

Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	Safety Study of Bintrafusp alfa in Combination with Other Anti-cancer Therapies in Participants with Locally Advanced or Advanced Cervical Cancer
Study Number:	MS200647_0046
Protocol Version:	06 July 2021/Version 2.0
Merck Compound:	M7824
Merck Registered Compound Name in Japan:	Not Applicable
Study Phase:	Phase Ib
Short Title:	Phase Ib Bintrafusp alfa Combination Therapy in Cervical Cancer
Acronym or Abbreviation:	INTR@PID 046
Coordinating Investigator:	PPD [REDACTED]

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Regulatory Agency Identifying Numbers:	IND: [REDACTED] EudraCT: 2020-001561-36

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	02-Jul-2020
2.0	Global Amendment	06-Jul-2021

Protocol Version 2.0 (06-July-2021)

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.

Overall Rationale for the Amendment

The primary purpose of this amendment is to update the risk classification.

Section # and Name	Description of Change	Brief Rationale
Title Page	Revised "Amendment Number" row Removed "Medical Responsible" field Removed "Protocol Version", "Replaces Version", "Approval Date" and "Medical Monitor Contact Information" rows.	To be consistent with current Sponsor protocol template (Version 15).
2.3 Benefit/Risk Assessment	Risk classification has been revised and the list of events has been updated accordingly. The statement referring to the number of patients treated with bintrafusp alfa monotherapy has been removed.	The risk reclassification was based on in-depth analysis of a pooled safety dataset of N = 765 participants who received bintrafusp alfa monotherapy at 1200 mg Q2W. The information on the number of participants treated with bintrafusp alfa is provided in the IB.
5 Study Population Appendix 2 Study Governance	Edits related to informed consent process.	To be consistent with current Sponsor protocol template (Version 15).
7.3 Lost to Follow-up	Edit related to Lost to Follow-up information.	To be consistent with current Sponsor protocol template (Version 15).

Section # and Name	Description of Change	Brief Rationale
6.8.2 Bintrafusp alfa 8.3.6 Adverse Events of Special Interest Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Risk categorization has been revised and the list of events has been updated accordingly.	The risk reclassification was based on in-depth analysis of a pooled safety dataset of N = 765 participants who received bintrafusp alfa monotherapy at 1200 mg Q2W.
8.3.6.1 Infusion-related Reactions Including Hypersensitivity	Infusion-related reactions are reclassified from “important identified risk” to “identified risk” for bintrafusp alfa.	
8.3.6.1, Table 10 Treatment Modification of Bintrafusp alfa for Symptoms of Infusion-Related Reactions Including Hypersensitivity	Additional details of treatment modifications for severe or life-threatening reactions have been added.	
8.3.6.2 Immune-related Adverse Events	Risk categorization has been revised and the list of events has been updated accordingly.	
8.3.6.3 TGF-β Inhibition Mediated Skin Reactions	Skin Adverse Events have been renamed to TGF-β Inhibition Mediated Skin Reactions.	
8.3.6.4 Anemia	Term “treatment-related anemia events” has been revised to “anemia” and reclassified from “important potential risk” to “important identified risk” for bintrafusp alfa.	
8.5.6.5 Bleeding Events	Bleeding events are reclassified from “potential risk” to “important identified risk” for bintrafusp alfa.	
8.3.7.1 Impaired Wound Healing	The risk name “Alterations in Wound Healing or Repair of Tissue Damage” has been changed to “Impaired Wound Healing”.	To clarify study procedures.
6.8.4.1 Risk Management for Chemotherapy	Text has been updated to clarify dosing delays requiring discontinuation of chemotherapy are >3 weeks from the day of scheduled administration.	
Note: Minor changes have been performed throughout the protocol to address consistency pertaining to major changes made in the protocol or to add further clarity and precision.		

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1 Protocol Summary

1.1 Synopsis

Protocol Title: Safety Study of Bintrafusp alfa in Combination with Other Anti-cancer Therapies in Participants with Locally Advanced or Advanced Cervical Cancer

Short Title: Phase Ib Bintrafusp alfa Combination Therapy in Cervical Cancer

CCI [REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of bintrafusp alfa in combination with (1) chemotherapy with or without bevacizumab in participants with recurrent, persistent, or metastatic cervical cancer or (2) platinum therapy and definitive radiation in participants with locally advanced cervical cancer	<ul style="list-style-type: none"> • Occurrence of DLTs • AEs
Secondary	
To evaluate the safety and tolerability of bintrafusp alfa in combination with (1) chemotherapy with or without bevacizumab in Japanese participants with recurrent, persistent, or metastatic cervical cancer or (2) platinum therapy and definitive radiation in Japanese participants with locally advanced cervical cancer	<ul style="list-style-type: none"> • Occurrence of DLTs • AEs
To characterize PK profile of bintrafusp alfa	<ul style="list-style-type: none"> • PK profile of bintrafusp alfa in terms of C_{eoi} and C_{trough} for all participants throughout the treatment period • PK profile of bintrafusp alfa in terms of AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{1/2}$ in Cycle 1
To evaluate the immunogenicity of bintrafusp alfa	<ul style="list-style-type: none"> • Immunogenicity of bintrafusp alfa, as measured by ADA assay, from Day 1 predose through the last Safety Follow-up Visit
<p>ADA=antidrug antibody, AE=adverse event, AUC_{0-t}=area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification calculated using the mixed log-linear trapezoidal rule (linear up, log down), $AUC_{0-\infty}$=AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last}, as estimated using the linear regression from λz determination, $AUC_{0-\infty}=AUC_{0-t} + C_{last\ pred}/\lambda z$, C_{eoi}=concentration immediately at the end of infusion, C_{max}=maximum serum concentration observed postdose, C_{trough}=concentration immediately before next dosing, DLT=dose-limiting toxicity, PK=pharmacokinetic, q3w=every 3 weeks, t_{max}=time at which the C_{max} occurs, $t_{1/2}$=elimination half-life determined as $0.693/\lambda z$, λz=terminal first order (elimination) rate constant.</p>	

Overall Design:

This study will be conducted with Cohort 1 (Cohort 1A and Cohort 1B) and Cohort 2 in parallel.

The allocation of participants to Cohort 1A or Cohort 1B will be based on Investigator decision and also other factors including but not limited to study inclusion/exclusion criteria and local standard of care.

Cohort 1

Participants must have primary Stage IVB, recurrent or persistent squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix not amenable to curative treatment with surgery and/or radiation therapy and not have been treated with systemic chemotherapy.

- Cohort 1A: 8 participants will be treated with bintrafusp alfa (2400 mg every 3 weeks) + cisplatin or carboplatin + paclitaxel + bevacizumab. Selection of cisplatin or carboplatin is at the Investigator discretion.
- Cohort 1B: 8 participants will be treated with bintrafusp alfa (2400 mg every 3 weeks) + cisplatin or carboplatin + paclitaxel. Selection of cisplatin or carboplatin is at the Investigator discretion.

If the first 8 participants of each subcohort separately include fewer than 3 participants from Japan, the Sponsor may elect to continue enrollment to include 3 participants from Japan to evaluate the safety of this combination in Japanese participants. If the first 8 participants of each subcohort separately include fewer than 3 participants from Europe or the United States, enrollment may continue in Europe and the United States to include at least 3 participants from any of these countries.

Cohort 2:

Participants with locally advanced cervical cancer will be treated with bintrafusp alfa (2400 mg every 3 weeks) combined with definitive radiation and radiation-sensitizing platinum therapy (cisplatin) during cCRT, followed by maintenance with bintrafusp alfa monotherapy (2400 mg every 3 weeks).

If the first 8 participants include fewer than 3 participants from Japan, enrollment may continue in Japan to include at least 3 participants from Japan to evaluate the safety of this combination in Japanese participants. If the first 8 participants of this cohort include fewer than 3 participants from Europe or the United States, enrollment may continue in Europe and the United States to include at least 3 participants from any of these countries.

Disclosure Statement: This is a non-randomized, non-blinded study conducted with Cohorts 1 (Cohort 1A and Cohort 1B) and 2.

Number of Arms: 3 cohorts (1A, 1B, and 2)

Blinding: No blinding

Number of Participants:

In total, approximately 24 participants will be enrolled in this study. For each of the cohorts (1A, 1B, and 2), at least 8 participants will be enrolled to evaluate the safety of each combination treatment.

The Safety Monitoring Committee (SMC) will evaluate the safety in each cohort separately after the 3rd and after the 8th evaluable participant completes the respective dose-limiting toxicity (DLT) period. In the case more participants are included and complete the DLT period as per enrollment, all the participants will continue to be evaluated by the SMC, if required. In addition, the SMC will evaluate the safety from all participants as needed.

During the DLT observation period, in the event a participant discontinues for reasons other than adverse events (AE) or is otherwise non-evaluable, the Sponsor may elect to add an additional participant.

Study Intervention Groups and Duration:

The study includes:

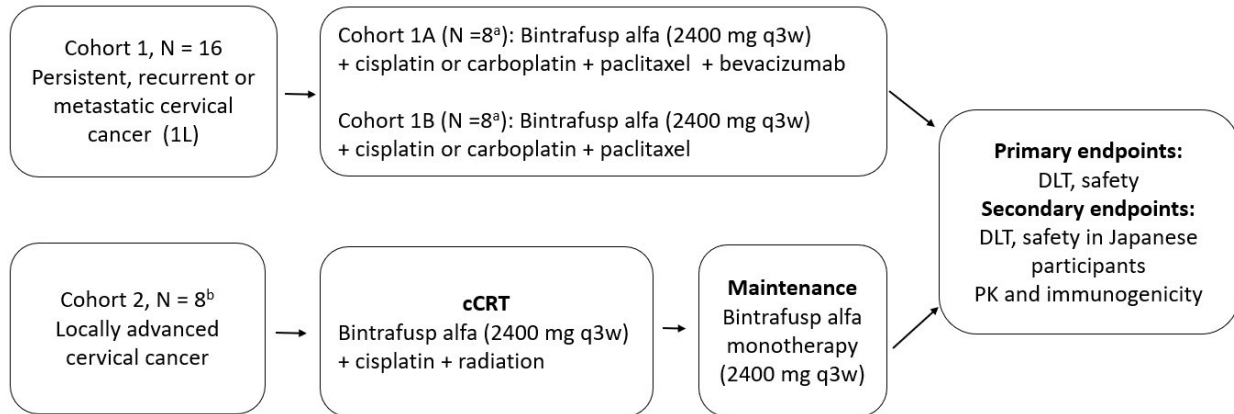
- Up to 28-day Screening period.
- The DLT observation period of 4 weeks from the Week 1, Day 1 (W1D1) visit for all cohorts.
- Treatment until progressive disease (PD) by Response Evaluation Criteria in Solid Tumors Version 1.1 and subsequent confirmation (at the next imaging visit at least 28 days after the detection of PD) unacceptable toxicity, study withdrawal, or death.
- In case of PD, treatment may continue if the participant's Eastern Cooperative Oncology Group Performance Status has remained at least stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment, and if other criteria are fulfilled as outlined in the protocol.
- Cohort 1 participants will continue chemotherapy until complete response (CR) (as clinically indicated) and/or unacceptable toxicity due to chemotherapy, after which, bintrafusp alfa ± bevacizumab (depending on cohort) may be continued until 2 years or unacceptable toxicity as indicated for bintrafusp alfa and/or bevacizumab. If the Investigator believes that a participant may benefit from treatment beyond 2 years, it may be permissible to continue treatment after discussion with the Medical Monitor and the Sponsor's Medical Responsible.
- Cohort 2 participants should continue maintenance treatment (bintrafusp alfa) for a maximum of 2 years (at the discretion of the Investigator). If the Investigator believes that a participant may benefit from treatment beyond 2 years, it may be permissible to continue treatment after discussion with the Medical Monitor and the Sponsor's Medical Responsible.
- All participants should continue treatment until confirmed disease progression or any other discontinuation criterion is met (e.g., unacceptable toxicity, withdrawal of consent).
- Safety Follow-up Visits are at 28 days (± 5 days) and 12 weeks (± 2 weeks) after the last dose of study intervention according to the Schedule of Activities.
- Long-term Follow-up should be performed every 12 weeks (± 2 weeks) after the Safety Follow-up.
- Survival Follow-up will continue until the end of study. After the stipulated end of study, Survival Follow-up may continue until the last participant has died or at the discretion of the Sponsor.

Involvement of Special Committee(s): Yes

The SMC will evaluate the safety (including DLTs) and other available data. The specific working procedures will be described in an SMC charter.

1.2 Schema

Figure 1 Study Schema



1L=first-line, cCRT= concomitant chemoradiation therapy, DLT=dose-limiting toxicity, PK=pharmacokinetics, q3w=every 3 weeks.

^a For Cohort 1A and Cohort 1B, if the first 8 participants of each subcohort separately include fewer than 3 participants from Japan, the Sponsor may elect to continue enrollment to include 3 participants from Japan to evaluate the safety of this combination in Japanese participants. If the first 8 participants of each subcohort separately include fewer than 3 participants from Europe or the United States, enrollment may continue in Europe and the United States to include at least 3 participants from any of these countries.

^b For Cohort 2, if the first 8 participants include fewer than 3 participants from Japan, enrollment may continue in Japan to include at least 3 participants from Japan to evaluate the safety of this combination in Japanese participants. If the first 8 participants of this cohort include fewer than 3 participants from Europe or the United States, enrollment may continue in Europe and the United States to include at least 3 participants from any of these countries.

1.3 Schedule of Activities

1.3.1 Schedule of Activities for Cohort 1

For Cohort 1 (Cohort 1A and Cohort 1B), Schedule of Activities are provided in [Table 1](#) (Schedule of Activities for Cohort 1) and [Table 2](#) (Schedule of Activities for PK and ADA Sampling in Cohort 1).

Table 1 Schedule of Activities for Cohort 1

Assessments & Procedures	Screening Day -28 to W1D1	Intervention Period (± 3 days)					EoT Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
		V1*	V4*	V5	V6	V7		28 Days (± 5 days) After Last Treatment	12 Weeks (± 2 weeks) After Last Treatment		
		W1	W4	W7	W10	W13					
		D1	D22	D43	D64	D85	Until EoT	On the Day of or Within 7 Days of Decision	Every 12 Weeks (± 2 weeks)		*Schedule for PK Samples is as Specified in Table 2
Administrative Procedures											
Written informed consent	X										Screening tests performed as part of routine care prior to informed consent signed will be accepted if they are within 28-day screening window (see Section 5.4).
Inclusion/exclusion/enrollment (if eligible)	X	X									
Demographic data	X										
Medical history	X										

Assessments & Procedures	Screening Day -28 to W1D1	Intervention Period (± 3 days)					EoT Visit	Safety Follow-up Visit		Long-term Follow-up	Notes	
		V1*	V4*	V5	V6	V7		28 Days (± 5 days) After Last Treatment	12 Weeks (± 2 weeks) After Last Treatment			
		W1	W4	W7	W10	W13						
		D1	D22	D43	D64	D85	Until EoT	On the Day of or Within 7 Days of Decision		Every 12 Weeks (± 2 weeks)		
Prior anti-cancer drug/ radiotherapy/ procedures for Baseline visit	X											Prior anti-cancer procedures and therapies should at least include prior therapy, prior diagnosis of premalignant lesions and treatments, surgical resection and recurrence, and details on anti-cancer treatments, treatment duration, and treatment responses.
Documentation of concomitant medication and procedures	X	X	X	X	X	X	Every 3 weeks	X	X	X	X	The 12-week Safety Follow-up and Long-term Follow-up may be conducted via telephone calls or patient chart reviews as necessary unless there is medical necessity requiring a clinical visit.
Drug Administration												
Bintrafusp alfa		X	X	X	X	X	Every 3 weeks					See Section 6 for dosing details and order of infusion. See Section 7 for stopping study interventions.
Cohort 1A: Cisplatin or carboplatin + paclitaxel + bevacizumab		X	X	X	X	X	Every 3 weeks					Cisplatin or carboplatin, paclitaxel, and bevacizumab are administered as indicated for standard of care treatment. Premedication is required for chemotherapy, see Section 6 for premedication and order of infusion and Section 7 for stopping study interventions.

Assessments & Procedures	Screening Day -28 to W1D1	Intervention Period (± 3 days)						EoT Visit On the Day of or Within 7 Days of Decision	Safety Follow-up Visit		Long-term Follow-up Every 12 Weeks (± 2 weeks)	Notes *Schedule for PK Samples is as Specified in Table 2
		V1*	V4*	V5	V6	V7	Until EoT		28 Days (± 5 days) After Last Treatment	12 Weeks (± 2 weeks) After Last Treatment		
		W1	W4	W7	W10	W13						
		D1	D22	D43	D64	D85						
Cohort 1B: Cisplatin or carboplatin + paclitaxel		X	X	X	X	X	Every 3 weeks					Cisplatin or carboplatin, plus paclitaxel are administered as indicated for standard of care treatment. Premedication is required for chemotherapy, see Section 6 for premedication and order of infusion and Section 7 for stopping study interventions.
Safety Assessment												
Documentation of AEs	X	X	X	X	X	X	Every 3 weeks	X	X	X ^a	X ^a	See Appendix 4 for safety recording and reporting. a: The 12-week Safety Follow-up and Long-term Follow-up may be conducted via telephone calls or patient chart reviews as necessary unless there is medical necessity requiring a clinical visit.
Physical examination	X	X	X	X	X	X	Every 3 weeks	X	X			Complete physical examination to be performed at Screening; subsequent focused examinations to be performed as described in Section 8.2.1.
Skin assessment	X			X		X	Every 6 weeks	X	X			See Section 8.3.6.3 for skin assessment.
Vital signs	X	X	X	X	X	X	Every 3 weeks	X	X			Including weight and height (height at Screening only). See Section 8.2.2.
ECOG PS	X	X	X	X	X	X	Every 3 weeks	X	X			
12-lead ECG	X	12-lead ECG will be repeated if clinically indicated										

Assessments & Procedures	Screening Day -28 to W1D1	Intervention Period (± 3 days)					Until EoT	EoT Visit On the Day of or Within 7 Days of Decision	Safety Follow-up Visit		Long-term Follow-up Every 12 Weeks (± 2 weeks)	Notes *Schedule for PK Samples is as Specified in Table 2
		V1*	V4*	V5	V6	V7			28 Days (± 5 days) After Last Treatment	12 Weeks (± 2 weeks) After Last Treatment		
		W1	W4	W7	W10	W13						
		D1	D22	D43	D64	D85						
Laboratory Assessments												
Virology serology (HIV)		As clinically indicated in participants with a history of HIV infection										HIV testing is not mandatory. Previous data should be collected in medical history. If a test is performed at any point at Screening or while on study, a site must consent the participant for HIV testing as per local standard guidance.
Viral serology (HBV and HCV)	X	As clinically indicated in participants with a history of HBV or HCV infection										
Hematology	X	Day 1, 8 and 15	X	X	X	X	Every 3 weeks	X	X			Hematology is listed in Appendix 5 for blood tests. Samples are drawn weekly during the first 4 weeks. Samples drawn on dosing days must also be drawn prior to dosing and results of selected laboratory tests (see Appendix 5) must be reviewed within 3 days prior to dosing.
Biochemistry	X	Day 1, 8 and 15	X	X	X	X	Every 3 weeks	X	X			Biochemistry is listed in Appendix 5 . Samples are drawn weekly during the first 4 weeks. Samples must be drawn prior to dosing and results of selected laboratory tests (see Appendix 5) must be reviewed within 3 days prior to dosing.
Coagulation parameters	X	As clinically indicated										See Appendix 5 .

Assessments & Procedures	Screening Day -28 to W1D1	Intervention Period (± 3 days)						EoT Visit On the Day of or Within 7 Days of Decision	Safety Follow-up Visit		Long-term Follow-up Every 12 Weeks (± 2 weeks)	Notes
		V1*	V4*	V5	V6	V7	Until EoT		28 Days (± 5 days) After Last Treatment	12 Weeks (± 2 weeks) After Last Treatment		
		W1	W4	W7	W10	W13						
		D1	D22	D43	D64	D85						
Proteinuria	X	X	X	X	X	X	Every 3 weeks	X	X			Results must be reviewed within 3 days prior to dosing. All participants with 2+ protein on dipstick urinalysis at Baseline must undergo a 24-hour urine collection prior to enrollment (Cohort 1A only, see Section 5.2).
Urinalysis	X	As clinically indicated										Routine urinalysis at the Screening visit. If the results abnormal, then a microscopic examination and/or culture should be performed as needed (see Appendix 5).
β-hCG pregnancy test (WOCBP only)	X	X	X	X	X	X	Every 3 weeks		X	X ^b		β-hCG should be determined at Screening and thereafter from a urine or serum sample. Results of the most recent pregnancy test should be available prior to dosing of study intervention. If a confirmation of a participant's postmenopausal status is necessary, follicle-stimulating hormone and estradiol tests will be performed at Screening. b: Participants may go to local laboratory to perform pregnancy test. Clinical visit is not required.
T4 and TSH	X			X		X	Every 6 weeks		X			
Survival Follow-up											X	Conducted via telephone calls unless there is medical necessity requiring a clinical visit.

Assessments & Procedures	Screening Day -28 to W1D1	Intervention Period (± 3 days)					EoT Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
		V1*	V4*	V5	V6	V7		28 Days (± 5 days) After Last Treatment	12 Weeks (± 2 weeks) After Last Treatment		
		W1	W4	W7	W10	W13					
		D1	D22	D43	D64	D85	Until EoT	On the Day of or Within 7 Days of Decision			*Schedule for PK Samples is as Specified in Table 2
Tumor Assessments											
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	CCI [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Assessments & Procedures	Screening Day -28 to W1D1	Intervention Period (± 3 days)					EoT Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
		V1*	V4*	V5	V6	V7		28 Days (± 5 days) After Last Treatment	12 Weeks (± 2 weeks) After Last Treatment		
		W1	W4	W7	W10	W13					
		D1	D22	D43	D64	D85	Until EoT	On the Day of or Within 7 Days of Decision		Every 12 Weeks (± 2 weeks)	*Schedule for PK Samples is as Specified in Table 2
PK, ADA and CCI											
See Table 2 for PK and ADA Sampling Schedule											
											CCI
CCI		X ⁱ									CCI
											CCI

ADA=antidrug antibody, AE=adverse event, β-hCG=β-human chorionic gonadotropin, CR=complete response, CT=computed tomography, D=Day, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EoT=End-of-Treatment, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, ICF=informed consent form, MRI=magnetic resonance imaging, PD=progressive disease, PK=pharmacokinetic, PR=partial response, T4=free thyroxine, TSH=thyroid-stimulating hormone, V=visit, W=Week, WOCBP=woman of childbearing potential.

Table 2 Schedule of Activities for PK and ADA Sampling in Cohort 1

Assessments & Procedures	Intervention Period										EoT Visit	Safety Follow-up Visit	Notes
	V1	V2	V3	V4	V5	V7	V9	V11					
	W1		W2	W3	W4	W7	W13	W19	W25	Until EoT	On Day of or Within 7 Days of Decision	28 (± 5) Days After Last Treatment	
	D1	D2	D8	D15	D22	D43	D85	D127	D169				
Blood sample for PK	X/X ^a (pre/eoi)	X ^b	X	X	X/- (pre/eoi)	X/X (pre/eoi)	X/- (pre/eoi)	X/- (pre/eoi)	X/- (pre/eoi)	X/- (pre/eoi) q12w from W25	X	X	<p>Samples for PK analysis are taken before (pre) infusion of bintrafusp alfa (as close to the start of the infusion as possible), immediately after the end of bintrafusp alfa infusion (eoi, as close to the completion as possible within 30 minutes after the end of infusion).</p> <p>The predose sample should still be drawn even if dosing is ultimately deferred at the study visit. The exact time of each draw must be recorded. A protocol deviation is defined by a sample not being drawn, or time of draw is not recorded.</p> <p>a: On <u>W1D1 only</u>, in addition to pre and eoi samples, collect a PK sample 4 hours after start of infusion.</p> <p>b: On <u>W1D2 only</u>, collect a PK sample 24 hours after start of infusion on Day 1.</p>
Blood Sample for ADA	X/- (pre/eoi)				X/- (pre/eoi)	X/- (pre/eoi)	X/- (pre/eoi)	X/- (pre/eoi)	X/- (pre/eoi)	X/- (pre/eoi) q12w from W25	X	X	<p>Predose ADA samples to be collected prior to study intervention infusions (as close to the start of the infusion as possible). The exact time of each draw must be recorded.</p>

ADA=antidrug antibody, D=day, eoi=end of infusion, EoT=End-of-Treatment, PK=pharmacokinetics, q12w=every 12 weeks, V=visit, W=week.

1.3.2 Schedule of Activities for Cohort 2

For Cohort 2, Schedule of Activities are provided in [Table 3](#) (Schedule of Activities During cCRT in Cohort 2), [Table 4](#) (Schedule of Activities After cCRT in Cohort 2), and [Table 5](#) (Schedule of Activities for PK and ADA Sampling in Cohort 2).

Table 3 Schedule of Activities During cCRT in Cohort 2

Assessments & Procedures During cCRT	Screening Day -28 to W1D1	cCRT-based Treatment (± 3 days)							End-of-cCRT Visit (+ 5 days)	Notes
		V1	V2	V3	V4	V5	V6	V7	End-of-cCRT Visit should be performed at completion of cCRT or within 5 days of decision to discontinue cCRT	
		W1	W2	W3	W4	W5	W6	W7		
		D1	D8	D15	D22	D29	D36	D43		
Administrative Procedures										
Written informed consent	X									Screening tests performed as part of routine care prior to informed consent signed will be accepted if they are within 28-day screening window (see Section 5.4).
Inclusion/exclusion/enrollment (if eligible)	X	X								
Demographic data	X									
Medical history	X									
Prior anti-cancer drug/radiotherapy/procedures for Baseline visit	X									Prior anti-cancer procedures and therapies should at least include prior therapy, prior diagnosis of premalignant lesions and treatments, surgical resection and recurrence, and details on anti-cancer treatments, treatment duration, and treatment responses.

Assessments & Procedures During cCRT	Screening Day -28 to W1D1	cCRT-based Treatment (± 3 days)							End-of-cCRT Visit (+ 5 days)	Notes
		V1	V2	V3	V4	V5	V6	V7	End-of-cCRT Visit should be performed at completion of cCRT or within 5 days of decision to discontinue cCRT	
		W1	W2	W3	W4	W5	W6	W7		
		D1	D8	D15	D22	D29	D36	D43		
Documentation of concomitant medication and procedures	X	X	X	X	X	X	X	X	X	
Treatment Administration										
Bintrafusp alfa		X			X			X	X	See Section 6 for dosing details and order of infusion/treatment. See Section 7 for stopping study interventions.
Cisplatin		X	X	X	X	X				Cisplatin is administrated as indicated for standard of care treatment as a radiation-sensitizing agent. Premedication is required for chemotherapy, see Section 6 for premedication and order of infusion/treatment and Section 7 for stopping study interventions.
Radiotherapy		X	Radiotherapy per standard of care							During site selection, clinical team will verify radiation oncology sites acceptable for this study. On study, sites must be prepared to submit radiation plans and final treatments for each participant enrolled to Cohort 2. The period for cCRT can be extended up to 1 week in case of technical and logistical issues and if participants require withholding of the study intervention due to toxicities (see Section 4.1).

Assessments & Procedures During cCRT	Screening Day -28 to W1D1	cCRT-based Treatment (± 3 days)							End-of-cCRT Visit (+ 5 days)	Notes	
		V1	V2	V3	V4	V5	V6	V7	End-of-cCRT Visit should be performed at completion of cCRT or within 5 days of decision to discontinue cCRT		
		W1	W2	W3	W4	W5	W6	W7			
		D1	D8	D15	D22	D29	D36	D43			
										CCI	
Safety Assessments											
Documentation of AEs	X	X	X	X	X	X	X	X	X	X	See Appendix 4 for safety recording and reporting.
Physical examination	X	X	X	X	X	X	X	X	X	X	Complete physical examination to be performed at Screening; subsequent focused examinations to be performed as described in Section 8.2.1 .
Skin assessment	X									X	See Section 8.3.6.3 for skin assessment.
Vital signs	X	X	X	X	X	X	X	X	X	X	Including weight and height (height at Screening only). See Section 8.2.2 .
ECOG PS	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X										

Assessments & Procedures During cCRT	Screening Day -28 to W1D1	cCRT-based Treatment (± 3 days)							End-of-cCRT Visit (+ 5 days)	Notes
		V1	V2	V3	V4	V5	V6	V7	End-of-cCRT Visit should be performed at completion of cCRT or within 5 days of decision to discontinue cCRT	
		W1	W2	W3	W4	W5	W6	W7		
		D1	D8	D15	D22	D29	D36	D43		
Laboratory Assessments										
Virology serology (HIV)		As clinically indicated in participants with a history of HIV infection								HIV testing is not mandatory. Previous data should be collected in medical history. If a test is performed at any point at Screening or while on study, a site must consent the participant for HIV testing as per local standard guidance.
Viral serology (HBV and HCV)	X	As clinically indicated in participants with a history of HBV or HCV infection								
Hematology	X	X	X	X	X	X	X	X	X	Hematology is listed in Appendix 5 for details on blood tests. Samples must also be drawn prior to dosing and results of selected laboratory tests (see Appendix 5) must be reviewed within 3 days prior to dosing.
Biochemistry	X	X	X	X	X	X	X	X	X	Biochemistry is listed in Appendix 5 . Samples must be drawn prior to dosing and results of selected laboratory tests (see Appendix 5) must be reviewed within 3 days prior to dosing.
Coagulation parameters	X	As clinically indicated								See Appendix 5 .
Urinalysis	X	As clinically indicated								Routine urinalysis at the Screening visit. If the results abnormal, then a microscopic examination and/or culture should be performed as needed (see Appendix 5).

Assessments & Procedures During cCRT	Screening Day -28 to W1D1	cCRT-based Treatment (± 3 days)							End-of-cCRT Visit (+ 5 days)	Notes	
		V1	V2	V3	V4	V5	V6	V7	End-of-cCRT Visit should be performed at completion of cCRT or within 5 days of decision to discontinue cCRT		
		W1	W2	W3	W4	W5	W6	W7			
		D1	D8	D15	D22	D29	D36	D43			
β-hCG pregnancy test (WOCBP only)	X	X			X				X	β-hCG should be determined at Screening and thereafter from a urine or serum sample. Results of the most recent pregnancy test should be available prior to dosing of study intervention. If a confirmation of a participant's postmenopausal status is necessary, follicle-stimulating hormone and estradiol tests will be performed at Screening.	
T4 and TSH	X								X		
Tumor Assessments											
											CCI [REDACTED]

Assessments & Procedures During cCRT	Screening Day -28 to W1D1	cCRT-based Treatment (± 3 days)							End-of-cCRT Visit (+ 5 days)	Notes
		V1	V2	V3	V4	V5	V6	V7	End-of-cCRT Visit should be performed at completion of cCRT or within 5 days of decision to discontinue cCRT	
		W1	W2	W3	W4	W5	W6	W7		
		D1	D8	D15	D22	D29	D36	D43		
PK, ADA, CCI										
See Table 5 for PK and ADA Sampling Schedule										
										CCI
CCI		X ^c								CCI
										CCI

ADA=antidrug antibody, AE=adverse events, β-hCG=β-human chorionic gonadotropin, cCRT=concomitant chemoradiation therapy, CR=complete response, CT=computed tomography, D=Day, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=Human immunodeficiency virus, ICF=informed consent form, MRI=magnetic resonance imaging, PD=progressive disease, PK=pharmacokinetics, PR=partial response, T4=free thyroxine, TSH=thyroid-stimulating hormone, V=visit, W=Week, WOCBP=woman of childbearing potential.

Table 4 Schedule of Activities After cCRT in Cohort 2

Assessments & Procedures after cCRT	Intervention Period after cCRT (± 3 days)							EoT Visit On the Day of or Within 7 Days of Decision	Safety Follow-up Visit		Long-term Follow-up Every 12 weeks (± 2 weeks)	Notes
	V8	V9	V10	V11	V12	V13	Until EoT		28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment		
	W10	W13	W16	W19	W22	W25						
	D64	D85	D106	D127	D148	D169						Overlapping assessments at the End-of-cCRT Visit and the first visit in maintenance only need to be performed once.
Administrative Procedures												
Documentation of concomitant medication and procedures	X	X	X	X	X	X	Every 3 weeks	X	X	X	X	The 12-week Safety Follow-up and Long-term Follow-up may be conducted via telephone calls or patient chart reviews as necessary unless there is medical necessity requiring a clinical visit.
Drug Administration												
Bintrafusp alfa	X	X	X	X	X	X	Every 3 weeks					See Section 6 for dosing details. See Section 7 for stopping study interventions.
Safety Assessments												
Documentation of AEs	X	X	X	X	X	X	Every 3 weeks	X	X	X ^a	X ^a	See Appendix 4 for safety recording and reporting. a: The 12-week Safety Follow-up and Long-term Follow-up may be conducted via telephone calls or patient chart reviews as necessary unless there is medical necessity requiring a clinical visit.
Physical examination	X	X	X	X	X	X	Every 3 weeks	X	X			Complete physical examination to be performed at Screening; subsequent focused examinations to be performed as described in Section 8.2.1.

Assessments & Procedures after cCRT	Intervention Period after cCRT (± 3 days)							EoT Visit On the Day of or Within 7 Days of Decision	Safety Follow-up Visit			Long-term Follow-up Every 12 weeks (± 2 weeks)	Notes
	V8	V9	V10	V11	V12	V13	Until EoT		28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment			
	W10	W13	W16	W19	W22	W25							
	D64	D85	D106	D127	D148	D169							
Skin assessment		X		X		X	Every 6 weeks	X	X			See Section 8.3.6.3 for skin assessment.	
Vital signs	X	X	X	X	X	X	Every 3 weeks	X	X			Including weight and height (height at Screening only). See Section 8.2.2.	
ECOG PS	X	X	X	X	X	X	Every 3 weeks	X	X				
12-lead ECG	12-lead ECG will be repeated if clinically indicated												
Laboratory Assessments													
Virology serology (HIV)	As clinically indicated in participants with a history of HIV infection												HIV testing is not mandatory. Previous data should be collected in medical history. If a test is performed at any point at Screening or while on study, a site must consent the participant for HIV testing as per local standard guidance.
Viral serology (HBV and HCV)	As clinically indicated in participants with a history of HBV or HCV infection												
Hematology	X	X	X	X	X	X	Every 3 weeks	X	X				Hematology is listed in Appendix 5 for details on blood tests. Samples must also be drawn prior to dosing and results of selected laboratory tests (see Appendix 5) must be reviewed within 3 days prior to dosing.

Assessments & Procedures after cCRT	Intervention Period after cCRT (± 3 days)							EoT Visit On the Day of or Within 7 Days of Decision	Safety Follow-up Visit		Long-term Follow-up Every 12 weeks (± 2 weeks)	Notes
	V8	V9	V10	V11	V12	V13	Until EoT		28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment		
	W10	W13	W16	W19	W22	W25						
	D64	D85	D106	D127	D148	D169						
Biochemistry	X	X	X	X	X	X	Every 3 weeks	X	X			Biochemistry is listed in Appendix 5 . Samples must be drawn prior to dosing and results of selected laboratory tests (see Appendix 5) must be reviewed within 3 days prior to dosing.
Coagulation parameters	As clinically indicated											See Appendix 5 .
Urinalysis	As clinically indicated											Routine urinalysis at the Screening visit. If the result is abnormal, then a microscopic examination and/or culture should be performed as needed (see Appendix 5).
β-hCG pregnancy test (WOCBP only)	X	X	X	X	X	X	Every 3 weeks		X	X ^b		β-hCG should be determined at Screening and thereafter from a urine or serum sample. Results of the most recent pregnancy test should be available prior to dosing of study intervention. If a confirmation of a participant's postmenopausal status is necessary, follicle-stimulating hormone and estradiol tests will be performed at Screening. b: Participants may go to local laboratory to perform pregnancy test. Clinical visit is not required.
T4 and TSH		X		X		X	Every 6 weeks		X			

Assessments & Procedures after cCRT	Intervention Period after cCRT (± 3 days)							EoT Visit On the Day of or Within 7 Days of Decision	Safety Follow-up Visit		Long-term Follow-up Every 12 weeks (± 2 weeks)	Notes Overlapping assessments at the End-of-cCRT Visit and the first visit in maintenance only need to be performed once.
	V8	V9	V10	V11	V12	V13	Until EoT		28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment		
	W10	W13	W16	W19	W22	W25						
	D64	D85	D106	D127	D148	D169						
Survival Follow-up											X	Conducted via telephone calls unless there is medical necessity requiring a clinical visit.
CCI												
												CCI
CCI												
PK, ADA and CCI												
See Table 5 for PK and ADA Sampling Schedule												
												CCI

Assessments & Procedures after cCRT	Intervention Period after cCRT (± 3 days)						Until EoT	EoT Visit On the Day of or Within 7 Days of Decision	Safety Follow-up Visit		Long-term Follow-up Every 12 weeks (± 2 weeks)	Notes Overlapping assessments at the End-of-cCRT Visit and the first visit in maintenance only need to be performed once.
	V8	V9	V10	V11	V12	V13			28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment		
	W10	W13	W16	W19	W22	W25						
	D64	D85	D106	D127	D148	D169						
[REDACTED]	[REDACTED]						[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	CCI [REDACTED]

ADA=antidrug antibody, AE=adverse events, β-hCG=β-human chorionic gonadotropin, cCRT=concomitant chemoradiation therapy, CT=computed tomography, CR=complete response, D=Day, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EoT=End-of-Treatment, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=Human immunodeficiency virus, MRI=magnetic resonance imaging, PD=progressive disease, PK=pharmacokinetics, PR=partial response, q12w=every 12 weeks, T4=free thyroxine, TSH=thyroid-stimulating hormone, V=visit, W=Week, WOCBP=woman of childbearing potential.

Table 5 Schedule of Activities for PK and ADA Sampling in Cohort 2

Assessments & Procedures	cCRT-based Treatment (-3 / +3 days)					Intervention Period after cCRT (-3 / +3 days)					Until EoT	EoT Visit	Safety Follow-up Visit	Notes
	V1	V2	V3	V4	V7	V8	V9	V11	V13	On Day of or Within 7 Days of Decision		28 (± 5) Days After Last Treatment		
	W1		W2	W3	W4	W7	W10	W13	W19				W25	
	D1	D2	D8	D15	D22	D43	D64	D85	D127				D169	
Blood sample for PK	X/X ^a (pre/eoi)	X ^b	X ^c	X ^c	X/- (pre/eoi)	X/- (pre/eoi)	X/X (pre/eoi)	X/- (pre/eoi)	X/- (pre/eoi)	X/- (pre/eoi)	X/- (pre/eoi) Every 12 weeks from W25	X	X	<p>Samples for PK analysis are taken before (pre) infusion of bintrafusp alfa (pre, as close to the start of the infusion as possible), immediately after the end of bintrafusp alfa infusion (eoi, as close to the completion as possible within 30 minutes after the end of infusion).</p> <p>The predose sample should still be drawn even if dosing is ultimately deferred at the study visit. The exact time of each draw must be recorded. A protocol deviation is defined by a sample not being drawn, or time of draw is not recorded.</p> <p>a: On W1D1 only, in addition to pre and eoi samples, collect a PK sample 4 hours after start of infusion.</p> <p>b: On W1D2 only, collect a PK sample 24 hours after start of infusion on Day 1.</p> <p>c: Samples for PK analysis are taken before chemotherapy on D8 and 15.</p>
Blood Sample for ADA	X/- (pre/eoi)				X/- (pre/eoi)	X/- (pre/eoi)	X/- (pre/eoi)	X/- (pre/eoi)	X/- (pre/eoi)	X/- (pre/eoi)	X/- (pre/eoi) Every 12 weeks from W25	X	X	<p>Predose ADA samples to be collected prior to study intervention infusions (as close to the start of the infusion as possible). The exact time of each draw must be recorded.</p>

ADA=antidrug antibody, cCRT=concomitant chemoradiation therapy, D=day, EoT=End-of-Treatment, PK=pharmacokinetics, V=visit, W=week.

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 receptor II (TGF- β RII or TGF- β Trap) covalently linked via a flexible linker to the C-terminus of each heavy chain of an immunoglobulin (IgG1) antibody blocking programmed death-ligand 1 (PD-L1).

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

Cervical cancer is the third most common cancer in women and remains one of the most common causes of cancer death among women worldwide. It is diagnosed in over 13,000 women in the United States each year. The human papilloma virus (HPV), the primary cause of cervical cancer, is implicated in over 90% of cases (Arbyn 2014; Howlader 2019). Although diagnosis is often made at earlier stages, metastatic or recurrent cervical cancer develop in a third of the women (Gadducci 2015; Howlader 2019).

For the majority of patients with recurrent, persistent, or metastatic cervical cancer, the first-line standard of care is chemotherapy with platinum and taxane in combination with bevacizumab with an overall response rate of 48% and a median OS of approximately 17 months (Dyer 2019; Tewari 2017). For women with locally advanced cervical cancer, with node involvement with International Federation of Gynecology and Obstetrics (FIGO) Stages IB2 to IVA, the standard of care is primarily chemoradiation. Benefit of chemoradiation decreases with increasing stage (CCCMAC 2008) and prognosis for patients with Stage III/IV disease is poor with 4-year OS rates of 55% (Dyer 2019) and 2-year rates of relapse over 40% (Rose 2015).

Recently, molecular characterization of cervical cancer by The Cancer Genome Atlas also identified both PD-L1 and TGF- β signaling as frequently dysregulated in this disease (The Cancer Genome Atlas Research Network 2017, Roszik 2018). TGF- β is historically known to be expressed in a majority of cervical cancer tissues, and its expression correlates with the extent of tumor stroma infiltrate (Hazelbag 2002). Furthermore, the role of TGF- β in cervical cancer pathogenesis is supported by data including 1) TGF- β 1 upregulation by HPV oncoprotein E6 and E7 (Peralta-Zaragoza 2006), and 2) the correlation of poor prognosis in cervical cancer and the expression of plasminogen activator inhibitor-1, a molecule strongly and dose-dependently induced by TGF- β (Hazelbag 2004).

Bintrafusp alfa has shown promising clinical activity with durable responses in participants with chemotherapy refractory cervical cancer in Phase I Study EMR200647-001. In the Phase I Study, as of 17 April 2019 (refer to current IB for more details), a total of 25 participants with recurrent or persistent cervical cancer following standard of care treatment were treated for advanced disease. The median treatment duration was 9.6 (range 2.0 to 72.0) weeks. The results are summarized:

- Objective response rate (ORR) of 24% (95% CI: 9.4, 45.1) with 6 confirmed responses per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1); 5/6 responses were ongoing at data cutoff (median duration of response [DoR] not reached; range, 4.2 to 30.4 months).
- One additional participant developed a partial response (PR) after initial confirmed disease progression, bringing the total clinical response rate to 28% (95% CI: 12.1, 49.4). This additional participant's PR was ongoing for 8.7 months at data cutoff, with 73.3% disease shrinkage after initial progressive disease (PD).

- No clear relationship between PD-L1 protein expression and clinical response was observed. One participant with negative tumor cell PD-L1 expression (via 73-10 assay) had a confirmed PR.

The above results were obtained in a Phase I Study that enrolled a heavily pretreated population (Boussios 2016, Marth 2017). For comparison, in second-line treatment of metastatic disease response rates are low and DoR is short. The reported rates are between 10% and 25%, but in general supported by limited data. As such, there is no consensus recommendation for second-line regimen. Similarly, the recent accelerated approval in the US of pembrolizumab in PD-L1-positive participants is based on an ORR of 14.3% with a DoR not yet reached at last report (Chung 2019).

CCI [REDACTED]

Based on the biological rationale and promising clinical activity of bintrafusp alfa in cervical cancer and manageable safety profile in participants with various cancer types (refer to IB), a first study of bintrafusp alfa monotherapy in platinum-experienced participants with cervical cancer (Study MS200647_0017) has been initiated.

In addition, bintrafusp alfa (2400 mg every 3 weeks) is currently being investigated:

- In combination with cisplatin or carboplatin + pemetrexed in participants with Stage IV NSCLC (MS200647_0024). As of the most recent data cutoff of PPD [REDACTED], 23 participants were dosed in the study, data from 8 participants were reviewed by a Safety Monitoring Committee (SMC) meeting. One dose-limiting toxicity (DLT) of Grade 3 nausea was reported and was assessed as related to carboplatin and pemetrexed by the Investigator, the study is continuing, and preliminary data does not indicate any tolerability issue.
- In combination with gemcitabine and cisplatin in participants with first-line biliary tract cancer in a Phase II/III Study (MS200647_0055). As of the most recent data cutoff of PPD [REDACTED] for DLT evaluation, 6 participants had been dosed and no DLTs were observed.

Overall, the observed safety profile from these 2 studies did not reveal any new or increased risks compared to what can be expected from current experience, respectively, with chemotherapy and bintrafusp alfa alone (refer to current IB).

2.3 Benefit/Risk Assessment

The current safety and efficacy data support further investigation of the safety and tolerability of the use of bintrafusp alfa (2400 mg intravenous every 3 weeks) in combination with chemotherapy with or without bevacizumab in participants with recurrent, persistent, or metastatic cervical cancer or chemoradiation followed by bintrafusp alfa in participants with locally advanced cervical cancer.

The overall safety profile of bintrafusp alfa as a monotherapy in participants with various cancer types is manageable (refer to IB), and no increased risks have been observed in 2 studies of bintrafusp alfa combined with chemotherapy, compared to what can be expected from current experience, respectively, with chemotherapy and bintrafusp alfa alone.

The following have been identified as important identified risks for bintrafusp alfa: immune-related adverse events (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 and other irAEs [myositis, myocarditis, encephalitis]), TGF- β inhibition mediated skin reactions, anemia and bleeding adverse events.

Infusion-related reactions (IRR) are classified as identified risk for the treatment with bintrafusp alfa. Infusion-related reactions observed with bintrafusp alfa were similar to those seen with monoclonal antibodies.

The identified and potential risks with bintrafusp alfa monotherapy were overall manageable and no new safety signals emerged in the Phase I studies (EMR200647-001, CCI [REDACTED]) compared with therapies targeting PD-L1 or TGF- β .

Bintrafusp alfa initial results have shown encouraging clinical efficacy in a heavily pretreated cervical cancer population with favorable response rate and durability compared to historical benchmarks (see Section 2.2).

This study is to investigate if the safety profile of bintrafusp alfa in combination with platinum therapy and paclitaxel with or without bevacizumab in participants with recurrent, persistent, or metastatic cervical cancer or platinum therapy and definitive radiation in participants with locally advanced can support future clinical development in these patient population.

Since the reporting of Gynecologic Oncology Group (GOG)-240, bevacizumab has frequently been used in combination with chemotherapy for the treatment of Stage IVB recurrent or persistent cervical cancer (Tewari 2017), although the cost-effectiveness of the addition of bevacizumab continues to be evaluated (Phippen 2015). In addition to the financial burden of bevacizumab, there are clinical factors that must be considered prior to initiating bevacizumab as a component for front-line therapy. The specific exclusion criteria for participants to receive bevacizumab in Cohort 1A (see Section 5.2) are to mitigate known bevacizumab toxicities such as history of vascular disease and/or hypertension, prior bleeding/coagulopathy, conditions that may increase risk of fistulation, wound healing, and proteinuria. These toxicities of bevacizumab largely do not overlap with the known bintrafusp alfa toxicity profile. It is noted that low grade mucosal bleedings and impaired wound healing or repair of tissue damage are considered risks for bintrafusp alfa and will be monitored in this study.

Cohorts 1 (Cohort 1A and Cohort 1B) and 2 will evaluate the addition of bintrafusp alfa to standard of care treatments for participants with cervical cancer that is metastatic/recurrent/persistent or locally advanced, respectively. Bintrafusp alfa has shown preliminary activity in heavily pretreated cervical cancer participants as a monotherapy. In addition, the safety profile of bintrafusp alfa has been well characterized as a manageable safety profile. Included in these evaluations is tolerability

with a variety of chemotherapy agents in combination (see Section 2.2). The addition of bevacizumab does provide some potential overlapping toxicities, and these will be closely monitored through the conduct of the study. In addition, the protocol includes exclusion criteria specific for participants enrolling to receive bevacizumab to enroll participants suitable for treatment with bevacizumab. Across all cohorts, the addition of bintrafusp alfa presents a reasonable risk-benefit profile for study based upon prior activity of bintrafusp alfa in cervical cancer participants with later stage disease and manageable safety profile for these combinations with appropriate selection and monitoring of participants in this Phase I setting.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of bintrafusp alfa may be found in Section 4.2 and the IB.

CCI

3 Objectives and Endpoints

Table 6 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of bintrafusp alfa in combination with (1) chemotherapy with or without bevacizumab in participants with recurrent, persistent, or metastatic cervical cancer or (2) platinum therapy and definitive radiation in participants with locally advanced cervical cancer	<ul style="list-style-type: none"> • Occurrence of DLTs • AEs
Secondary	
To evaluate the safety and tolerability of bintrafusp alfa in combination with (1) chemotherapy with or without bevacizumab in Japanese participants with recurrent, persistent, or metastatic cervical cancer or (2) platinum therapy and definitive radiation in Japanese participants with locally advanced cervical cancer	<ul style="list-style-type: none"> • Occurrence of DLTs • AEs
To characterize PK profile of bintrafusp alfa	<ul style="list-style-type: none"> • PK profile of bintrafusp alfa in terms of C_{eoi} and C_{trough} for all participants throughout the treatment period • PK profile of bintrafusp alfa in terms of AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{1/2}$ in Cycle 1
To evaluate the immunogenicity of bintrafusp alfa	<ul style="list-style-type: none"> • Immunogenicity of bintrafusp alfa, as measured by ADA assay, from Day 1 predose through the last Safety Follow-up Visit

CCI



4 Study Design

4.1 Overall Design

This Phase Ib open-label study is to evaluate the safety and tolerability of bintrafusp alfa in combination with other anti-cancer therapies in participants with locally advanced or advanced cervical cancer. Bintrafusp alfa will be combined with platinum therapy and paclitaxel with or without bevacizumab in participants with recurrent, persistent, or metastatic cervical cancer (Cohort 1A and 1B) or with platinum therapy and definitive radiation in participants with locally advanced cervical cancer (Cohort 2). Further combination regimens with other anti-cancer therapies may be added by protocol amendment.

See Section 5 for more details on the patient population.

This study will be conducted with Cohort 1 (Cohort 1A and Cohort 1B) and Cohort 2 in parallel.

The allocation of participants to Cohort 1A or Cohort 1B will be based on Investigator decision and also other factors including but not limited to study inclusion/exclusion criteria and local standard of care.

Cohort 1

Participants must have primary Stage IVB, recurrent or persistent squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix not amenable to curative treatment with surgery and/or radiation therapy and not have been treated with systemic chemotherapy.

- Cohort 1A: 8 participants will be treated with bintrafusp alfa (2400 mg every 3 weeks) + cisplatin or carboplatin + paclitaxel + bevacizumab. Selection of cisplatin or carboplatin is at the Investigator discretion.
- Cohort 1B: 8 participants will be treated with bintrafusp alfa (2400 mg every 3 weeks) + cisplatin or carboplatin + paclitaxel. Selection of cisplatin or carboplatin is at the Investigator discretion.

If the first 8 participants of each subcohort separately include fewer than 3 participants from Japan, the Sponsor may elect to continue enrollment in Japan to include at least 3 participants from Japan. If the first 8 participants of each subcohort separately include fewer than 3 participants from Europe or the United States, enrollment may continue in Europe and the United States to include at least 3 participants from any of these countries.

In cases where toxicity is readily attributable to 1 (or more) agents of the combination, it is acceptable to discontinue 1 (or more) agent while continuing other components of the combination treatment, if deemed appropriate by Investigator. Scan should be performed when any of the study intervention is discontinued (see Section 7.1 for details).

Cohort 2:

Participants with locally advanced cervical cancer will be treated with bintrafusp alfa (2400 mg every 3 weeks) combined with definitive radiation and radiation-sensitizing platinum therapy (cisplatin) during cCRT, followed by maintenance with bintrafusp alfa monotherapy (2400 mg every 3 weeks).

If the first 8 participants include fewer than 3 participants from Japan, enrollment may continue in Japan to include at least 3 participants from Japan to evaluate the safety of this combination in Japanese participants. If the first 8 participants of this cohort include fewer than 3 participants from Europe or the United States, enrollment may continue in Europe and the United States to include at least 3 participants from any of these countries.

The cCRT period is approximately 5 weeks plus any additional period for brachytherapy not exceeding a total of 8 weeks as detailed in Table 3 and Table 4. The cCRT period is considered from the first dose of radiation to the last dose of radiation or chemotherapy, whichever occurs last. The period for cCRT can be extended up to 1 week in case of technical and logistical issues

and if participants require withholding of the study intervention due to toxicities.

In case cCRT is terminated early due to toxicity, participants in Cohort 2 are allowed to continue bintrafusp alfa; similarly, if bintrafusp alfa is discontinued, cCRT may continue. The first dose of bintrafusp alfa during maintenance should be at least 3 weeks from the last dose of bintrafusp alfa and not before tumor assessment and End-of-cCRT Visit has been performed. The first dose of maintenance bintrafusp alfa may be delayed to next scheduled dose if clinically indicated.

The overall study design is shown in [Figure 1](#). A detailed Schedule of Activities is provided in [Section 1.3](#).

The study includes:

- Up to 28-day Screening period. Screening will be performed within 28 days prior to Day 1 of study intervention administration. If there are no clinically significant findings at Screening and the individual meets all the protocol-defined inclusion and none of the exclusion criteria, the individual will be considered eligible for participation in the study. See [Section 5.4](#) for screen failures.
- The DLT (as defined in [Section 6.6.2](#)) observation period of 4 weeks from the Week 1, Day 1 (W1D1) visit for all cohorts.
- Treatment until PD by RECIST 1.1 and subsequent confirmation (at the next imaging visit at least 28 days after the detection of PD), unacceptable toxicity, study withdrawal, or death.
- The treatments for Cohorts 1 (Cohort 1A and Cohort 1B) and 2 are as specified in [Section 1.3](#).
- In case of PD, treatment may continue 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, and if other criteria are fulfilled as outlined in the protocol (see [Section 7.1.3](#)).
- Cohort 1 participants will continue chemotherapy until complete response (CR) (as clinically indicated) and/or unacceptable toxicity due to chemotherapy, after which, bintrafusp alfa ± bevacizumab (depending on cohort) may be continued until 2 years or unacceptable toxicity as indicated for bintrafusp alfa and/or bevacizumab. If the Investigator believes that a participant may benefit from treatment beyond 2 years, it may be permissible to continue treatment after discussion with the Medical Monitor and the Sponsor's Medical Responsible.
- Cohort 2 participants should continue maintenance treatment (bintrafusp alfa) for a maximum of 2 years (at the discretion of the Investigator). If the Investigator believes that a participant may benefit from treatment beyond 2 years, it may be permissible to continue treatment after discussion with the Medical Monitor and the Sponsor's Medical Responsible.
- All participants should continue treatment until confirmed disease progression or any other discontinuation criterion is met (e.g., unacceptable toxicity, withdrawal of consent).

- Safety Follow-up Visits are at 28 days (± 5 days) and 12 weeks (± 2 weeks) after the last dose of study intervention according to the Schedule of Activities (see Section 1.3). The 12-week Safety Follow-up is allowed to be conducted via telephone calls or patient chart reviews unless there is medical necessity requiring a clinical visit.
- Long-term Follow-up should be performed every 12 weeks (± 2 weeks) after the Safety Follow-up according to the Schedule of Activities (see Section 1.3). Long-term Follow-up should be performed by chart reviews or telephone calls unless there is medical necessity requiring a clinical visit.
- Survival Follow-up will continue until the end of study as defined in Section 4.4. After the stipulated end of study, Survival Follow-up may continue until the last participant has died or at the discretion of the Sponsor.

See Section 4.4 for the end of study definition.

4.2 Scientific Rationale for Study Design

4.2.1 Endpoints

The primary endpoint of the study is occurrence of DLTs and AEs.

4.2.2 Selection of Combination and Study Population

In Cohort 1, bintrafusp alfa will be combined with standard of care treatment regimens for participants with recurrent, persistent, or metastatic cervical cancer. The global Phase III Study GOG-240 evaluated cisplatin plus paclitaxel \pm bevacizumab as well as nonplatinum containing doublet \pm bevacizumab (Tewari 2017). The results have led to the wide use of carboplatin or cisplatin plus paclitaxel \pm bevacizumab as a standard of care for the treatment of metastatic/recurrent/persistent cervical cancer. Bevacizumab use with this combination may vary depending on factors such as access and reimbursement depending on local restrictions as well as clinical conditions.

Given the activity of bintrafusp alfa seen in more heavily pretreated cervical cancer participants, there is a rationale to combine an active, novel immunotherapy with a standard of care regimens (Cohort 1A: carboplatin or cisplatin plus paclitaxel and bevacizumab; Cohort 1B: carboplatin or cisplatin plus paclitaxel) in first-line recurrent, persistent or metastatic participants for evaluation. This study will assess the safety of this combination as well as antitumor activity, pharmacokinetics (PK), and immunogenicity.

In Cohort 2, bintrafusp alfa will be combined with standard of care treatment for participants with locally advanced cervical cancer. Concurrent chemoradiotherapy using weekly cisplatin has been the backbone of standard of care treatment for patients with locally advanced cervical cancer for over 2 decades and continues to be the backbone for active investigation as to how to further refine and improve this regimen to build upon its success but also improve outcomes for patients. In this setting there is strong rationale to incorporate immunotherapies that may further enhance tumor

response. Incorporation of bintrafusp alfa is justified in this setting as early activity in more refractory patients shows promise in generating antitumor response.

4.3 Justification for Dose

The dose for bintrafusp alfa in this study is 2400 mg administered as an intravenous infusion once every 3 weeks. Since most chemotherapies are administered every 3 weeks, the same dosing interval for bintrafusp alfa is preferred for convenience and compliance.

The 2400 mg every 3 weeks dose selection was based on the following:

- Phase I data, population PK and exposure-response modeling and simulations were used to select 1200 mg every 2 weeks for bintrafusp alfa monotherapy studies and estimate target efficacious $C_{\text{trough,ss}}$ (refer to the IB). Specifically, the following data from Phase I Study EMR200647-001 and Study CCI [REDACTED] were used: safety/tolerability and PK, such as PD-L1 target occupancy in peripheral blood mononuclear cells and TGF- β trapping in blood, as well as efficacy in second-line NSCLC cohorts from Study EMR200647-001. Modeling and simulation were used to select 2400 mg every 3 weeks dose as the dose that maintains target efficacious $C_{\text{trough,ss}}$ of bintrafusp alfa. Available safety/tolerability data at 2400 mg dose and exposures associated with 2400 mg dose in monotherapy Phase I studies were evaluated.
- Assessment of potential of PK interactions and overlapping toxicities with chemotherapies was conducted to support 2400 mg every 3 weeks dose of bintrafusp alfa in Studies MS200647_0024 and MS200647_0055. 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 participants treated at lower doses (monotherapy setting). No new safety issues were observed in participants treated at a dose of 2400 mg (see Section 2.2 and current IB for more details).

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 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 3 years after treatment start of the last participant or until all the participants discontinued the study, whichever occurs first.

The Sponsor may terminate the study at any time once access to study intervention for participants still benefitting is provided via a rollover study, expanded access, marketed product, or another mechanism of access as appropriate. See 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](#).

5.1 Inclusion Criteria

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

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 her parent or guardian will be required in addition to the participant's written consent.

Type of Participant and Disease Characteristics

a) Specifically, criteria for participants enrolling into Cohort 1:

2. Are participants with documented persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix.
3. Have not been treated with systemic chemotherapy (including neoadjuvant and adjuvant regimens) and is not amenable to curative treatment (such as with surgery and/or radiation).
4. Prior radiation with or without radio-sensitizing chemotherapy is allowed.

b) Criteria for participants enrolling into Cohort 2:

5. Are participants with documented evidence of cervical adenocarcinoma, squamous cell carcinoma, or adenosquamous carcinoma FIGO 2018 ([Bhatla 2019](#), [Corrigendum 2019](#)) Stages IB2 to IVA.
6. Have not received prior chemotherapy or radiotherapy for cervical cancer.

Criteria for all participants:

7. Archival tumor tissue sample or newly obtained (preferred) core or excisional biopsy of a tumor lesion is required and should be made available during the Screening period prior to enrollment. Specifications for tumor material are described in the Laboratory Manual. Patients for which a new biopsy is not possible or medically inadvisable, may be deemed eligible after consultation with the Medical Monitor/Sponsor. Participants enrolled in Cohort 1A should also consult Exclusion Criteria [26](#) with regards to timing of new biopsy.

8. Have ECOG PS of 0 to 1 at study entry and Day 1 of treatment with bintrafusp alfa.
9. Life expectancy ≥ 12 weeks as judged by the Investigator.
10. Have adequate organ function:
 - a. Adequate hematological function defined by absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, and hemoglobin ≥ 9 g/dL.
 - b. Adequate hepatic function defined by a total bilirubin level \leq the upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels $\leq 1.5 \times$ ULN and alkaline phosphatase $\leq 2.5 \times$ ULN. For participants with liver involvement in their tumor, AST $\leq 5.0 \times$ ULN, ALT $\leq 5.0 \times$ ULN, and bilirubin $\leq 3.0 \times$ ULN are acceptable.
 - c. Adequate renal function defined by creatinine $\leq 1.5 \times$ ULN or calculated creatinine clearance (CrCL) ≥ 50 mL/min for participant with creatinine $> 1.5 \times$ ULN (glomerular filtration rate can also be used).

Note: CrCL should be calculated per institutional standard. If no local guideline is available, CrCL should be calculated using the Cockcroft-Gault Method:

$$\text{CrCL} = ([140 - \text{age}] \times \text{weight [kg]} \times [0.85 \text{ for females only}]) / (72 \times \text{creatinine})$$
 - d. Adequate coagulation function defined as international normalized ratio (INR) or prothrombin time $\leq 1.5 \times$ ULN unless the participant is receiving anticoagulant therapy, and activated partial thromboplastin time (aPTT) $\leq 1.5 \times$ ULN unless the participant is receiving anticoagulant therapy.
11. Participants with known human immunodeficiency virus (HIV) infections are eligible if the following criteria are met ([FDA Guidance on Cancer Clinical Trial Eligibility 2019](#)):
 - a. If clinically indicated, patients must be stable on antiretroviral therapy (ART) for at least 4 weeks and agree to adhere to ART. If not clinically indicated, consult Medical Monitor.
 - b. Participants with HIV infection should have no evidence of documented multidrug resistance that would prevent effective ART.
 - c. Have an HIV viral load of < 400 copies/mL at Screening.
 - d. Have CD4+ T-cell (CD4+) counts ≥ 350 cells/ μ L.
 - e. For patients with a history of an AIDS-defining opportunistic infection within the last 12 months, patients may be eligible only after consultation and agreement with the Medical Monitor.
 - f. If prophylactic antimicrobial drugs are indicated, patient may still be considered eligible upon agreement with the Medical Monitor.
12. Participants with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infections are eligible if the following criteria are met ([FDA Guidance on Cancer Clinical Trial Eligibility 2019](#)):

- a. Patients with serologic evidence of chronic HBV infection must have an HBV viral load below the limit of quantification and, if medically indicated, be on a stable dose of antiviral therapy.
- b. Patients with a history of HCV infection should have completed curative antiviral treatment and require HCV viral load below the limit of quantification.
- c. Patients on concurrent HCV treatment should have HCV below the limit of quantification.

Sex

13. Are female.

A female is eligible if she is **not** pregnant or breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential

OR

- If a woman of childbearing potential, use a highly effective contraceptive method (i.e., with a failure rate of < 1% per year), preferably with low user dependency, as described in [Appendix 3](#) for the following time periods:
 - Before the first dose of the study intervention(s), if using hormonal contraception:
 - Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses.

OR

- Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay.
- During the intervention period
- After the study intervention period (i.e., after the last dose of study intervention is administered) for at least 2 months (6 months for participants who receive bevacizumab). Contraceptive measures should be continued as per guidance specified in labeling document for approved chemotherapies. If not specified, continue measures similar to the investigational agent, i.e., for at least 2 months (6 months for participants who receive bevacizumab) after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period.

The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

Have a negative serum or highly sensitive urine pregnancy test, as required by local regulations, within 24 hours before the first dose of study intervention. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required.

Additional requirements for pregnancy testing during and after study intervention are in Sections 8.2.4 and 8.3.5.

The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.

Informed Consent

14. 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:

For all participants:

Medical Conditions

1. Participants with active central nervous system (CNS) metastases causing clinical symptoms or metastases that require therapeutic intervention are excluded. Participants with a history of treated CNS metastases (by surgery or radiation therapy) are not eligible unless they have fully recovered from treatment, demonstrated no progression for at least 4 weeks, and are not using steroids for at least 7 days prior to the start of study intervention.
2. Receipt of any organ transplantation, including allogeneic stem-cell transplantation, but with the exception of transplants that do not require immunosuppression (e.g., corneal transplant, hair transplant).
3. Significant acute or chronic infections including but not limited to:
 - a. Participants with active tuberculosis (history of exposure or history of positive tuberculosis test; plus presence of clinical symptoms, physical, or radiographic findings).
 - b. Active bacterial or fungal infection requiring systemic therapy (except as indicated, discuss alternative scenarios with the Medical Monitor).
4. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent, except:
 - a. Participants with diabetes Type 1, vitiligo, alopecia, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
 - b. Participants requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg of prednisone or equivalent per day.

- c. Administration of steroids for other conditions through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) is acceptable.
5. Any history of anaphylaxis, or recent (within 5 months) history of uncontrollable asthma, known severe hypersensitivity (Grade ≥ 3 National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0 [NCI-CTCAE v5.0]) to any study intervention or any component in the formulations.
 6. Persisting Grade > 1 NCI-CTCAE v5.0 toxicity (except alopecia and vitiligo) related to prior therapy; however, sensory neuropathy Grade ≤ 2 is acceptable.
 7. Has drug-induced interstitial lung disease OR has had a history of drug-induced pneumonitis that has required oral or intravenous steroids.
 8. Clinically significant cardiovascular/cerebrovascular disease including: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class \geq II), or serious cardiac arrhythmia.
 9. Participants with history of bleeding diathesis or recent major bleeding events (i.e., Grade ≥ 2 bleeding events in the month prior treatment) considered by the Investigator as high risk for investigational drug treatment are also excluded.
 10. Severe and/or clinically relevant acute or chronic diseases which, in the opinion of the Investigator, might impair the participant's tolerance for the study or ability to consistently participate in study procedures.

Prior/Concomitant Therapy

11. Has received prior cancer treatment with any other immunotherapy or checkpoint inhibitors, such as anti-programmed death-1 (PD-1), anti-PD-L1, anti-PD-L2, anti-cytotoxic T-cell lymphocyte-associated antigen-4 (CTLA-4), or any other immune-modulating mAb (e.g., any other antibody or drug specifically targeting T-cell co-stimulation, checkpoint pathways or immune-suppressive pathways [e.g., TGF- β]). Also see Section 5.1.
12. Concurrent treatment with prohibited drugs (see Section 6.5.2).
13. Systemic therapy with immunosuppressive agents within 7 days before the start of study intervention; or use of any investigational drug within 28 days before the start of study intervention.
14. Has received or will receive a live vaccine within 30 days prior to the first administration of study intervention. Seasonal flu vaccines that do not contain a live virus are permitted.

Prior/Concurrent Clinical Study Experience

15. Participants, who received chemotherapy, radiation therapy (with the exception of palliative radiotherapy delivered in a normal organ-sparing technique), or biological therapy (e.g., antibodies) within 4 weeks, or who have been treated with small molecule therapeutics or investigational agents within 4 weeks prior to starting bintrafusp alfa or

who have not recovered from the side effects of such therapy (except for alopecia or potentially neuropathy).

Other Exclusions

16. Major surgery within 28 days before the start of study intervention (diagnostic biopsy, for example, is not considered major surgery).
17. Pregnancy or breast feeding.
18. Known active alcohol or drug abuse.
19. Grade ≥ 2 peripheral neuropathy as defined by NCI-CTCAE v5.0 criteria (paclitaxel).

Exclusion Specific to Participants Enrolling in Cohort 1A:

Given the specific toxicities related to bevacizumab, the local physician is responsible for ensuring a participant is clinically appropriate to receive bevacizumab. The following specific exclusion criteria are applicable only for participants enrolling in Cohort 1A (exclusion criteria related to bevacizumab):

20. Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg). Anti-hypertensive therapy to achieve these parameters is allowable.
21. Prior history of hypertensive crisis or hypertensive encephalopathy.
22. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Screening.
23. History of hemoptysis (\geq one-half teaspoon of bright red blood per episode) within 1 month prior to Screening.
24. Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation).
25. Current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes.
 - Prophylactic anticoagulation for the patency of venous access devices is allowed, provided the activity of the agent results in an INR $< 1.5 \times$ ULN and aPTT is within normal limits within 14 days prior to Screening.
 - Prophylactic use of low-molecular-weight heparin (i.e., enoxaparin 40 mg/day) is permitted.
26. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to the first dose of bevacizumab.
27. History of abdominal or tracheoesophageal fistula or gastrointestinal (GI) perforation within 6 months prior to Screening.
28. Clinical signs of GI obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding.
29. Evidence of abdominal free air not explained by paracentesis or recent surgical procedure.

30. Serious, nonhealing wound, active ulcer, or untreated bone fracture.

31. Proteinuria, as demonstrated by urine dipstick or > 1.0 g of protein in a 24-hour urine collection. All participants with $\geq 2+$ protein on dipstick urinalysis at Baseline must undergo a 24-hour urine collection and must demonstrate ≤ 1 g of protein in 24 hours.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once within 2 weeks from original screen failure date. Rescreened participants will be assigned a new participant number.

For the participants whose indication for screen failure may resolve (e.g., abnormal laboratory value that may correct, or prohibited concomitant medication that will be discontinued, or prohibited procedure that will be completed), Screening period may be extended for up to 2 weeks after discussion with the Medical Monitor.

For participants who have been rescreened or their Screening period was extended, baseline tumor scans must be within indicated time window (See Section 1.3).

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

Cohort 1A: the order of infusion is bintrafusp alfa → bevacizumab → cisplatin or carboplatin plus paclitaxel.

Cohort 1B: the order of infusion is bintrafusp alfa → cisplatin or carboplatin plus paclitaxel.

Cohort 2: the order of treatment during cCRT is bintrafusp alfa → cisplatin → radiotherapy.

6.1.1 Bintrafusp alfa

Table 7 Administration of Bintrafusp alfa (M7824)

Intervention Name	bintrafusp alfa (M7824)
Dose Formulation	Sterile concentrate solution for infusion
Unit Dose Strength(s)/ Dosage Level(s)	10 mg/mL in single-use glass vials
Route of Administration	Intravenous infusion
Dosing Instructions	Flat dose of 2400 mg administered over a minimum of 1 hour and up to 2 hours
Sourcing	Provided centrally by the Sponsor
Packaging and Labeling	Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

Current experience in 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 (see Section 8.3.6.1).

If an Investigator deems necessary to administer a premedication to a particular participant, an antihistamine (e.g., 25 to 50 mg diphenhydramine) and paracetamol (acetaminophen, 500 to 650 mg intravenously or equivalent oral dose) 30 to 60 minutes prior to bintrafusp alfa infusion is recommended. Premedication should be administered for subsequent bintrafusp alfa doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

6.1.2 Chemotherapy and Bevacizumab

Study interventions other than bintrafusp alfa are to be administered as indicated for standard of care treatment. Refer to each agent's Summary of Product Characteristics or package insert for more information. The descriptions below are general guidelines; modifications per local standard of care are allowed after prior agreement with the Sponsor medical representative.

Depending on the local regulations, chemotherapy agent(s) may be either sourced from a local hospital pharmacy or supplied by the Sponsor (or designated service provider) and will be packaged/labeled according to local requirements. All participants may be premedicated with oral or injectable steroids according to the approved product label and/or standard practice. A corticosteroid-sparing approach for antiemetic prophylaxis should be preferred and evaluated on a case-by-case and chemotherapy regimen basis. Drugs used in premedication must be reported in the electronic case report form (eCRF). See specific labels for dose modification.

Cisplatin

Cisplatin is administered intravenously as per standard of care, for example 50 mg/m² every 3 weeks in Cohort 1 or 40 mg/m² (a maximum of 70 mg as total dose) weekly for 5 weeks in Cohort 2. All the medications used as hydration (drugs and fluids) must be reported in the eCRF.

Carboplatin

Carboplatin is administered intravenously as per standard of care, for example AUC 5 every 3 weeks in Cohort 1.

Paclitaxel

Paclitaxel is administered intravenously as per standard of care (e.g., 175 mg/m² over 3 hours) every 3 weeks in Cohort 1.

Bevacizumab

Bevacizumab is to be administered as indicated for standard of care treatment, 15 mg/kg every 3 weeks in Cohort 1A. First infusion is to be administered over 90 minutes. Second infusion is to be administered over 60 minutes if first infusion was tolerated; all subsequent infusions are to be administered over 30 minutes if infusion over 60 minutes was tolerated.

6.1.3 Radiation

Radiation is intended to be administered per standard of care practices. As a general guideline, this is anticipated to be 40 to 50 Gy External Beam Radiation Therapy (EBRT). Brachytherapy is allowed per local standard of care with typical doses of 25 to 30 Gy. Variations to the guidelines/practices above are allowed after prior agreement with the Sponsor medical representative.

The Schedule of Activities (Section 1.3.2) reflects an example of standard of care EBRT administration of 5 fractions per week over 5 weeks. Radiotherapy should be completed within 8 weeks. The period for cCRT can be extended up to 1 week in case of technical and logistical issues and if participants require withholding of the study intervention due to toxicities.

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. CCI
[REDACTED]
- 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, 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.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- 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.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Pharmacy Manual.

CCI [REDACTED]

CCI [REDACTED]

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Participants will be assigned to each cohort based on the eligibility criteria and the Investigator's assessment. The allocation of participants to cohorts per determination by the Investigator will be recorded in the Interactive Web Response System (IWRS). Enrollment will be controlled by IWRS to ensure that over enrollment into a single cohort does not occur.

The IWRS will be used to assign a unique participant identifier number to eligible participants at the time of informed consent signature. Participant identifiers will be comprised of digits representing the study number, the site number, and the participant number, which is allocated sequentially.

6.3.2 Blinding

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

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 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.

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 eCRF 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 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 Permitted Medicines

The only permitted medications are the following:

1. Any medications (other than prohibited in Section 6.5.2) 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).
3. Blood transfusions and erythroid growth factors are permitted as clinically indicated.
4. Secondary prophylaxis with granulocyte-colony stimulating factor (G-CSF) is allowed if clinically indicated per Investigator assessment.
5. Corticosteroids use on study as a premedication for intravenous contrast allergies/reactions (related to scans).
6. Corticosteroids use for hormonal replacement and at low doses (typically ≤ 10 mg of prednisone or equivalent per day).
7. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intraocular, or inhalation) is acceptable.

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.

6.5.2 Prohibited Medicines

The following treatments must not be administered during the 28-day Screening period and for 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. Exceptions are allowed for short-term treatment of allergic reactions, as otherwise described in the protocol, 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) 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 prednisolone per day.
- Premedication with steroids for bintrafusp alfa is not allowed.
- Concomitant local or regional treatment (radio/chemo-embolization) is prohibited.
- Other systemic anti-cancer therapy.
- Live vaccines are prohibited. Administration of inactivated vaccines is allowed (e.g., inactivated influenza vaccines).
- Any traditional Chinese medication used as anti-cancer treatment (regardless of the type of cancer) is prohibited. Traditional Chinese medication for indications other than anti-cancer 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, anti-anxiety medications, and medication for pain management, including narcotic agents.

6.5.3 Other Interventions

Palliative organ-sparing radiotherapy may be administered only for specific clinical indications during the study. The assessment of PD will be made according to RECIST 1.1 and not based on the necessity for palliative radiotherapy.

6.6 Dose Selection and Modification

Doses cannot be delayed beyond the treatment window. Participants must skip dose if the treatment window is missed. Every attempt should be made to perform applicable assessments as in Section 1.3 for any missed visits. Complete the next visit following the Schedule of Activities.

Dose modification of bintrafusp alfa is not allowed. For other study interventions used in this study, dose modification may be performed as per label.

6.6.1 Safety Monitoring Committee

During this study, the SMC will periodically evaluate the safety (including DLTs) and other available data. Evaluations will be done once the 3rd as well as the 8th evaluable participant of a respective cohort has finished the DLT period.

The SMC will decide if the combinations as defined in this protocol should be continued and are safe for future studies. The SMC will recommend appropriate risk mitigation measures, if

necessary. Furthermore, if deemed appropriate by SMC, additional participants could be enrolled to further evaluate the safety of a specific cohort. All participants will be reviewed by the SMC once the last evaluable participant has completed the DLT period.

Specifically, the SMC will evaluate:

- If DLTs are observed in ≥ 1 out of 3 participants or ≥ 3 of the 8 participants, respectively, the SMC will give a recommendation regarding clearing the corresponding combination or risk mitigation measures, as appropriate, based on a review of all relevant parameters including AEs and serious adverse events (SAEs) and risk-benefit assessment for that cohort. Furthermore, if deemed appropriate by SMC, additional participants could be enrolled to further evaluate the safety of a specific cohort.
- The corresponding combination will be cleared when DLTs are observed in ≤ 2 out of 8 participants.

The probability for observing DLTs in ≥ 3 out of 8 participants is 4% if the underlying true rate is 10%, increases to 52% if the underlying true rate is 33%. Similarly, the probability for observing DLTs in ≥ 1 out of 3 participants is 27% if the underlying true rate is 10%, increases to 70% if the underlying true rate is 33% and to 78% if the underlying true rate is 40%.

The specific working procedures including the full membership, mandate, and processes will be described in an SMC charter, which will be established before first informed consent signed.

6.6.2 Definition of Dose-limiting Toxicity

This is not a dose escalation study. However, this study is evaluating DLTs in order to assess the safety and tolerability of the combination of bintrafusp alfa plus existing standard of care treatments in Cohort 1 (Cohort 1A and Cohort 1B) and 2 (treatments are described in Section 4.1).

A DLT is defined as any of the following AEs according to the NCI-CTCAE v5.0 assessed by the Investigator and/or the Sponsor and judged to be related to study intervention occurring during the DLT observation period of 4 weeks following the first dose of bintrafusp alfa (W1D1 visit) for each participant.

A DLT must be confirmed by the SMC.

During the DLT observation period, in the event a participant discontinues for reasons other than AE or is otherwise non-evaluable, the Sponsor may elect to add an additional participant. Participants with severe hypersensitivity reaction to paclitaxel during the DLT period should be discontinued from study and replaced for DLT assessment.

DLTs are defined as:

- Grade 4 nonhematologic toxicity (not laboratory)
- Grade 4 hematologic toxicity lasting ≥ 7 days despite medical intervention
- Grade 3 nausea, vomiting, and diarrhea lasting ≥ 3 days despite optimal supportive care

- Any Grade 3 or Grade 4 nonhematologic laboratory value if:
 - The abnormality leads to hospitalization, or
 - The abnormality persists for ≥ 7 days
- Febrile neutropenia Grade 3 or Grade 4:
 - Grade 3 is defined as $ANC < 1,000/mm^3$ with a single temperature of $> 38.3^\circ C$ ($101^\circ F$) or a sustained temperature of $\geq 38^\circ C$ ($100.4^\circ F$) for more than 1 hour
 - Grade 4 is defined as $ANC < 1,000/mm^3$ with a single temperature of $> 38.3^\circ C$ ($101^\circ F$) or a sustained temperature of $\geq 38^\circ C$ ($100.4^\circ F$) for more than 1 hour, with life-threatening consequences and urgent intervention indicated
- Thrombocytopenia $< 25,000/mm^3$ if associated with:
 - A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or
 - A life-threatening bleeding event which results in urgent intervention and admission to an intensive care unit
- Bleeding events \geq Grade 3 that occur within 5 days of bintrafusp alfa treatment (regardless of causality)
- Prolonged delay (> 3 weeks) in initiating Cycle 2 due to treatment-related toxicity
- Grade 5 toxicity

The following are NOT considered as DLTs:

- Grade 3 IRRs resolving within 6 hours from the end of infusion and controlled with medical management.
- Transient (< 3 days) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1 .
- Transient (< 2 days) Grade 3 flu-like symptoms or fever, which is controlled with medical management.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor that resolve to Grade ≤ 2 within 7 days.
- Skin lesion related to TGF- β inhibition (i.e., keratoacanthoma [KA], squamous cell carcinoma) that is local and can be resected with negative resection margins.
- Grade 3 skin toxicity other than radiation dermatitis that resolves to \leq Grade 1 in less than 7 days after medical management (e.g., immunosuppressant treatment) has been initiated.
- Grade 3 radiation dermatitis that resolves to Grade ≤ 2 with supportive measures within 5 weeks.
- Grade 3 asymptomatic increases in liver function tests: AST, ALT, alkaline phosphatase, or lipase that resolve to \leq Grade 1 within 7 days after medical management (e.g., immunosuppressant treatment) has been initiated.

- Single laboratory values out of normal range that are assessed as unrelated to study intervention according to the Investigator and/or do not have any clinical correlate and resolve to \leq Grade 1 within 7 days with adequate medical management.
- Grade 3 diarrhea persisting $<$ 3 days after initiation of medical management.
- Isolated Grade 4 lymphopenia without clinical correlate.
- Any Grade 3 autoimmune thyroid-related toxicity that clinically resolves to \leq Grade 2 within 7 days of initiating therapy.
- Any death due to the underlying disease or extraneous causes.

Additionally, the SMC may identify DLT as:

- Related AEs (outside of the DLT period) that in the opinion of the SMC is of potential clinical significance and considered to reflect an unacceptable risk.

6.7 Study Intervention After the End of the Study

After a participant has completed the study, has withdrawn consent, or has been withdrawn early, symptom guided appropriate treatment will be administered, if required, in accordance with the study site's standard of care and 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.

The Sponsor will not provide any additional care to participants after they leave the study because such care would not differ from what is normally expected for patients with advanced cervical cancer.

6.8 Special Precautions

6.8.1 General Guidance

In any case, if ≥ 2 doses of bintrafusp alfa are missed due to AE, the Medical Monitor should be consulted. The Medical Monitor should also be notified in the event of significant delay/omission of standard of care therapy due to AE.

During the DLT period, if one drug in a combination is delayed due to toxicity in a participant, the other drugs in the combination should be delayed in the participant. After the DLT period, if one drug in a combination needs to be delayed, the Medical Monitor should be consulted if the participant should be allowed to receive other drugs in the combination.

6.8.2 Bintrafusp alfa

Any treatment-emergent adverse event (TEAE) that is assessed as related to bintrafusp alfa, may require permanent or transient discontinuation of bintrafusp alfa treatment.

Single laboratory values out of the normal range that do not have any clinical correlate do not necessarily need treatment interruption. Questions or concerns with regard to management and/or follow-up of TEAEs should be discussed with the Medical Monitor.

Immune-related AEs, IRRs including hypersensitivity, anemia, TGF- β inhibition mediated skin reactions, and bleeding events are managed and followed up in their respective sections as indicated below. Permanent study intervention discontinuation may be recommended, so the relevant section must be reviewed:

- For suspected irAEs, general management by NCI-CTCAE v5.0 toxicity grading is listed 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 guidance are presented in Section 8.3.6.1.
- Anemia guidance is presented in Section 8.3.6.4.
- Potential TGF- β inhibition mediated skin reactions guidance and management are provided in Section 8.3.6.3.
- For guidance and management of bleeding events, see Section 8.3.6.5.

General guidance for bintrafusp alfa:

- Inability to reduce corticosteroid dose to 10 mg or less of prednisolone or equivalent per day within 12 weeks after an irAE is an indication for permanent treatment discontinuation (except for use of steroids as hormone substitution).
- Persistent endocrinopathies controlled with hormone replacement therapy generally do not require permanent treatment discontinuation, however, persistent Grade 2 treatment-related AEs that either do not resolve or improve to Grade 1 within 12 weeks after last dose of study intervention is an indication for permanent treatment discontinuation.

In general, the following applies for TEAEs related to bintrafusp alfa that are not covered by the recommendations for irAE management in the current NCCN guideline available at <http://www.nccn.org>:

Grade 4 treatment-related TEAEs

1. 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 alternative explanation is identified for Grade 4 non-tumor bleeding.

See the current NCCN guideline available at <http://www.nccn.org> for guidance on specific Grade 4 irAEs, as most require permanent treatment discontinuation.

Grade 3 treatment-related TEAE

1. Participants with any recurrent Grade 3 treatment-related AEs that recur should be permanently discontinued. Exceptions may be considered for the following after discussion with Medical Monitor:
 - 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 \leq 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 \geq 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis.
 - e. Grade 3 hemoglobin decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor use.
 - f. Increases in 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 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.).
2. AST or ALT > 5 times ULN or total bilirubin > 3 times ULN must be permanently discontinued, except for participants with liver metastases (for example) who begin treatment with Grade 2 AST or ALT. These participants should be discontinued if AST or ALT increases by $\geq 50\%$ relative to baseline and lasts for at least 1 week.
3. Persistent Grade 3 AEs (excluding endocrinopathies controlled with hormone replacement therapy) that either do not resolve or improve to Grade 1 within 12 weeks after last dose of treatment must be permanently discontinued.

See the current NCCN guideline available at <http://www.nccn.org> for guidance on specific Grade 3 irAEs as many require permanent treatment discontinuation, including pneumonitis and nephritis.

Grade 2 treatment-related TEAE

1. If a Grade 2 treatment-related TEAE resolves to Grade ≤ 1 by the day before the next infusion, study intervention may be continued.
2. If a Grade 2 treatment-related TEAE does not resolve to Grade ≤ 1 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.

Note that treatment recommendations regarding continuation, hold, or discontinuation by grade are different depending on the specific toxicity (see the current NCCN guideline available at <http://www.nccn.org>). Toxicity grading is assigned based on NCI-CTCAE v5.0.

6.8.3 Bevacizumab

Participants who receive bevacizumab must be monitored as per local standards and approved labeling documents recommendations for GI perforations, GI, GI-vaginal and tracheoesophageal fistula, wound healing complications, hemorrhage, arterial and venous thromboembolic events, hypertension, posterior reversible encephalopathy syndrome, renal injury and proteinuria, IRRs, embryofetal toxicity, ovarian failure, congestive heart failure.

6.8.3.1 Risk Management for Bevacizumab

In general, bevacizumab will not be dose reduced; however, if the patient's weight changes by $\geq 10\%$ during the study, the dose of bevacizumab will be recalculated.

If chemotherapy is held for a low ANC or thrombocytopenia, bevacizumab will also be held.

Bevacizumab should be withheld or discontinued according to approved product label and/or standard practice for GI perforations and fistulae, wound healing complications, hemorrhage, thromboembolic events, hypertension, posterior reversible encephalopathy syndrome, renal injury and proteinuria, IRR, and congestive heart failure.

6.8.4 Cisplatin, Carboplatin, and Paclitaxel

Cisplatin

Participants who receive cisplatin must be monitored for nephrotoxicity, ototoxicity, neuropathy, and hepatic toxicities in addition to myelosuppression and hypersensitivities, including anaphylaxis. Cisplatin should not be employed in participants with hearing impairment. Caution must be observed in case of nausea, vomiting, and dehydration. Premedication with antiemetics and hydration and other precautionary measures are performed according to local standards and approved labeling documents.

Carboplatin

Participants who receive treatment with carboplatin should be monitored for symptoms of myelosuppression and hematologic toxicities, hypersensitivity reactions, nausea and vomiting, hepatic toxicity/portal hypertension, renal toxicity, ototoxicity, central and peripheral neurotoxicities as per labeling recommendations. Hemolytic uremic syndrome has been reported rarely. Precautionary measures and premedication with antiemetics should be performed according to approved label and local treatment standards. Use of desensitization protocols according to local standards and approved labeling documents is allowed.

Paclitaxel

Participants who receive treatment with paclitaxel should be monitored for severe hypersensitivity reactions including anaphylaxis. All participants should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists as per labeling recommendations. Participants who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug. It is required to monitor for myelosuppression, cardiac function, and peripheral neuropathies. Precautionary measures as per local standards and approved labeling documents have to be followed.

6.8.4.1 Risk Management for Chemotherapy

Refer to the respective label for a full list of adverse reactions for each of the chemotherapy agent used in this study.

The Investigator should consider chemotherapy discontinuation for any of the following:

- Any drug-related AE which recurs after 2 prior dose reductions for the same drug-related AE requires discontinuation of the chemotherapy agent(s) which was/were previously dose reduced.
- Any Grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the chemotherapy agent(s) assessed as causing the reaction. The other study intervention(s) assessed as not related to the hypersensitivity reaction or infusion reaction may be continued.
- Any Grade 4 drug-related AE deemed by the Investigator as inappropriate to be managed by dose reduction(s) requires discontinuation of chemotherapy agent(s) assessed as causing the event. The other study intervention(s) assessed as not related to the event may be continued.
- Any event that leads to delay in dosing of any study intervention(s) for > 3 weeks from the day of scheduled administration requires discontinuation of the chemotherapy agent(s) with the following exception:
 - Dosing delays lasting > 2 weeks from the scheduled administration that occur for non-drug-related reasons may be allowed after discussion with Medical Monitor.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued chemotherapy dosing. Investigators should consult the local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose discontinuation.
- If the participant experienced Grade 3 or 4 nonhematological toxicity (except for fatigue, transient arthralgia, and myalgia), treatment with chemotherapy should be withheld until the participant recovers completely or to Grade 1 toxicity. If recovery to Grade 1 toxicity does not occur within 2 weeks, chemotherapy should be discontinued. At the discretion of the Investigator, administration of bintrafusp alfa could be continued according to the treatment schedule. A discussion between the Investigator and Sponsor's Medical

Responsible should take place. Dose delays outside the allowed window (± 3 days) and dose reductions for bintrafusp alfa are not permitted.

Dose modifications (dose delays) and dose reductions for toxicities should be made according to the approved product label(s) and/or standard practice. Discontinuation of chemotherapy due to AEs should also be done in accordance with the approved product label and/or standard practice and discussed with the Sponsor.

- See [Table 8](#) for pre dosing considerations for cisplatin.
- See [Table 9](#) for pre dosing considerations for carboplatin.

Table 8 Predosing Consideration for Cisplatin

Issue/Indication	Recommended Steps
Pre-emesis	Follow current MASCC/ESMO ^a or NCCN ^b guidelines for chemotherapy-induced nausea and vomiting for a “high risk” regimen
Hydration/ nephrotoxicity	<p>Per package insert/SmPC for cisplatin^c. Cisplatin causes severe cumulative nephrotoxicity. A urine output of 100 mL/hour or greater will tend to minimize cisplatin nephrotoxicity. Adequate hydration must therefore be maintained to cause sufficient diuresis prior to, during and after treatment with cisplatin. Next to intravenous infusion, forced diuresis may be required and moreover participants are to be requested to drink appropriate quantities of liquids for 24 hours after cisplatin infusion to ensure adequate urine secretion.</p> <p>Some institute may provide inpatient planned hydrated to reduce the risk of renal toxicity due to cisplatin; such planned hospital admission will not be considered for SAE reporting criteria.</p>
Myelosuppression/ neutropenia	<p>Refer to the current package insert/SmPC for modifications in dose and schedule of cisplatin^c. First dose of cisplatin should be withheld if platelet count is less than 100,000 cells/mm³ or neutrophil count is less than 1,500 cells/mm³. Dose modifications for subsequent administrations will be based on the neutrophil and platelet nadir from the preceding cycle.</p> <p>According to NCI-CTCAE v5.0 FN is defined as ANC < 1,000/mm³ and a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour. FN treatment should be done per local practice and reported in eCRF. FN Prophylaxis: Primary prophylaxis with G-CSF in order to reduce the risk of FN is not recommended, according to NCCN guidelines for the use of myeloid growth factors (v1.2018)^d. Secondary prophylaxis with G-CSFs should be considered and the benefit-risk associated with their use must be carefully evaluated. Investigators must be aware that the use of G-CSF during chemoradiation is associated with increased incidence of severe thrombocytopenia and anemia. Participants receiving G-CSF during chemoradiation must be closely monitored for these adverse events. The dosage instructions should follow the local guidelines or the NCCN guidelines.</p>
Ototoxicity/ neurotoxicity	Per SmPC for cisplatin ^c . Cisplatin is proven to be cumulative ototoxic and neurotoxic. Neurologic examination and monitoring of potential ototoxicity are to be performed prior to each cisplatin dosing and during the treatment.
<p>ANC=absolute neutrophil count, ASCO=American Society of Clinical Oncology, eCRF=electronic case report form, ESMO=European Society for Medical Oncology, FN=febrile neutropenia, G-CSF=granulocyte-colony stimulating factor, MASCC=Multinational Association of Supportive Care in Cancer, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, NCCN=National Comprehensive Cancer Network, SAE=serious adverse events, SmPC=summary of product characteristics.</p> <p>^a Annals of Oncology 21 (Supplement 5): v232–v243, 2010.</p> <p>^b NCCN Guideline for Patients[®] - Antiemesis version 1/2019.</p> <p>^c https://www.medicines.org.uk/emc/medicine/25944.</p> <p>^d NCCN guidelines Myeloid growth factors version 1, 2018.</p>	

Table 9 **Predosing Consideration for Carboplatin**

Adverse Reaction	Recommended Steps
Nausea or vomiting	Follow current MASCC/ESMO or NCCN ^a guidelines for chemotherapy-induced nausea and vomiting for a “high risk” regimen.
Hematological toxicities	Per package insert/SmPC of carboplatin ^b can cause leukopenia, neutropenia, and thrombocytopenia which are dose-dependent and dose-limiting. Peripheral blood counts should be monitored before start of treatment with carboplatin and then at weekly intervals and, in case of toxicity, until recovery is achieved.
Neurotoxicity	Refer to the current package insert/SmPC and local guidance for modifications in dose and schedule. Carboplatin dose should be reduced for Grade 3 or Grade 4 neurotoxicity.
Renal toxicity	Per SmPC of carboplatin, impairment of renal function is more likely in patients who have previously experienced nephrotoxicity as a result of cisplatin therapy. Dosage reduction or discontinuation of carboplatin therapy is required in the presence of severe alteration in renal function tests.
Ototoxicity	Auditory defects have been reported during carboplatin therapy; concomitant use of Carboplatin with aminoglycosides should be approached with caution because of nephrotoxicity and ototoxicity, particularly in patients with kidney failure.
<p>ESMO=European Society for Medical Oncology, MASCC = Multinational Association of Supportive Care in Cancer, NCCN=National Comprehensive Cancer Network, SmPC = summary of product characteristics.</p> <p>^a NCCN Guidelines Antiemesis version 2/2016.</p> <p>^b https://www.medicines.org.uk/emc/product/3787/smpc.</p> <p>Carboplatin should be discontinued in case of severe and persistent myelosuppression as per SmPC recommendation.</p>	

Calculated CrCL must be ≥ 50 mL/min prior to the administration of platinum chemotherapy. Platinum may be delayed for up to 2 weeks to allow the participant time to recover from the toxicity. If a participant’s CrCl value has not returned to ≥ 50 mL/min within 2 weeks after the previous dose, platinum must be discontinued.

For treatments held due to toxicity, treatment should be resumed only after toxicity has decreased to Grade ≤ 1 . Toxicities that are not able to resolve to Grade ≤ 1 within 2 weeks should warrant consideration for discontinuing agent(s) responsible for toxicity.

Cardiac rhythm disturbances have occurred infrequently in patients treated with paclitaxel in clinical studies; however, most patients were asymptomatic, and cardiac monitoring is not required. Cardiac events should be managed as follows:

- Asymptomatic bradycardia: no treatment required.
- Symptomatic arrhythmia during infusion: stop paclitaxel infusion, manage arrhythmia according to standard practice. Paclitaxel treatment will be discontinued.
- Chest pain and/or symptomatic hypotension ($< 90/60$ mmHg or requires fluid replacement): stop paclitaxel infusion. Perform an electrocardiogram (ECG). Administer intravenous diphenhydramine and dexamethasone if hypersensitivity is considered. Also consider epinephrine or bronchodilators if chest pain is not thought to be cardiac. Paclitaxel

treatment will be discontinued, and cardiovascular support should be given as appropriate. If appropriate, the advice of a cardiologist should also be sought.

Patients who had a mild to moderate hypersensitivity reaction to paclitaxel have been successfully rechallenged, but the administration of prophylactic medication and intensive monitoring of vital signs is recommended:

- Mild symptoms: complete paclitaxel infusion. Supervise at bedside. No treatment required.
- Moderate symptoms: stop paclitaxel infusion. Administer intravenous diphenhydramine 25 to 50 mg and dexamethasone 10 mg. Resume paclitaxel infusion after recovery of symptoms at a low rate, 20 mL/hour for 15 minutes, then 40 mL/hour for 15 minutes, then if no further symptoms, at full-dose rate until infusion is complete. If symptoms recur, stop paclitaxel infusion. Paclitaxel treatment will be discontinued.
- Severe life-threatening symptoms: stop paclitaxel infusion. Administer intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. Paclitaxel treatment will be discontinued.
- Moderate or severe hypersensitivity reactions should be recorded as an AE.

6.8.5 Chemoradiation

Toxicities of cCRT may arise to different degrees at different timepoints in various subpopulations and scenarios. First, with regards to chemotherapy, the presence of important variables such as age, PS, and pre-existing comorbidities plays a large role in how well the participants can tolerate cCRT. Some participants may also benefit from chemotherapy alterations in doses, intervals or even specific compounds and regimens. Second, from the radiotherapy perspective, because advanced radiotherapy techniques have developed, and image-guided radiotherapy has now become the standard of care, fewer radiotherapy-related toxicities are expected (Verma 2017). Risk management of chemoradiation side effects mainly includes early detection, study intervention modification and prompt toxicity management. If feasible, radiotherapy interruptions and dose reductions for manageable acute toxicities should be avoided by employing supportive care.

Management and work-up must be done in accordance with labeling instructions and local institutional guidelines and in discussion with the Medical Monitor.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Participants may be discontinued from study intervention for any of the following reasons, one reinitiating course of treatment may be allowed (see Section 7.1.2).

- A participant may discontinue from the study intervention at any time at her own request (i.e., withdrawal of consent), and without giving a reason.

- Occurrence of an exclusion criterion, which is clinically relevant and affects the participant's safety, 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 (see Sections 6.8, 8.3.6, and 8.3.6.5 for TEAEs and adverse events of special interest [AESIs] that require treatment discontinuation).
- Progressive Disease per RECIST 1.1, subsequently confirmed, with the exception that participants receiving treatment may continue past PD if the participant's ECOG PS has remained at least stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment (see Section 7.1.3 for all details).
- Unacceptable toxicity.
- Some TEAEs and AESIs require withdrawal from treatment. See Sections 6.8, 8.3.6, and 8.3.6.5 for additional details. Participants who discontinue study intervention will be followed on study until resolution of toxicity or until disease progression.
- Drug must not be given to a known pregnant participant.
- Use of a prohibited concomitant drug, as defined in Section 6.5.2, if discontinuation is considered necessary by Investigator/Sponsor.
- Participants should be discontinued per discontinuation recommendation in approved labeling documents for chemotherapies and bevacizumab.

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for follow-up. The Schedule of Activities indicates data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that needs to be completed.

In case of discontinuation from the study intervention(s):

- For participants in Cohort 1A, a scan should be performed within approximately 2 weeks when any drug of the combination is discontinued. Scheduling this scan should be evaluated based on current timing relative to next planned scan and/or most recently completed scan. In situations where local regulations do not permit this additional scan, omission will not be a deviation. The rest of the treatments should continue to follow Schedule of Activities.
- For participants in Cohort 1A, a scan should be performed when any regimen of the combination is discontinued, the rest of the treatment should follow Schedule of Activities.
- The day of End-of-Treatment will correspond to the day of withdrawal (or within 7 days) when all study interventions in a participant are discontinued.
- 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. After completion of the follow-up period or after the End-of-Treatment Visit, whichever is applicable, the appropriate eCRF section for Study Termination must be completed.
- 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 28-day Safety Follow-up period.

The Schedule of Activities specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that needs to be completed.

7.1.1 Temporary Discontinuation

See Sections 6.8, 8.3.6, and 8.3.6.5 for guidance on temporary discontinuation from study intervention.

7.1.2 Reinitiation

One reinitiating course of treatment of bintrafusp alfa at the same dose and schedule is allowed at the discretion of the Investigator and agreement of the Study Medical Responsible for:

- Participants who are experiencing stable disease (SD), a PR, or CR at the time of discontinuation, and then subsequently develop disease progression after stopping therapy, but prior to the end of the study.

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

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. A discussion with the study team is warranted to determine whether PK/biomarker testing is indicated upon restarting treatment.

7.1.3 Treatment Beyond Progression

7.1.3.1 Treatment Beyond Initial Progression

Participants will receive bintrafusp alfa as outlined in the Schedule of Activities until disease progression. Bintrafusp alfa may continue past the initial determination of disease progression according to RECIST 1.1 as long as the following criteria are met:

- Treatment with bintrafusp alfa is ongoing
- 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 (e.g., CNS metastases).

A radiographic assessment should be performed within 4 to 9 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.

7.1.3.2 Treatment Beyond Confirmed Progression

After confirmed PD, if the Investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the study and continue to receive monitoring according to the Schedule of Activities (see Section 1.3). The decision to continue treatment beyond confirmed PD should be discussed with the Medical Monitor and documented in the study records.

Participants who continue beyond progression will be evaluated for further tumor response as per the protocol schedule. Treatment should be discontinued permanently upon documentation of further, unequivocal disease progression unless there are no alternative therapeutic options and the benefit-risk assessment is favorable in consultation between the Investigator and the Medical Monitor. In case of continuation of treatment beyond PD, treatment will be discontinued once any other criteria for withdrawal are met.

7.1.3.3 Continuation of Study Intervention After Local Treatment of Disease Progression

If disease progression is due to brain metastases, 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 1.1. 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 1.1 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 withdraw from the study at any time, at her own request or may be withdrawn at any time 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 Schedule of Activities. The Schedule of Activities specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that needs to be completed.
- If the participant withdraws consent for future involvement in 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 (refer to the ICF).
- 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.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if 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, 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 Schedule of Activities.
- 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 Schedule of Activities, is essential and required for study conduct.
- All screening evaluations will be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- 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](#).
- Procedures conducted as part of the participant’s routine medical care (e.g., blood count) and obtained before signing of the 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 Schedule of Activities.

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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, electrocardiograms, and laboratory tests.

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 Schedule of Activities (Section 1.3). 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.

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.

The SMC will evaluate the safety (including DLTs) and other available data (see Section 6.6.1).

8.2.1 Physical Examinations

- A complete physical examination at Screening will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems.
- Vital signs, physical examinations, and ECOG PS will be conducted at Screening and at subsequent visits as indicated in the Schedule of Activities (Section 1.3). These should be documented in the eCRF.

- A brief physical examination (at all other scheduled visits other than Screening) 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 will be measured and recorded.
- Vital signs including body temperature, pulse rate, respiratory rate, and blood pressure will be assessed and recorded in the eCRF.
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.
- Blood pressure and pulse measurements will be assessed 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 preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Blood oxygen saturation (SpO₂) 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 Schedule of Activities (Section 1.3) 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 5](#) at the time points listed in the Schedule of Activities (Section 1.3). 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 eCRF. The laboratory reports will be filed with the source documents.
- If a participant has a clinically significant abnormal laboratory test value that is not present at Baseline, the test should be closely monitored until the test value has returned to the normal range or the Investigator has determined that the abnormality is chronic or stable.
- The report of the results must be retained as a part of the participant's medical record or source documents.
- Pregnancy testing (serum or highly sensitive urine test, as required by local regulations) will be conducted at monthly intervals during study intervention administration and at the time points specified in the Schedule of Activities (Section 1.3), including at the end of relevant systemic exposure of the study intervention.
- HIV testing is not mandatory. History of HIV infection will be collected, if known, as part of the medical history. If a test is performed at any point at Screening or while on study, a site must consent the participant for HIV testing as per local standard guidance.
- If a liver function test is elevated in an HBV- or HCV-positive participant, HBV deoxyribonucleic acid (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.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and a SAE are in [Appendix 4](#).

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 or study, 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 SAEs and related nonserious AEs will be collected from the signing of the ICF until 12 weeks Safety Follow-up Visit at the time points specified in the Schedule of Activities (Section 1.3).

Beyond this reporting period, any new unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed.

All AEs will be collected from the signing of the ICF until the 28 days Safety Follow-up Visit at the time points specified in the Schedule of Activities (Section 1.3).

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 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 AESI (as defined in Section 8.3.6), 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 current version of the Investigator Brochure 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 serious adverse event 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 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

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 Adverse Events of Special Interest

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

For this study, AESI for bintrafusp alfa include the following:

- Infusion-related reactions including hypersensitivity
- Immune-related AEs
- TGF- β inhibition mediated skin reactions
- Anemia
- Bleeding AEs

Continuous monitoring of such events for bintrafusp alfa is required. Upon Sponsor's decision, expedited reporting of AESIs in this study is not required, as there is already a high amount of experience with bintrafusp alfa from previous studies of the program.

8.3.6.1 Infusion-related Reactions Including Hypersensitivity

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

Infusion-Related Reactions

Infusion-related reactions are defined as any signs or symptoms experienced by participants occurring during or within 1 day of study intervention administration. An assessment for possible IRR should be triggered based upon the development of specific symptoms within 24 hours of an infusion.

These possible IRRs are identified based on a list of Medical Dictionary for Regulatory Activities preferred terms and criteria based on the timely relationship to an infusion. Events are divided into reactions versus signs and symptoms:

- Infusion-related reactions should be considered when onset is on the day of infusion (during or after the infusion) or the day after the infusion (irrespective of resolution date) for IRR, drug hypersensitivity, anaphylactic reaction, hypersensitivity, and Type 1 hypersensitivity.
- Signs and symptoms of IRR and hypersensitivity/allergic reactions should be considered when onset is on the day of infusion (during or after the infusion) and resolved completely with the end date within 2 days after onset of (but not limited to) pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria.

Management of Infusion-Related Reactions

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

If an Investigator deems necessary to administer a premedication to a particular participant, an antihistamine (e.g., 25 to 50 mg diphenhydramine) and paracetamol (acetaminophen, 500 to 650 mg intravenously or equivalent oral dose) 30 to 60 minutes prior to bintrafusp alfa infusion is recommended. Premedication should be administered for subsequent bintrafusp alfa doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

Management of symptoms should follow the guidelines shown in [Table 10](#).

Table 10 Treatment Modification of Bintrafusp alfa for Symptoms of Infusion-Related Reactions Including Hypersensitivity

NCI-CTCAE v5.0 Grade	Treatment Modification
<p>Grade 1 – mild</p> <ul style="list-style-type: none"> Mild transient reaction; infusion interruption not indicated; intervention not indicated. 	<ul style="list-style-type: none"> Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator.
<p>Grade 2 – moderate</p> <ul style="list-style-type: none"> Therapy or infusion interruption indicated but if responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours. 	<ul style="list-style-type: none"> Stop the infusion of the study intervention-caused IRR. Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator. If symptoms resolve quickly or decreased to Grade 1, resume infusion at 50% of original rate with close monitoring of any worsening otherwise dosing held until resolution of symptoms with mandated premedication for the next scheduled visit. If worsens to Grade 3 or 4, follow treatment modification guidelines accordingly.
<p>Grade 3 or Grade 4 – severe or life-threatening</p> <ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> Stop the infusion of study intervention-caused IRR 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.
<p>IRR=infusion-related reactions, IV=intravenous, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, NSAIDs=nonsteroidal anti-inflammatory drugs. Once the bintrafusp alfa infusion is interrupted or rate reduced to 50% of previous infusion rate, it must remain decreased for all subsequent infusions. For Grade 3 or 4 IRRs, bintrafusp alfa discontinuation is mandated. For all types and grades of infusion reactions, details about drug physical constitution, method of preparation, and infusion must be recorded.</p>	

In the event of a Grade 2 IRR that does not improve or worsens after implementation of the treatment modifications indicated in [Table 10](#) (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids and the infusion should be stopped for that day. At the next infusion, the Investigator may consider the addition of H2 blocker antihistamines (e.g., famotidine), in addition to the above provided recommended optional premedication regimen, for selected participants. However, prophylactic steroids are not permitted. At the next dose, if the participant has a second IRR Grade ≥ 2 on the slower infusion rate, with the addition of further medication to premedication, the infusion should be stopped, and the Investigator may consider withdrawal of this participant from the study.

Hypersensitivity Reaction

If a hypersensitivity reaction occurs, the participant must be treated according to the best available medical practice. 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>. Participants should be instructed to report any delayed reactions to the Investigator immediately.

Symptoms may include, but are not limited to:

- Impaired airway
- Decreased oxygen saturation (< 92%)
- Confusion
- Lethargy
- Hypotension
- Pale/clammy skin
- Cyanosis.

Management of hypersensitivity includes:

- Epinephrine injection and intravenous dexamethasone
- Participant should be placed on cardiac, blood pressure, heart rate, and oxygen saturation monitoring immediately
- Alert intensive care unit for possible transfer if required.

Prophylaxis of Flu-Like Symptoms

For prophylaxis of flu-like symptoms, a nonsteroidal anti-inflammatory drug, e.g., ibuprofen 400 mg or comparable nonsteroidal anti-inflammatory drug dose, may be administered 2 hours before and 8 hours after the start of each intravenous 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 considered AESIs.

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 following irAEs are important identified risks for bintrafusp alfa:

- Immune-related hepatitis
- Immune-related pneumonitis
- 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.

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 as provided in the current NCCN guideline available at <http://CCI>

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

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

Permanent treatment discontinuation is required in case of immune-related Grade 4 rash/inflammatory dermatitis, nephritis, autoimmune hemolytic anemia, hemolytic uremic

syndrome, aplastic anemia, immune thrombocytopenia, acquired thrombotic thrombocytopenic purpura, inflammatory arthritis, myositis, and polymyalgia-like syndrome.

- 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.

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

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

8.3.6.3 TGF- β Inhibition Mediated Skin Reactions

TGF- β inhibition mediated skin reactions, including hyperkeratosis, KA, and/or cSCCs, are important identified risks and AESI for bintrafusp alfa.

Skin assessments are performed at Screening period and every 6 weeks for all participants per Schedule of Activities (see Section 1.3). Baseline skin assessments include a detailed medical history of genetic or iatrogenic skin conditions, skin type, significant ultraviolet exposure/sun damage of skin, geographical location, and occupational or environmental exposure to radiation or chemicals.

Management guidelines for potential TGF- β 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 TGF- β inhibition mediated skin lesions such as hyperkeratosis, KA, and cSCC should be based on local guidelines/standard of care. 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 Medical Monitor, as needed, for management of TGF- β inhibition mediated reactions.

8.3.6.4 Anemia

Anemia is an AESI (refer to IB) 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. Participants must enter the study with hemoglobin values at least 9 g/dL; routine blood test parameters are required in the Schedule of Activities (see Section 1.3).
2. All relevant hematologic testing for anemias should be done prior to a blood transfusion, if clinically feasible.
3. Transfusion should be performed at the discretion of the Investigator based on clinical assessment and considered when the participant experiences significant 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 anemias is provided in [Table 11](#).

Table 11 Evaluation Guidance of Suspected Anemia

Baseline Anemia Evaluation	
<ul style="list-style-type: none"> a. CBC with emphasis on red cell indices (e.g., Hgb, hematocrit, MCV, RDW, MCH, MCHC, reticulocyte counts). b. If indicated and at clinical discretion, the following should be considered: <ul style="list-style-type: none"> a. Iron studies (TIBC, Ferritin, Fe) b. Serum folate and Vitamin B12 values c. Coagulation factors (PT, aPTT, 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 Baseline 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
aPTT=activated partial thromboplastin time, CBC=complete blood count, Fe=Iron, 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, RDW=red blood cell distribution width, TIBC=total iron binding capacity, TSH=thyroid-stimulating hormone.	

8.3.6.5 Bleeding Events

Bleeding events are AESIs and considered an important identified risk for bintrafusp alfa (refer to the IB).

8.3.6.5.1 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 6.8.2 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.

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

8.3.6.5.2 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 . Treatment should be permanently discontinued if the Investigator considers the participant to be at risk for additional severe bleeding.

8.3.7 Other Potential Risks for Bintrafusp alfa

8.3.7.1 Impaired Wound Healing

Impaired wound healing is considered an important potential risk (a theoretical risk based on literature findings) for bintrafusp alfa, given the role of TGF- β in wound healing. 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.

8.3.7.2 Embryofetal Toxicity

Embryofetal toxicities are a known risk of the PD-1/PD-L1 targeting class and are considered important potential risks 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. Embryofetal toxicity is an important potential risk of bintrafusp alfa. An appropriate contraception warning is provided as part of the inclusion criteria. Pregnant and breastfeeding women are not allowed in the bintrafusp alfa study, and adequate contraceptive measures are recommended during the study to minimize or eliminate the potential risk to the developing fetus.

Respective safety measures to mitigate risks comprise inclusion/exclusion criteria for participation in clinical studies with bintrafusp alfa, guidance for prevention, monitoring, and medical management of potential risks, as well as guidance on study intervention interruption or discontinuation.

8.4 Treatment of Overdose

For this study, any dose of bintrafusp alfa greater than 2 times (i.e., > 4800 mg) more than 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 DLT at 30 mg/kg and not reaching maximum tolerated dose (refer to the IB). Safety at significantly higher doses has not been clinically evaluated.

For chemotherapeutic agents used in this study, any single dose exceeding 20% of recommended chemotherapy dose regimen will be considered overdose.

- 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

The following PK parameters will be calculated, when appropriate:

Table 12 Pharmacokinetic Parameters

Symbol	Definition
C_{eoi}	The observed concentration at the end of the infusion period
C_{trough}	The concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing)
AUC_{0-t}	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log-linear trapezoidal rule (linear up, log down)
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last} , as estimated using the linear regression from λ_z determination. $AUC_{0-\infty} = AUC_{0-t_{\text{last}}} + C_{\text{last pred}} / \lambda_z$
C_{max}	Maximum observed concentration
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the first occurrence in case of multiple/identical C_{max} values)
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2) / \lambda_z$

- Whole blood samples of approximately 3.5 mL will be collected for measurement of serum concentrations of bintrafusp alfa. Collection times are specified in the Schedule of Activities (Section 1.3). A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration. The sampling timing may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The quantification of bintrafusp alfa in serum will be performed using a validated immunoassay method. Concentrations will be used to evaluate the PK of bintrafusp alfa.
- Remaining samples collected for analyses of bintrafusp alfa concentration may also be used to evaluate immunogenicity and safety or efficacy aspects related to concerns arising during or after the study.

- Details on processes for collection and handling of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.
- Pharmacokinetics and antidrug antibody (ADA) samples will be collected according to Schedule of Activities for PK and ADA Sampling in Cohort 1 (1A and 1B; [Table 2](#)) and Cohort 2 ([Table 5](#)). Pharmacokinetics and ADA samples collected at the same time points may be used interchangeably if the dedicated sample has insufficient quantity as the participants will have consented to all collections and tests.
- The PK parameters will be summarized using descriptive statistics ([Table 12](#)). Individual as well as mean concentration-time plots will be depicted.

8.6 Pharmacodynamics

Not applicable.

CCI



CCI



8.10 Health Economics

Not applicable.

CCI

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CCI

[REDACTED]

9.3 Populations for Analyses

The analysis populations are specified below (Table 13). The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock (except for the DLT population). Decision for inclusion in DLT population depends on SMC's decision.

Table 13 Analysis Set

Analysis Set	Description
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's study intervention status in the study.
DLT Analysis Set	The DLT set will include all participants who received at least 1 dose of study intervention and meet at least 1 of the following criteria: <ul style="list-style-type: none"> Experienced at least 1 DLT during the DLT period, regardless of the administered number of doses of study intervention/completion of the DLT period. Received at least 80% of the planned cumulative dose during the DLT period of each treatment and completed the DLT period. Analyses will include participants as treated.
Safety/Full Analysis Set (SAF/FAS)	All participants, who were administered any dose of any study intervention. Analyses will include participants as treated.
PK Analysis Set	All participants who complete at least 1 infusion of bintrafusp alfa, and who provide at least 1 sample with a measurable concentration of bintrafusp alfa. Analyses will include participants as treated.
CCI [REDACTED]	[REDACTED]
ADA=antidrug antibody, DLT=dose-limiting toxicity, PK=pharmacokinetic.	

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

The efficacy analyses will be done on the Safety/Full Analysis Set (SAF/FAS) for each cohort separately.

Table 14 Efficacy Analysis

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary	Not applicable

CCI [REDACTED]

IAP=Integrated Analysis Plan.

9.4.2 Safety Analyses

Except for the analysis of DLTs (a primary endpoint), all safety analyses will be performed on the SAF/FAS. The analyses are specified in [Table 15](#).

Table 15 Safety Analysis

Endpoint	Statistical Analysis Methods
Primary	
<ul style="list-style-type: none"> • Occurrence of DLTs • AEs 	<p>Count and rate of DLT per cohort will be presented with 95% Clopper-Pearson CI in the DLT analysis set.</p> <p>The Safety Analysis will include all safety analysis reporting outcomes, e.g., AEs, AESIs and laboratory tests outcomes.</p> <p>The safety endpoints will be tabulated using descriptive statistics including:</p> <ul style="list-style-type: none"> • The incidence of TEAEs, SAEs, treatment-related AEs, and AESIs, irAEs will be summarized by Preferred Term and System Organ Class for each treatment cohort and will be described in terms of severity and relationship to treatment. • The worst on-treatment grades for chemistry and hematology laboratory results will be summarized. • Shifts in toxicity grading from Baseline to highest grade during the on-treatment period will be displayed. • For laboratory tests without an NCI-CTCAE grade definition results will be presented categorically (e.g., below, within, or above normal limits). <p>Further details of safety analyses (including AEs, clinical laboratory assessments, vital signs, physical examination, ECG parameters, and ECOG PS) will be provided in the IAP.</p>
<p>AE=adverse event, AESIs=adverse events of special interest, CI=confidence interval, DLT=dose-limiting toxicity, ECOG PS= Eastern Cooperative Oncology Group Performance Status, ECG=electrocardiogram, IAP=Integrated Analysis Plan, irAE=immune-related AE, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, SAE=serious adverse event, TEAE=treatment-emergent adverse event.</p>	

9.4.3 Other Analyses

Subgroup Analysis of Efficacy

Analysis of efficacy variables may be performed on subgroups of interest as needed. The detailed subgroups will be outlined in the IAP.

PK and Immunogenicity Analyses

Samples for PK and ADA assessments will be collected as per the Schedule of Activities (see Section 1.3).

Serum concentrations of bintrafusp alfa will be determined by a validated method at the times listed in the Schedule of Activities (see Section 1.3).

Details on the PK, CCI [REDACTED] and CCI [REDACTED] analyses will be in the IAP that will be finalized before database lock. Integrated analyses across studies, such as the population PK analysis and pharmacodynamic analyses will be presented separately from the main CSR. The population pharmacokinetic analysis and exposure-response may be performed using combined data from several bintrafusp alfa clinical studies and will be specified in a separate IAP.

Analyses of PK endpoints will be specified in the IAP finalized before database lock.

CCI

Listings of drug concentration, TEAEs, and efficacy measures may be prepared for ADA ever-positive and/or nAb positive participants.

9.4.4 Sequence of Analyses

More details will be described in the IAP.

The following analyses will be performed:

- The SMC will evaluate DLT in each cohort after the 3rd as well as after the 8th evaluable participant completes the DLT observation period in the respective cohort.
- In the case more participants are included and complete the DLT period as per enrollment, all the participants will continue to be evaluated by the SMC, if required. The SMC will evaluate further information on a regular basis to evaluate the safety of the combination in each cohort, details will be available in the SMC charter.
- The main analysis of each cohort will include safety and efficacy assessment and will be conducted at least 12 months after the treatment start in the last recruited participant in the respective cohort.
- The final analysis will be conducted after end of study for safety assessment CCI [REDACTED]

Additional analysis during the study might be conducted, e.g., for publication or decision-making purposes. More details will be described in the IAP.

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11 Appendices

Appendix 1 Abbreviations

ADA	Antidrug antibody
AEs	Adverse events
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
cCRT	Concomitant chemoradiation therapy
CNS	Central nervous system
CR	Complete response
CrCL	Creatinine clearance
CRF	Case Report Form
CRO	Contract Research Organization
cSCC	Cutaneous squamous cell carcinoma
CSR	Clinical study report
CT	Computed tomography
CCI	
D	Day
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
EBRT	External Beam Radiation Therapy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FAS	Full Analysis Set
FIGO	International Federation of Gynecology and Obstetrics
GCP	Good Clinical Practice

G-CSF	Granulocyte-colony stimulating factor
GI	Gastrointestinal
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
CCI	
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
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
IRR	Infusion-related reaction
IWRS	Interactive Web Response System
KA	Keratoacanthoma
CCI	
N	Number of participants
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response

PS	Performance status
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	Ribonucleic acid
SAE	Serious adverse event
SAF	Safety Analysis Set
SD	Stable disease
SMC	Safety Monitoring Committee
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
TGF- β	Transforming growth factor- β
TMB	Tumor mutational burden
ULN	Upper limit of normal
W1D1	Week 1 Day 1

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with enough, 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 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; International Council for Harmonisation (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.
- Participants who are rescreened are required to sign a new ICF.

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 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 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 CSR.

The study will appear in the following clinical studies registries: ClinicalTrials.gov.

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

This will be prepared under the supervision of the Clinical Trial Leader in close collaboration with the responsible units at the Sponsor.

The Sponsor will coordinate the study and will provide the support for a Contract Research Organization (CRO) for some activities of the study. Sponsor Global Clinical Operations will perform oversight of the activities performed by the CRO.

The Clinical Trial Supplies department of the Sponsor will supply the study medication of bintrafusp alfa, which will be distributed to the sites by Fisher Clinical Services.

Participants enrollment will be managed by an interactive voice response system or an Interactive Web Response System.

Safety laboratory assessments will be performed locally by investigational sites. Pharmacokinetic (PK), CCI [REDACTED] will be performed under the responsibility and/or supervision of the Sponsor.

The Global Drug Safety Department, Merck KGaA, Darmstadt, Germany, or its designated representatives will supervise drug safety and the timely reporting of AEs and SAEs.

Quality assurance of the study conduct will be performed by the Development Quality Assurance Department, Merck KGaA, Darmstadt, Germany.

The department of Global Biostatistics will supervise the statistical analyses (with the exception of the PK data analyses that will be outsourced to a CRO).

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
- The Japanese ministerial ordinance on GCP
- Applicable laws and regulations

The Investigator will submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC will review and approve them before the study is initiated.

For study sites in Japan, 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 Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
- Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures.
- Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

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.

Review Committees

The following committee will be involved in the study:

Safety Monitoring Committee:

To ensure participants' safety during the study, a SMC will periodically review safety data. The SMC consists of permanent members of the Sponsor and/or CRO (GPS Product Lead, Medical Lead, Biostatistician, Medical Advisor) and the Coordinating Investigator. The SMC charter will specify whether additional members, e.g., external experts, treating Investigators will be required. The full membership, mandate, and processes of the SMC is detailed in the SMC charter.

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 CSR in consultation with the Coordinating Investigator.

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. In this case, a Coordinating Investigator will be designated by agreement.

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 CSR will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 and will be submitted in accordance with local regulations.

Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the

Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff who had been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study intervention and therefore may be disclosed as required to other clinical Investigators, to the USA Food and Drug Administration, and to other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement.

Data Quality Assurance

All participant study data will be recorded on printed or electronic CRFs 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 Operations 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.

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 keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file will identify each participant, contain the following demographic and medical information for the participant, and will be as complete as possible:
 - Participant's full name, date of birth, sex, height, and weight
 - Medical history and concomitant diseases
 - Prior and concomitant therapies (including changes during the study)
 - Study identifier (i.e., the Sponsor's study number) and participant's study number.
 - Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
 - Any medical examinations and clinical findings predefined in the protocol
 - All AEs
 - Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.
- All source data will be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document will have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records will be performed, documented, signed and dated by the Investigator.
- Data recorded on printed or electronic 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.
- The Study Monitors will use printouts of electronic files for source data verification. These printouts will be signed and dated by the Investigator and kept in the study file.
- 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 in Japan: 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 eCRF guidelines.

Study and Site Start and Closure

First Act of Recruitment

- The study start date is the date when the clinical study will be open for recruitment.
- The first act of recruitment is when the first participant is screened and signs the ICF and will be the study start date.

Study Closure and Site Termination

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and enough notice is given in advance of the intended termination.
- 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 CROs 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.

The whole study may also be terminated prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the study intervention, for example, due to:
 - evidence of inefficacy of the study intervention,
 - occurrence of significant previously unknown treatment-related adverse events or unexpectedly high intensity or incidence of known treatment-related adverse events, or
 - other unfavorable safety findings.

(Note: Evidence of inefficacy may arise from this study or from other studies; unfavorable safety findings may arise from clinical or nonclinical examinations, for example, toxicology.)

- Sponsor's decision that continuation of the study is unjustifiable for medical or ethical reasons.

Health Authorities and IECs/IRBs will be informed about the termination of the study in accordance with applicable regulations (Head of study site will also be informed in Japan).

The whole study may be terminated or suspended upon request of Health Authorities.

Appendix 3 Contraception

Contraceptive use by females will be consistent with local regulations on contraception methods for those participating in clinical studies.

Woman of Childbearing Potential

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 woman of childbearing potential is **not**:

1. Premenarchal
2. A premenopausal female with 1 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 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 follicle-stimulating hormone 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.

CONTRACEPTIVES ALLOWED DURING THE STUDY

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 woman of childbearing potential and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

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
- 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 needs to be evaluated in relation to the duration of the study.

Notes:

Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants.

Highly effective methods are those with a failure rate of < 1% per year when used consistently and correctly.

Typical use failure rates differ from those when used consistently and correctly.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure with friction).

*Not approved in Japan.

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

AE Definition

AE Definition
<ul style="list-style-type: none">• 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 unfavourable 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 <u>Meeting</u> the AE Definition
<ul style="list-style-type: none">• 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 <u>NOT</u> Meeting the AE Definition
<ul style="list-style-type: none">• 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 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 <ul style="list-style-type: none">• 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 or 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 or 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.

- If an AE constitutes a DLT this is documented accordingly.
- 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 1 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 1 of the predefined criteria specified in the definition of an SAE, NOT when it is rated as severe.

Investigators will reference the 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 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 or 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 or designee with a copy of any post-mortem findings including histopathology. Specific guidance is in the CRF Completion and Monitoring Conventions provided by the Sponsor.

- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to Sponsor or 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.

Recording and Reporting of DLTs

- Each event that meets the DLT criteria, as specified in Section 6.6.2, will be recorded in the CRF within 24 hours after awareness of the event.
- Serious DLTs will be reported in an expedited manner, using the SAE reporting process, as specified above.
- Notification of each DLT related event (non-serious and serious) will be reported to the Sponsor or its designee within 24 hours from the date of awareness.

Reporting of AESIs

Infusion-related reactions including hypersensitivity, irAEs, TGF- β inhibition mediated skin reactions, anemia, and bleeding AEs are all considered as AESIs for bintrafusp alfa.

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 Clinical Laboratory Tests

Table 16 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters				
Hematology	Platelet count ^d	Mean Corpuscular Volume (MCV)	White blood cell (WBC) Count with Differential ^d : <ul style="list-style-type: none"> • 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 (for patients with active tuberculosis (see Section 5.2), perform at Baseline and as clinically indicated)	
	Lipase	Chloride	Albumin		
	C-reactive protein	Amylase			
Routine Urinalysis	<ul style="list-style-type: none"> • Specific gravity • Physical appearance (color, transparency), pH, glucose, protein, blood/hemoglobin, ketones, bilirubin, urobilinogen, nitrite, leukocytes by dipstick • Extensive analysis (If indicated according to findings of routine analysis) one or both of the following: <ul style="list-style-type: none"> • Microscopic examination (if blood or protein is abnormal). • Culture / Antibigram 				
Other Screening Tests	<ul style="list-style-type: none"> • FSH and estradiol (as needed if not a woman of childbearing potential only) • Serum or highly sensitive urine β-hCG pregnancy test • Free T4 and TSH • 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 				

Laboratory Assessments	Parameters
	<p>^a Coagulation parameters collected at Baseline and as clinically indicated, thereafter (See Section 1.3).</p> <p>^b If hepatitis B surface antigen positive and hepatitis B core antibody positive, then reflex to quantitative HBV DNA (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).</p> <p>^c Not required for all patients. Testing required for patients with known history of HIV. Participants must be adequately consented per local regulations for any HIV-related testing.</p> <p>^d Results must be reviewed by the Investigator within 3 days prior to dosing.</p>

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Appendix 8 Protocol Amendment History

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

Appendix 9 Sponsor Signature Page

Study Title: Safety Study of Bintrafusp alfa in Combination with Other Anti-cancer Therapies in Participants with Locally Advanced or Advanced Cervical Cancer

Regulatory Agency Identifying Numbers: PPD [redacted] EudraCT: 2020-001561-36

Clinical Study Protocol Version: 06 July 2021/Version 2.0

I approve the design of the clinical study:

PPD [redacted]

Signature

PPD [redacted]

Date of Signature

Name, academic degree:

PPD [redacted]

Function/Title:

Institution:

EMD Serono Research & Development Institute, Inc.
an affiliate of Merck KGaA, Darmstadt, Germany

Address:

PPD [redacted]

Telephone number:

Fax number:

E-mail address:

Appendix 10 Coordinating Investigator Signature Page

Study Title: Safety Study of Bintrafusp alfa in Combination with Other Anti-cancer Therapies in Participants with Locally Advanced or Advanced Cervical Cancer

Regulatory Agency Identifying Numbers: PPD [redacted], EudraCT: 2020-001561-36

Clinical Study Protocol Version: 06 July 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 for Harmonisation Good Clinical Practice (Topic E6) and all PPD [redacted] national laws.

PPD [redacted]

Signature

PPD [redacted]

Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

PPD [redacted]

Appendix 11 Principal Investigator Signature Page

Study Title: Safety Study of Bintrafusp alfa in Combination with Other Anti-cancer Therapies in Participants with Locally Advanced or Advanced Cervical Cancer

Regulatory Agency Identifying Numbers: PPD [REDACTED], EudraCT: 2020-001561-36

Clinical Study Protocol Version: 06 July 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 for 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: