponsor will immediately notify all Investigators of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IRB's approval/favorable opinion to continue the study. An unanticipated problem is a SAE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report, specified in Section 2.3.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until the outcome of the pregnancy is known.

- If a pregnancy is reported, the Investigator will inform the Sponsor within 24 hours of learning of the pregnancy and will follow the procedures specified below for collection of pregnancy information.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner, who becomes pregnant while the participant is in this study.
- After obtaining signed consent from the pregnant female partner directly, the Investigator will record the pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the Follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while she is in the study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of the pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect Follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, Follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or stillbirth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as specified in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.6 Management of Adverse Events of Special Interest

Adverse events of special interest (AESIs) are serious or nonserious AEs that are of clinical interest and should be closely followed.

For this study, AESIs include only the following:

- Infusion-related reactions including immediate hypersensitivity.
- Immune-related adverse events.
- TGFβ inhibition mediated skin reactions.
- Anemia.
- Bleeding AEs.

8.3.6.1 Infusion-related Reactions Including Immediate Hypersensitivity

Infusion-related reactions, including immediate hypersensitivity, are defined in this section. IRRs are AESIs and identified risks for bintrafusp alfa.

Infusion-Related Reactions

Infusion-related reactions are signs or symptoms experienced by participants during study intervention administration or within 1 day thereafter. An assessment for possible IRR should be triggered based on the clinical picture and temporal relationship to drug administration.

Possible IRRs are defined based on following 2 lists of Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) and temporal relationship criteria. Events are divided into reactions versus signs and symptoms:

- Reactions include the PTs Infusion-Related Reaction, Drug-Hypersensitivity, Hypersensitivity, Type-1-Hypersensitivity and Anaphylactic Reaction. These PTs should be considered when onset is during the infusion or within 1 day thereafter.
- Signs and symptoms of infusion-related reactions include the PTs Pyrexia, Chills, Flushing, Hypotension, Dyspnea, Wheezing, Back Pain, Abdominal Pain and Urticaria. These PTs should be considered, if the onset occurs during or within 1 day after an infusion and resolves within 2 days.

Management of Infusion-Related Reactions

Current experience in more than 700 study participants revealed that IRRs to bintrafusp alfa occur seldomly and are generally mild to moderate in severity. Therefore, administration of a premedication is generally not required.

If an investigator deems necessary to administer a premedication prior to bintrafusp alfa infusion to a particular participant, an antihistamine (e.g., 25 to 50 mg diphenhydramine) and paracetamol (acetaminophen, 500 to 650 mg intravenously or equivalent oral dose) is recommended.

Premedication should be administered based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic glucocorticoids.

Management of symptoms should follow the guidelines shown in Table 5.

Table 5 Treatment Modification Guidance for Symptoms of Infusion-Related Reactions Including Immediate Hypersensitivity

NCI-CTCAE v5.0 Grade	Treatment Modification
Grade 1 – mild Mild transient reaction: in general, infusion interruption not indicated; intervention not indicated.	Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator. Hold infusion if deemed necessary by the Investigator.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop the infusion of the study intervention Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator. If symptoms resolve quickly, resume infusion at 50% of original rate with close monitoring of any worsening otherwise dosing held until resolution of symptoms with mandated premedication for the next scheduled visit. If not improving, consider administration of glucocorticoids and stop the infusion for that day. If the participant has a second IRR Grade ≥ 2 on the slower infusion rate despite premedication, the infusion should be stopped and the investigator may consider withdrawal of this participant from the study.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the infusion of study intervention- immediately and disconnect infusion tubing from the participant with additional appropriate medical measures and closely monitor until deemed medically stable by the attending Investigator. Hospitalization and/or close monitoring is recommended. Administration of glucocorticoids may be required For Grade 3 or 4 IRRs, permanent discontinuation of study intervention is mandated.
Once the infusion is interrupted or rate reduced to 50% of previous infusion rate, it must remain decreased for all subsequent infusions. For all types and grades of infusion reactions, details about drug physical constitution, method of preparation, and infusion must be recorded. Participants should be instructed to report any delayed reaction immediately.	

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

Immediate Hypersensitivity Reaction

Hypersensitivity reactions may require immediate intensive care. Bintrafusp alfa should be administered in a setting that allows immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Potent steroids (e.g., dexamethasone), catecholamines (e.g.

epinephrine), allergy medications (IV antihistamines), bronchodilators, or equivalents and oxygen should be available for immediate access.

A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council United Kingdom and can be found at https://www.resus.org.uk/pages/reaction.pdf.

Flu-Like Symptoms

Treatment is based on clinical assessment and at the discretion of the Investigator. For prophylaxis of flu like symptoms, a nonsteroidal anti-inflammatory drug (NSAID), e.g., ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each IV infusion.

8.3.6.2 Immune-related Adverse Events

Immune-related AEs are specific to immunotherapies and vary by organ system. Immune-related AEs are AESIs.

The following irAEs are important identified risks for bintrafusp alfa.

- Immune-related pneumonitis
- Immune-related hepatitis
- Immune-related colitis
- Immune-related nephritis and renal dysfunction
- Immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, Type 1 diabetes mellitus, pituitary disorders)
- Immune-related rash
- Other immune-related events (myositis, myocarditis, encephalitis).

The following irAEs are important potential risks for bintrafusp alfa:

- Guillain-Barré syndrome
- Uveitis
- Pancreatitis
- Myasthenia gravis/myasthenic syndrome.

In general, the spectrum of irAEs is similar for bintrafusp alfa compared with other checkpoint inhibitors. Effective risk management of these toxicities (irAEs) primarily caused due to inhibition of PD-L1 and PD-1 pathways is based on key recommendations (Champiat 2016). Participant education for on-time reporting of symptoms of potential irAEs and prompt clinical assessment is critical for effective management and quicker resolution of immune-mediated toxicities, thus preventing progression into severe forms of toxicity that otherwise may become life-threatening and difficult to manage or warrant permanent discontinuation from the study.

The Medical Monitor may be involved as needed for Follow-up. Details of the diagnostic work-up will be requested by the study team.

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

Requirements in addition to NCCN guidelines:

- Permanent treatment discontinuation is required in case of immune-related Grade 4 rash/inflammatory dermatitis, nephritis, autoimmune hemolytic anemia, hemolytic uremic syndrome, aplastic anemia, immune thrombocytopenia, acquired thrombotic thrombocytopenic purpura, inflammatory arthritis, myositis, and polymyalgia-like syndrome.
- For Grade 4 immune-related lymphopenia, permanent treatment discontinuation will be required, if lymphopenia is considered immune-related in nature, no clear alternative explanation exists for the event, and Grade 4 lymphopenia does not resolve within 14 days. Permanent treatment discontinuation is not required when the AE is manifest by a single laboratory value out of normal range without any clinical correlates. In this case, treatment should be held until the etiology is determined. If the event is not considered immune related and resolves to Grade ≤ 1, restarting treatment may be considered.
- For Grade 1 immune-related pneumonitis: continue treatment. If clinically indicated, monitor participants weekly or more frequently as needed with history, physical examination, and pulse oximetry. If symptoms appear and/or changes in the physical examination are noted, treat as Grade 2.
- For myositis: in case of management with rituximab, treatment should be discontinued.

8.3.6.3 TGFβ inhibition mediated Skin Reactions

Skin assessments will be performed for all participants per the SoA (see Table 1). For participants who are reinitiating treatment with bintrafusp alfa after treatment discontinuation within the rollover study, a rebaseline skin assessment should also be performed.

Skin AEs, possibly due to TGFβ inhibition, including hyperkeratosis, KA, and/or cSCC, are AESIs and important identified risks for bintrafusp alfa. The distribution of lesions tends to be in sun-exposed areas.

Management guidelines for potential TGFβ inhibition mediated skin reactions are:

1. Discontinuation or interruption is not required in most cases. Continuation of treatment should be evaluated by the Investigator.

2. Emollients may continue to be used.

3. Diagnostic and treatment plan should be developed in collaboration between Investigator and dermatologist. In general, treatment of TGFβ mediated skin lesions such as hyperkeratosis, KA and cSCC should be based on local guidelines/SoC. Lesion evaluation should include excision biopsy of one representative lesion to confirm diagnosis.

4. Treatment and Follow-up for KA and cSCC will depend on number and localization of lesions.
    - For single lesions: Full excision may be recommended.
    - In case of multiple lesions or location not suitable for full excision, other treatment options may be offered by the dermatologist, such as:
        - Mohs surgery, cryotherapy, or other standard treatment options depending on the pathology,
        - Use of retinoids, if recommended by dermatologist, may be considered after discussion with Medical Monitor.

5. Close clinical Follow-up for re-evaluation, resolution, or potential recurrence should be implemented.

6. Spontaneous resolution of KA lesions without surgical intervention has been observed, typically occurring within weeks after discontinuing bintrafusp alfa.

7. The number and localization of lesions, diagnosis (including histopathological diagnosis), treatment, and outcome should be appropriately documented in the eCRF.

Consult with study Medical Monitor, as needed, for management of TGFβ mediated skin lesions.

8.3.6.4 Anemia

Anemia is an AESI and important identified risk for bintrafusp alfa. Notably, there are many reasons for anemia in patients with advanced cancer, therefore a thorough investigation of new anemia cases of unspecified etiology is requested.

For new anemia events items queried may include, but are not limited to, detailed relevant past medical and treatment history, bruising tendency, history of blood transfusions and/or dependency, and a request for an updated eCRF including details such as concomitant medications, all laboratory data, updated dosing information and, recent tumor evaluation scans.

General guidance for anemia management and evaluation:

1. Routine blood test parameters are required in this rollover study per the SoA (see Table 1).

2. Transfusion should be performed at the discretion of the Investigator based on clinical assessment and considered when the participant experiences severe anemia. An attempt should be made to initiate work-up (as specified below) for the cause of anemia prior to transfusion, if clinically feasible, to not confound this work-up. In general, blood transfusions and erythroid growth factors are permitted as clinically indicated.

Guidance for evaluation of suspected treatment-related anemias is provided in Table 6.

Table 6 Evaluation Guidance of Suspected Anemia

Basic Anemia Evaluation	
1. CBC with emphasis on red cell indices (e.g., Hgb, hematocrit, MCV, RDW, MCH, MCHC, reticulocytes counts). 2. If indicated and at clinical discretion, the following should be considered: a. Iron studies (TIBC, Ferritin, Fe) b. Serum Folate and Vit B12 values c. Coagulation factors (PT, PTT, INR) d. Fecal occult blood testing e. Urinalysis f. Hormone panel: TSH, Erythropoietin g. Peripheral blood smear for cell morphological assessment	
Further Recommendation Based on Suspected Etiology (in Addition to Basic Anemia Testing)	
Suspected hemolysis:	Bilirubin level, LDH, Coombs test, fibrinogen, haptoglobin, d-Dimer Consider Hematology consultation.
Suspected bleeding:	Consider imaging/interventional radiology consultation as indicated Consider endoscopy, as clinically indicated. Consider imaging, as clinically indicated.
Suspected aplastic anemia:	Hematology consultation. Consider bone marrow aspiration/morphologic evaluation.

CBC = complete blood count; Hgb = hemoglobin; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RDW = red blood cell distribution width; TIBC = total iron binding capacity; and TSH = thyroid-stimulating hormone.

8.3.6.5 Bleeding Adverse Events

Bleeding AEs are AESIs and considered important identified risk.

Mucosal/Non-tumor Bleeding

Participants treated with bintrafusp alfa were commonly reported with mild to moderate mucosal AEs such as epistaxis, hemoptysis, gingival bleeding and hematuria. In general, these reactions resolve without discontinuation of treatment.

For Grade 2 non-tumor bleeding, see Section 7 for general management of Grade 2 treatment-related TEAEs.

For Grade ≥ 3 non-tumor bleeding, study treatment must be permanently discontinued unless an alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic event, etc.). In case of alternative explanations for the Grade ≥ 3 bleeding event, study treatment should be held until the event recovers to Grade ≤ 1. If Grade ≥ 3 bleeding event is observed, regardless of causality with the study intervention, upon resumption of study intervention bintrafusp alfa dose should be reduced by 50% (600 mg once every 2 weeks for participants dosed with 1200 mg, 1200 mg once every 2 weeks for participants dosed with

2,400 mg). Once there is stable resolution and no recurrence of bleeding on reduced dose, Investigator is encouraged to communicate with Medical Monitor on potential dose re-escalation after careful benefit-risk assessment.

For Grade 4 non-tumor bleeding, treatment must be permanently discontinued if no alternative explanation is identified.

In case of rapid decrease of hemoglobin (Hgb), such as a decrease greater than 2.0 g/dL across a 2 weeks period (or 3.0 g/dL across a 3 week period), withhold the subsequent cycles of study intervention until Hgb is stabilized and do a thorough assessment of bleeding (for example, upper and lower GI endoscopy, enhancement CT etc.); if Grade 1 or greater bleeding is observed or suspected, withhold the bintrafusp alfa until the bleeding is resolved/controlled and resume the dose of bintrafusp alfa reduced by 50%. Once Hgb decrease is recovered to ≤ Grade 1 or baseline and stably controlled, the Investigator is encouraged to communicate with Medical Monitor to re-escalate the dose. The dose of bintrafusp alfa may be re-escalated to full dose once Hgb is stabilized without further need for blood transfusion in the subsequent cycles. The timing of re escalation may need a case-by-case decision. See Section 8.3.6.4 regarding stabilization of anemia.

Tumor Bleeding

Participants treated with bintrafusp alfa were reported in lower frequencies, with Grade ≥ 3 hemorrhages including tumor bleeding. For Grade ≥ 2 tumor bleeding, study treatment must be held until the event recovers to Grade ≤ 1. If Grade ≥ 3 bleeding event had been observed, regardless of causality with the study intervention, upon resumption of the study intervention bintrafusp alfa dose should be reduced by 50%. Once there is stable resolution and no recurrence of bleeding on reduced dose, Investigator is encouraged to communicate with Medical Monitor potential dose re-escalation after careful benefit-risk assessment. Treatment should be permanently discontinued if the Investigator considers the participant to be at risk for additional severe bleeding. In case of rapid decrease of Hgb, see Section 8.3.6.5 Mucosal/Non-tumor Bleeding.

8.4 Treatment of Overdose

For this study, any dose of bintrafusp alfa greater than 2 times of the planned dose within a 24-hour time period will be considered an overdose. This is based on dose escalation study data in which participants safely received up to 30 mg/kg bintrafusp alfa every 2 weeks (including with doses > 2400 mg) with no observed dose limiting toxicity at 30 mg/kg and not reaching maximum tolerated dose (refer to the IB). Safety at significantly higher doses has not been clinically evaluated.

- In case of overdose with clinical correlation, symptomatic treatment must be used; there are no known antidotes for the compound.
- In the event of an overdose, the study intervention infusion should be discontinued, and participants should be observed closely for any signs of toxicity. Supportive treatment should be provided if clinically indicated.

- Even if not associated with an AE or a SAE, any overdose is recorded in the eCRF and reported to global patient safety in an expedited manner. Overdoses are reported on a SAE and Overdose Report Form, following the procedure in Appendix 4.

8.5 Pharmacokinetics

Not applicable

8.10 Health Economics OR Medical Resource Utilization and Health Economics

Not applicable

9.3 Populations for Analyses

The analysis populations are specified below (see Table 7). The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock.

Table 7 Analyses Sets

Analysis Set	Description
Full (FAS)	For each parent study, the FAS will be defined as in the protocol of the parent study.
Safety (SAF)	For each parent study, the SAF will be defined as in the protocol of the parent study.

FAS = Full Analysis Set; SAF = Safety Analysis Set.

9.4 Statistical Analyses

Full details of all planned analyses will be described in the study IAP. Additional specifications may be provided in separate IAPs or addenda to existing Statistical Analysis Plans (SAPs) or IAPs of parent protocols. Major modifications of planned analyses will be reflected in a protocol amendment or in the clinical study report.

For the purpose of statistical analyses, data from the respective parent protocol will be merged with the data that were recorded under the rollover protocol for the participants of the parent study. Endpoint analyses will be based upon the analysis sets defined in the respective parent protocols.

For the rollover study, Follow-up analyses of safety and efficacy will be performed using the methodology described in the respective parent study protocol. The baseline time point from the parent study will be the baseline for safety and efficacy analyses.

In order to provide overall estimates of treatment effects, data will be pooled across study centers. The factor ‘center’ will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of participants randomized at each center.

In general, continuous variables will be summarized using number (n), mean, standard deviation, median, first and third quartiles, minimum, and maximum. Categorical variables will be summarized using counts and percentages of participants in each category.

The calculation of proportions will be based on the number of participants in the analysis set of interest, unless otherwise specified in the study IAP. Statistical analyses will be performed using SAS® Software, Version 9.4 (SAS Institute Inc., Cary, NC, USA) or higher or (R Core team, 2013).

9.4.1 Efficacy Analyses

All efficacy analyses will be performed on the Full Analysis population.

As stated in the previous section, endpoint analyses will be based on the analysis sets defined in the respective parent protocols. Further details on efficacy endpoint analyses will be specified in the IAP and finalized before database lock.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis population defined in the protocol of the respective parent study.

The on-treatment period is defined as the time from the first dose of study intervention administration in the parent study to the last study intervention administration date + 30 days or the earliest date of subsequent anticancer drug therapy minus 1 day, whichever occurs first, unless otherwise stated.

Safety endpoints include, but are not limited to, TEAEs, SAEs, treatment-related AEs, AESIs, irAEs, and IRRs, as well as clinical laboratory assessments, vital signs, and ECOG PS as described in Section 8.2.

The definitions, procedures for recording, evaluating, Follow-up, and reporting of AEs are described in Appendix 4.

TEAEs are those events with onset dates occurring during the on-treatment period or if the worsening of an event is during the on-treatment period. Severity of AEs will be graded using the version of CTCAE toxicity grades used in the respective parent study.

All premature terminations will be summarized by primary reason for treatment discontinuation/withdrawal.

As stated in the previous section, safety analyses will focus on the occurrence of new AEs that have not been reported in the parent studies to assess if they lead to changes in the safety assessment, as given in the clinical study report of the respective parent study.

Participants will be analyzed according to the actual treatment they receive. The specifics for analysis methods will be defined in the IAP and finalized before database lock.

Endpoint	Statistical Analysis Methods
Primary To evaluate clinical safety of bintrafusp alfa in participants with solid tumors who continue treatment after completion of the primary/main analyses in parent bintrafusp alfa studies.	The safety endpoints will be tabulated using descriptive statistics using MedDRA preferred terms and system organ class.
Secondary	Not applicable

9.4.3 Other Analyses

Not applicable

9.4.4 Sequence of Analyses

Analyses will be conducted once the last participant is off treatment. Any other analyses per indication or per parent protocol will be conducted at time points that remain to be determined, e.g., for the purpose of reporting to Health Authorities or for scientific publications.

10 References

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11 Appendices

Appendix 1 Abbreviations

AE(s)	Adverse event(s)
AESIs	Adverse events of special interest
AECI	Adverse events of clinical importance
anti-PD-L1	Antibody blocking programmed death-ligand 1
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
BOR	Best overall response
CI	Confidence Interval
CR	Complete response
CRF	Case report form
cSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
CCI	[redacted]
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
IWRS	Interactive Web Response System
FAS	Full Analysis Set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

HRT	Hormonal replacement therapy
IAP	Integrated Analysis Plan
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
irAEs	Immune-related adverse events
IRB	Institutional Review Board
IRR	Infusion-related reactions
IV	Intravenous
KA	Keratoacanthoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NCCN	National Comprehensive Cancer Network
NIMP	Non-Investigational Medicinal Product
NSCLC	Non-small cell lung carcinoma
OS	Overall survival
ORR	Overall response rate
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
CCI	[redacted]
PK	Pharmacokinetic(s)

PR	Partial response
PT	Preferred term
PS	Performance status
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE(s)	Serious adverse event(s)
SD	Stable disease
SoA	Schedule of activities
SoC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TGFβ	Transforming growth factor β
TNBC	Triple-negative breast cancer
TEAE(s)	Treatment-emergent adverse event(s)
WOCBP	Woman of childbearing potential

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative (where allowed by local laws and regulations) and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants or their legally-authorized representative (where allowed by local laws and regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; the Japanese ministerial ordinance on Good Clinical Practice (GCP); local regulations; internal conference on harmonization (ICH) guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent will also sign the ICF.
- If the ICF is updated during their participation in the study, participants will be re-consented to the most current, approved version.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor will inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant and pregnant partners (if applicable), who will be required to give consent for their data to be used, as specified in the informed consent.
- The participant will be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

The Coordinating or Principal Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will

provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.

Details of structures and associated procedures will be defined in a separate Operations Manual.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH GCP Guidelines
  - For studies with Japanese site, the Japanese ministerial ordinance on GCP
  - Applicable laws and regulations
- The protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) will be submitted to an IRB/IEC for review and approval before the study is initiated.
- For studies with Japanese sites. The Sponsor initiates the study at a site after obtaining written approval from the Head of the study site, based on favorable opinion/approval from the concerned IRB.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

  When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor (or designee) physician. This includes provision of a 24-hour contact number at a

call center, whereby the health care providers will be given access to the appropriate Sponsor (or designee) physician to assist with the medical emergency.

Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating in the study. Insurance conditions will meet good local standards, as applicable.

The Sponsor is entirely responsible for AEs that are associated with this study and cause damage to the health of the participants, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the study site, and/or the participant. The Sponsor takes out insurance to fulfill the responsibility.

Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Coordinating Investigator or other relevant study-appointed committees or groups.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

After completion of the study, a Clinical Study Report according to ICH Topic E3 will be written by the Sponsor or the designated CRO in consultation with the Coordinating Investigator. The first publication will be a publication of the results of the analysis of the endpoints that will include data from all study sites that participated in the parent study. The Investigators will inform the Sponsor in advance of any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations etc), either in whole or in part, by Investigators or their representatives will require pre-submission review by the Sponsor.

The Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

Data Quality Assurance

- All participant study data will be recorded on printed or eCRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Study Reference Manual.

- The Investigator will maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- Quality Tolerance Limits (QTLs) will be pre-defined in the applicable project management database to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan or contracts.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.
- Study Monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, the Japanese ministerial ordinance on GCP, and all applicable regulatory requirements.
- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator will maintain source documents that support the data recorded in the CRFs.
- Data recorded on CRFs that are transcribed from source documents will be consistent with the source documents or the discrepancies will be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records will be available.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator or a record retainer designated by the Head of the study site ensures that no destruction of medical records is performed without the Sponsor's written approval.

- Definition of what constitutes source data is found in case report form guidelines.

Study and Site Start and Closure

- The study start date is the date when the clinical study will be open for recruitment.

Study and Site Termination

- The Investigator may initiate site closure at any time, provided there is reasonable cause and enough notice is given in advance of the intended closure.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of participants by the Investigator
  - Discontinuation of further development of the Sponsor’s compound
- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any third-party service providers used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or Follow-up.

Appendix 3 Contraception

Woman of Childbearing Potential

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

A WOCBP is **not**:

1. Premenarchal
2. A premenopausal female with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Documentation can come from the site personnel's review of the female's medical records, medical examination, or medical history interview.

   For a female with permanent infertility due to an alternate medical cause other than the above, (e.g. mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.
3. A postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.
   - A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation*
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

* Not approved in Japan

Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal*
  - Transdermal*
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - Oral
  - Injectable*
- Sexual abstinence: a highly effective method **only** if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence is evaluated in relation to the duration of the study.
- * Not approved in Japan

Acceptable Methods

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide**. Male condom and female condom cannot be used together (due to risk of failure with friction)
- Cervical cap*, diaphragm, or sponge with spermicide*
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)

* Not approved in Japan
** Not available in Japan

Contraceptive use by men or women is consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

Highly effective methods have a failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Acceptable methods are considered effective, but **not** highly effective (i.e. have a failure rate of ≥ 1% per year). Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are **not** acceptable methods of contraception.

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not.
- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or a SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or a SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Unless judged by the Investigator to be more severe than expected for the participant's condition, any clinically significant abnormal laboratory findings, other abnormal safety assessments that are associated with the underlying disease, the disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) will not be reported as AEs/SAEs, unless the participant's general condition is more severe than expected for his/her condition and/or unless the outcome is fatal within the AE reporting period, as defined in Section 8.3.1.

Other Adverse Events to be Reported Using a Specialized Procedure or Form

Not applicable.

SAE Definition

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE will be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is **not** intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are usually considered as serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Any suspected transmission of an infectious agent via a study intervention is also considered an SAE for reporting purposes, as specified below for reporting SAEs.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- As needed, Sponsor/designee may ask for copies of certain medical records (e.g., autopsy reports, supplemental lab reports, documents on medical history/concomitant medications, discharge letters), as supporting source documentation. All participant identifiers, except the participant number, will be redacted on these copies before submission to Sponsor/designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- Specific guidance is in the CRF Completion and Monitoring Conventions.

Assessment of Intensity

The Investigator will assess the intensity of each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. Do not confuse an AE that is assessed as severe with a SAE. Severe is a category used to rate the intensity of an event; both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least one of the predefined criteria specified in the definition of an SAE, NOT when it is rated as severe.

Investigators will reference the National Cancer Institute - Common Terminology Criteria for AEs (NCI-CTCAE), version 5.0 (publication date: 27 November 2017), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria specified below.

If death occurs, the primary cause of death or event leading to death will be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might then be reported as an SAE.

Assessment of Causality

- The Investigator will assess the relationship between study intervention and each AE/SAE occurrence:
- Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention. A reasonable alternative explanation will be available.
- Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator will document in the medical notes that he/she has reviewed the AE/SAE and assessed causality.
- There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. To meet the reporting timeline, the causality assessment is not required for the initial report.
- The Investigator may change his/her causality assessment after considering follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by Sponsor/designee to elucidate the nature and/or causality of the AE or SAE, as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Sponsor/designee with a copy of any post-mortem findings including histopathology
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to Sponsor/designee within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting by an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor or its designee will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool, specified below, to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Sponsor's safety department.
- By exception, an SAE (or follow-up information) may be reported by telephone. The site will complete the electronic SAE data entry immediately thereafter.

SAE Reporting by a Paper Form

- SAE reporting on a paper report form is used as a back-up method for an electronic data capture (EDC) system failure. The form includes completion instructions for the Investigator, names, addresses, and telephone and fax numbers. All information from the paper form will be transcribed into the electronic form as soon as the system becomes available.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the form within 24 hours after becoming aware of the event.
- Additional documents (e.g. laboratory reports, autopsy report, hospital discharge letter) and relevant pages from the CRF may be required in addition (e.g. medical history, concomitant medication). The data provided will be consistent with the information in the CRF.

Reporting of Pregnancies

- Pregnancy will be reported whether related to the study intervention using the applicable paper form.
- The applicable form will be used to report if an abnormal outcome of the pregnancy occurs and the child/fetus sustains an event.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.

Appendix 5 Liver Safety: Suggested Actions and Follow-up Assessments

Not applicable

Appendix 6 Clinical Laboratory Tests

Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count[d]		Mean corpuscular volume (MCV)	White blood cell (WBC) Count with Differential[d]: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Reticulocytes (%)		Mean corpuscular hemoglobin concentration (MCHC)	
	Hemoglobin[d]		Mean corpuscular hemoglobin (MCH)	
	Hematocrit		Activated partial thromboplastin time (aPTT)[a]	
	Red blood cell count[d]		Prothrombin time[a]	
	Absolute lymphocyte count[d]		International normalized ratio (INR)[a]	
	Absolute neutrophil count[d]			
Biochemistry	Blood Urea Nitrogen/Total urea	Potassium	Aspartate Aminotransferase[d]	Bilirubin (total, indirect/direct)[d]
	Creatinine[d]	Sodium	Alanine Aminotransferase[d]	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Tuberculin skin test, QuantiFERON-TB-Gold, or T-SPOT
	Lipase	Chloride	Albumin	
	C-reactive protein	Amylase		
Routine Urinalysis	Physical appearance (color and transparency) • Specific gravity by dipstick • pH, glucose, protein, blood/hemoglobin, ketones, bilirubin, urobilinogen, nitrite, leukocytes by dipstick Microscopic examination (if blood or protein is abnormal). Urine culture by suspicion of urinary tract infection			
Other Screening Tests	• Follicle-stimulating hormone (FSH) and estradiol (as needed if **not** a woman of childbearing potential [WOCBP] only) • Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (WOCBP only) • Hepatitis Screening[b]: Hepatitis B surface antigen; Hepatitis B core antibody and Hepatitis C antibody • HIV; HIV virus RNA, quantitative; and CD4 lymphocyte count[c]			

[a] Coagulation parameters collected at Baseline and as clinically indicated, thereafter (See Table 1).

[b] As clinically indicated in participants with a history of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. If hepatitis B surface antigen positive and hepatitis B core antibody positive, then reflex to quantitative HBV DNA polymerase chain reaction (PCR); if hepatitis B core antibody positive alone, then reflex to quantitative hepatitis B DNA (PCR); if hepatitis C antibody positive, then reflex to quantitative hepatitis C RNA (PCR).

Laboratory Assessments	Parameters
[c] Not required for all participants. Only applicable for participants with a history of HIV. Testing as clinically indicated for participants with known history of HIV. Participants must be adequately consented per local regulations for any HIV-related testing. [d] Results must be reviewed by the Investigator within 3 days prior to dosing.	

Appendix 7 Pharmacokinetic Parameters

Not applicable

CCI

Appendix 9 Country-specific Requirements

Not applicable

Appendix 10 List of Bintrafusp alfa Studies from Which Participants May be Enrolled

A list of the potential parent bintrafusp alfa studies from which participants may be enrolled into this rollover study is provided below. For the other parent studies, the Sponsor will inform investigators when participants may be transferred to the rollover study.

- EMR200647-001: A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of MSB0011359C in subjects with metastatic or locally advanced solid tumors and expansion to selected indications.
- MS200647_0005: A Multicenter, Double Blind, Randomized, Controlled Study of M7824 with Concurrent Chemoradiation Followed by M7824 versus Concurrent Chemoradiation Plus Placebo Followed by Durvalumab in Participants with Unresectable Stage III Non-small Cell Lung Cancer.
- MS200647-0008: A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of MSB0011359C in subjects with metastatic or locally advanced solid tumors with expansion to selected indications in Asia.
- MS200647_0017: A Phase II, Multicenter, Open Label Study of Bintrafusp alfa (M7824) Monotherapy in Participants with Advanced, Unresectable Cervical Cancer with Disease Progression During or After Platinum-Containing Chemotherapy.
- MS200647_0020: A Phase II, Multicenter, Open Label Study of Bintrafusp alfa (M7824) Monotherapy in Participants with HMGA2-expressing Triple-Negative Breast Cancer.
- MS200647_0024: A Phase Ib/II, Open-Label Study of M7824 in Combination with Anti-cancer Therapies in Participants with Stage IV Non-small Cell Lung Cancer.
- MS200647_0037: An Adaptive Phase III, Multicenter, Randomized, Open-Label, Controlled Study of M7824 (bintrafusp alfa) versus Pembrolizumab as a First line Treatment in Patients with PD-L1 Expressing Advanced Non-small Cell Lung Cancer.
- MS200647_0046: Safety Study of Bintrafusp alfa in Combination with Other Anti-cancer Therapies in Participants with Locally Advanced or Advanced Cervical Cancer.
- MS200647_0047: A Phase II, Multicenter, Open label Study to Investigate the Clinical Efficacy of M7824 Monotherapy in Participants With Locally Advanced or Metastatic Biliary Tract Cancer Who Fail or are Intolerant to First line Platinum Based Chemotherapy.
- MS200647_0055: A Phase II/III, Multicenter, Randomized, Placebo controlled Study of Gemcitabine Plus Cisplatin With or Without Bintrafusp alfa (M7824) as First line Treatment of Biliary Tract Cancer.

Appendix 11 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

The text below was obtained from the following reference: Eisenhauer 2009.

Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the RECIST Committee (Version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
- 10 mm caliper measurement by clinical exam (when superficial)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

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

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other local regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as **target lesions** and recorded and measured at Baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at Baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g.,'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation, using calipers if clinically assessed. All Baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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

No photographs, no skin lesion measurement by calipers and no measurements on chest X-ray will be done in this study.

CT, MRI: Computed Tomography is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II of the original source article cited above, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from 1 assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following CR or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit; however, they must normalize for a participant to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic

Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential AE of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and PD.

RESPONSE CRITERIA

Evaluation of Target Lesions

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

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

PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).

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

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the Baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms (CRFs) or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at Baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at Baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely

that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

When the participant also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the participant has only non-measurable disease. This circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concept applies here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing participants for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be

required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the participant should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (e.g., some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the participant's Baseline lesions show partial or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at Baseline is considered a new lesion and will indicate PD. An example of this is the participant who has visceral disease at Baseline and while on study has a brain CT or MRI ordered which reveals metastases. The participant's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at Baseline.

If a new lesion is equivocal, e.g., because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

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

a. Negative FDG-PET at Baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at Baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The best overall response (BOR) is the best response recorded from the start of the study intervention until the end of treatment taking into account any requirement for confirmation. On occasion, a response may not be documented until after the end of therapy, so protocols should be clear if post-treatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The participant's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either 1 the 'BOR'.

The BOR is determined once all the data for the participant is known. Best response determination in studies where confirmation of complete or PR IS NOT required: Best response in these studies is defined as the best response across all time points (for example, a participant who has SD at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When SD is believed to be best response, it must also meet the protocol-specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the participant's best response depends on the subsequent assessments. For example, a participant who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same participant lost to follow-up after the first SD assessment would be considered inevaluable.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	Partial response
CR	Not Evaluated	No	Partial response
Partial response	Non-PD or not all evaluated	No	Partial response
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, NE=not evaluable, PD=progressive disease, SD=stable disease.
See text for more details.

Note:

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of 'zero' on the eCRF.

In studies where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be addressed in determination of response and progression. For example, in most studies, it is reasonable to consider a participant with time point responses of PR-NE-PR as a confirmed response.

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy.

Conditions that define 'early progression, early death, and inevaluability' are study-specific and should be clearly described in each protocol (depending on treatment duration, and treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. The use of FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In non-randomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure the responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies. However, in all other circumstances, i.e., in randomized studies (Phase II or III) or studies where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of the study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 to 8 weeks) that is defined in the study protocol.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

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

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of participants achieving SD for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.

Note: The DOR and SD as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

Appendix 12 Protocol Amendment History

The information for the current amendment is on the title page.

Appendix 13 Sponsor Signature Page

Study Title:	An Open-label, Multicenter Follow-up Study to Collect Long-term Data on Participants from Multiple Bintrafusp alfa (M7824) Clinical Studies
Regulatory Agency Identifying Numbers:	CCI [redacted] EudraCT: 2021-000179-36
Clinical Study Protocol Version:	30 November 2021/Version 2.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	Protocol Lead
Institution:	Merck Healthcare KGaA, Darmstadt, Germany
Address:	EMD Serono Research & Development Institute, Inc. | 45A Middlesex Turnpike | Billerica, MA 01821 | USA
Telephone number:	PPD
Fax number:	Not Applicable
E-mail address:	PPD

Appendix 14 Coordinating Investigator Signature Page

Study Title:	An Open-label, Multicenter Follow-up Study to Collect Long-term Data on Participants from Multiple Bintrafusp alfa (M7824) Clinical Studies
Regulatory Agency Identifying Numbers:	CCI [redacted] EudraCT: 2021-000179-36
Clinical Study Protocol Version:	30 November 2021/Version 2.0
Site Number:	

I approve the design of the clinical study, am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

Alexander Spira MD

Digitally signed by Alexander Spira MD
Date: 2021.12.02 08:08:05 -05'00'

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	Coordinating Investigator
Institution:	US Oncology
Address:	PPD
Telephone number:	
Fax number:	
E-mail address:	

Appendix 15 Principal Investigator Signature Page

Study Title:	An Open-label, Multicenter Follow-up Study to Collect Long-term Data on Participants from Multiple Bintrafusp alfa (M7824) Clinical Studies
Regulatory Agency Identifying Numbers:	IND: CCI EudraCT: 2021-000179-36
Clinical Study Protocol Version:	30 November 2021/Version 2.0
Site Number:	

I am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: