Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase II, Multicenter, Open Label Study of Bintrafusp alfa (M7824) Monotherapy in Participants with Advanced, Unresectable Cervical Cancer with Disease Progression During or After Platinum-Containing Chemotherapy
Study Number:	MS200647_0017
Merck Compound:	M7824
Merck Registered Compound Name in Japan:	Not applicable
Study Phase:	Phase II
Short Title:	Phase II Bintrafusp alfa Monotherapy in Platinum-Experienced Cervical Cancer
Coordinating Investigator:	PPD

Sponsor Name and Legal Registered Address:	Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US, Canada, and Japan: Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 Darmstadt, Germany In the US and Canada: EMD Serono Research & Development Institute, Inc. an affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, 01821, USA Local Sponsor for Sites in Japan: Merck Biopharma Co., Ltd.: Japan an affiliate of Merck KGaA, Darmstadt, Germany Arco Tower, 1-8-1 Shimomeguro Meguro-ku, Tokyo 153-8926, Japan
Regulatory Agency Identifying Numbers:	CCI [redacted], EudraCT: 2019-003583-40
Protocol Version:	22 June 2021/Version 3.0

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	30-Aug-2019
1.0	Original Protocol including FDA Feedback	18-Oct-2019
2.0	Global Amendment 1.0	23-Jun-2020
3.0	Global Amendment 2.0	22-Jun-2021

Protocol Version 3.0 (22-June-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. In addition, the primary analysis time point has been moved from 8 months to 12 months after the accrual of the last global participant.

Section # and Name	Description of Change	Brief Rationale
Title Page	Removed “Medical Responsible” field Removed “Amendment number”, “Replaces Version” and “Approval Date” rows	To be consistent with current Sponsor protocol template (Version 15)
2.3 Benefit/Risk Assessment	Text updated to address risk reclassification	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.
5. Study Population Appendix 2	Edits related to informed consent procedure	To be consistent with current Sponsor protocol template (Version 15)
6.9 Management of Adverse Events of Special Interest Appendix 4	Risk reclassification has been done and the list of events has been updated accordingly	
6.9.1 Infusion-related Reactions Including Immediate Hypersensitivity	Infusion-related reactions are reclassified from “important identified risk” to “identified risk” for bintrafusp alfa	
CCI [redacted]		

Section # and Name	Description of Change	Brief Rationale
6.9.3. TGF-β Inhibition Mediated Skin Reactions	Skin Adverse Events have been renamed as TGF-β Inhibition Mediated Skin Reactions	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 as reflected in Investigator's Brochure, v7.0.
6.9.4 Anemia	Term "treatment-related anemia events" has been revised to "anemia" and reclassified from "important potential risk" to "important identified risk" for bintrafusp alfa	
6.9.5 Bleeding Events	Bleeding events are reclassified from "potential risk" to "important identified risk" for bintrafusp alfa	
6.9.6.1 Impaired Wound Healing	The risk name "Alterations in Wound Healing or Repair of Tissue Damage" has been changed to "Impaired Wound Healing"	
7.3 Lost to Follow-up	Edits are done related to Lost to Follow-up information	To be consistent with current Sponsor protocol template (Version 15)
8.1.2 Patient-reported Outcomes	Information added that PRO responses should not be reviewed or used to inform care decisions	To update protocol in accordance with administrative letter sent to sites
	Update to PGIC responses	To update protocol in accordance with administrative letter sent to sites, which was to address an error in the responses
9.4.4 Sequence of Analyses	The primary analysis timing has been updated from 8 to 12 months after the accrual of the last planned global participant	To have 12 months of follow up for all participancts and allowing a longer follow up of potential late responders.
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:

A Phase II, Multicenter, Open Label Study of Bintrafusp alfa (M7824) Monotherapy in Participants with Advanced, Unresectable Cervical Cancer with Disease Progression During or After Platinum-containing Chemotherapy

Short Title:

Phase II Bintrafusp alfa Monotherapy in Platinum-Experienced Cervical Cancer

Rationale:

Globally, cervical cancer is one of the most common and lethal gynecologic cancers. Advanced/metastatic disease is typically treated with chemotherapy, often with poor response rates and short durations of response (DOR). Improved treatment options are needed for patients with advanced cervical cancer. For patients with advanced, unresectable and/or metastatic cervical cancer with disease progression during or after platinum-based chemotherapy there is no established consensus for second-line treatment options due to low response rates that are typically short-lived with variable toxicities. The majority of studies of systemic anticancer treatments (including chemotherapy and targeted agents) in platinum-experienced cervical cancer patients have resulted in meager clinical response with reported objective response rates (ORR) ranging from 3% to 10%.

Pembrolizumab is the first checkpoint inhibitor that received accelerated approval from the Food and Drug Administration (FDA) in 2018 for use as monotherapy for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express programmed death-ligand 1 (PD-L1) (Combined Positive Score (CPS) $\geq$ 1) as determined by an FDA-approved test. While the overall response rates with pembrolizumab (12.2% to 14.3%) are comparable to other treatment options for platinum-experienced cervical cancer patients, the durability of responses with pembrolizumab are noteworthy and have presented immunotherapy as a promising treatment for this disease. Notably, the limited response rates leave significant room for improvement.

A novel agent such as bintrafusp alfa, which targets the tumor microenvironment where it blocks both the cell intrinsic PD-L1/programmed death-1 (PD-1) interaction and the immunosuppressive transforming growth factor-β (TGF-β), is hypothesized to be more effective than agents that target only a single pathway.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate clinical efficacy of bintrafusp alfa based on ORR	• Confirmed objective response according to RECIST 1.1 assessed by an IRC
Secondary	
• To evaluate clinical efficacy of bintrafusp alfa based on DOR	• DOR according to RECIST 1.1 assessed by an IRC
• To evaluate clinical efficacy of bintrafusp alfa based on DRR	• Durable response of at least 6 months according to RECIST 1.1 assessed by an IRC
• To evaluate clinical safety of bintrafusp alfa	• Occurrence of TEAEs and treatment-related AEs including AEs of special interest
• To evaluate clinical efficacy based on PFS	• PFS according to RECIST 1.1 assessed by an IRC
• To evaluate ORR, DOR, DRR and PFS by Investigator read	• Confirmed objective response, DOR, DRR, and PFS according to RECIST 1.1 assessed by Investigator
• To evaluate clinical efficacy based on OS	• OS
• To characterize the PK profile of bintrafusp alfa	• The concentration observed immediately at the end of infusion (C_{EOI}) of bintrafusp alfa • The concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration [C_{trough}] for multiple dosing) of bintrafusp alfa
• To characterize the immunogenicity of bintrafusp alfa	• Immunogenicity of bintrafusp alfa as measured by ADA assay from Screening through Safety Follow-up visit (up to 28 days after last treatment)
• To evaluate clinical efficacy of bintrafusp alfa according to PD-L1 expression	• Efficacy endpoints by PD-L1 expression in tumor
ADA=antidrug antibody, AE=adverse event, DOR=duration of response, DRR=durable response rate, IRC=Independent Review Committee, NCI-CTCAE v5.0=National Cancer Institute-Common Terminology Criteria for Adverse Events v5.0, OS =overall survival, PD-L1=programmed death-ligand 1, ORR=objective response rates, PFS=progression-free survival, PK=pharmacokinetic, RECIST 1.1=Response Evaluation Criteria in Solid Tumors Version 1.1, TEAE=Treatment-emergent adverse event.	

Overall Design: This Phase II, multicenter, international, single-arm study is to evaluate bintrafusp alfa monotherapy in participants with advanced unresectable and/or metastatic cervical cancer with disease progression during or after platinum-based chemotherapy.

The study plans to enroll approximately 135 eligible participants from multiple study sites globally. The study is intended to enroll at least 15% of participants from China. After reaching the completion of the global study enrollment, if the number of participants enrolled in China does not meet the 15% target, enrollment may continue in China to meet local requirement until the target (at least 15%) participants from China is met.

Participants will receive an intravenous (IV) infusion of bintrafusp alfa at a dose of 1200 mg over 1 hour (-10 minutes/+ 20 minutes, i.e., over 50 to 80 minutes) once every 2 weeks.

The study includes:

- 28-day Screening period.
- Treatment with bintrafusp alfa at a dose of 1200 mg once every 2 weeks until confirmed progressive disease (PD) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1), death, unacceptable toxicity, or study withdrawal.
  - In the case of PD, treatment may continue if the participant's performance status (PS) has remained at least stable, in the opinion of the Investigator, the participant may benefit from continued treatment, and if other criteria are fulfilled as outlined in the protocol (refer to Section 7.1.3).
  - Participants who have experienced a confirmed complete response (CR) should continue treatment for a maximum of 24 months after confirmation of response (at the discretion of the Investigator). If the Investigator believes that a participant with confirmed CR may benefit from treatment beyond 24 months, it may be permissible to continue treatment after discussion with the Medical Monitor and the Sponsor's Medical Responsible.
  - Participants with stable disease (SD) or partial response (PR) should continue treatment until disease progression or any other discontinuation criterion is met.
- Safety Follow-up will continue until 12 weeks after the last dose of bintrafusp alfa. The 12-week Safety Follow-up is allowed to be conducted via telephone calls or patient chart reviews unless there is a medical necessity requiring a clinical visit.
- Long-term Follow-up should be performed every 12 weeks after the Safety Follow-up according to the Schedule of Activities until the end of study and should be performed by chart reviews or telephone calls.
- Survival Follow-up will continue until the end of study. After stipulated the end of study, Survival Follow-up may continue until the last participant has died or at the discretion of the Sponsor.

Number of Participants:

The planned total sample size is 135 participants for addressing the primary objective, and further efficacy and safety assessments. The study is intended to enroll at least 15% of participants from China. After reaching completion of the global study enrollment, if the number of participants enrolled in China does not meet the 15% target, enrollment may continue in China to meet local requirement until the target (at least 15%) participants from China is met.

CCI [redacted]

Study Intervention Groups and Duration:

The planned maximum study duration for a participant is estimated to be up to 24 months (in certain instances, this duration may be lengthened if it is in the best interest of the participant to continue further treatment). This includes a 28-day Screening period (decision will be made in this period for the participants' study inclusion if all eligibility criteria are met); a treatment duration until confirmed PD, unacceptable toxicity, or study withdrawal occurs, a 28-day Safety Follow-up visit and a 12-week Safety Follow-up phone call after the last dose of bintrafusp alfa. Treatment beyond radiologic disease progression may be allowed if the patient is stable without clinical deterioration.

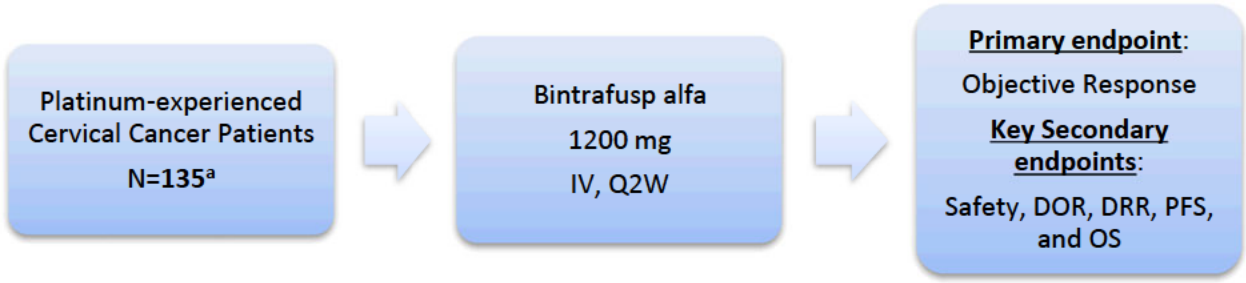
Involvement of Special Committee(s): Yes

The following committee will be involved in the study: Independent Review Committee (IRC).

The role of the IRC will be to review radiographic image findings, physical findings, and other clinical data for the determination of the best overall response (objective response) and date of disease progression for each participant. In addition, the IRC will review radiographic imaging findings for each patient to confirm presence of measurable disease per RECIST 1.1 prior to inclusion in the study. The full membership, mandate, and processes of the IRC will be detailed in the IRC charter.

1.2 Schema

Figure 1 Study Design Diagram



DOR=duration of response, DRR=durable response rate, OS=overall survival, PFS=progression-free survival, Q2W=every 2 weeks.

[a] The study plans to enroll approximately 135 eligible participants from multiple study sites globally. The Sponsor will monitor enrollment in the study and may make determinations to limit enrollment in certain countries and/or regions in order to obtain a study population representative of global standard of care, including prior bevacizumab treatment, and representative enrollment across the participating global regions (for example, asian versus non-asian countries). The study is intended to enroll at least 15% of participants from China. After reaching the completion of the global study enrollment, if the number of participants enrolled in China does not meet the 15% target, enrollment may continue in China to meet local requirement until the target (at least 15%) participants from China is met.

1.3 Schedule of Activities

Table 1 Schedule of Assessments

Assessments & Procedures	Screen-ing	Intervention Period (± 3 days)										End-of-Intervention Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day - 28 to First intervention	V1	V2	V3	V4	V5	V6	V7	V8	V9	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13	W15	W17						
		D1	D15	D29	D43	D57	D71	D85	D99	D113						
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 criteria/ Enrollment (if eligible)	X	X														
Demographic data	X															
Medical history	X															See Appendix 2.

Assessments & Procedures	Screen-ing	Intervention Period (± 3 days)										End-of-Intervention Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day - 28 to First intervention	V1	V2	V3	V4	V5	V6	V7	V8	V9	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13	W15	W17						
		D1	D15	D29	D43	D57	D71	D85	D99	D113						
Prior anticancer drug/radiotherapy / procedures for baseline visit	X															Prior anticancer procedures and therapies should at least include prior therapy, prior diagnosis of pre-malignant lesions and treatments, surgical resection and recurrence, and details on anticancer treatments, treatment duration, and treatment responses.
Documentation of concomitant medication and procedures	X	X	X	X	X	X	X	X	X	X	Q2W	X	X			
Documentation of non protocol related hospitalizations, emergency room visits, and outpatient hospital visits		X	X	X	X	X	X	X	X	X	Q2W	X	X	X	X	

Assessments & Procedures	Screen-ing	Intervention Period (± 3 days)										End-of-Intervention Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day - 28 to First intervention	V1	V2	V3	V4	V5	V6	V7	V8	V9	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13	W15	W17						
		D1	D15	D29	D43	D57	D71	D85	D99	D113						
CCI [redacted]																
Bintrafusp alfa Drug Administration																
Bintrafusp alfa administration		X	X	X	X	X	X	X	X	X	Q2W					See Section 4.1 for treatment duration.
Safety Assessments																
Documentation of AEs	X	X	X	X	X	X	X	X	X	X	Q2W	X	X	X[b]	X[b]	See Appendix 4 for safety recording and reporting. [b] 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. See Section 7.1 for discontinuation of study intervention.

Assessments & Procedures	Screen-ing	Intervention Period (± 3 days)										End-of-Intervention Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day - 28 to First intervention	V1	V2	V3	V4	V5	V6	V7	V8	V9	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13	W15	W17						
		D1	D15	D29	D43	D57	D71	D85	D99	D113						
Physical examination	X	X	X	X	X	X	X	X	X	X	Q2W	X	X			Complete PE to be performed at Screening; subsequent focused examinations to be performed as described in Section 8.2.1.
Skin assessment	X				X			X			Q6W	X	X			See Section 6.9.3 for skin assessment.
Vital signs	X	X	X	X	X	X	X	X	X	X	Q2W	X	X			Including weight and height (height at Screening only).
ECOG PS	X	X	X	X	X	X	X	X	X	X	Q2W	X	X			
12-Lead ECG	X	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 in Screening or while on study, a site must consent the participant for HIV testing as per local standard guidance.
Virology serology (HBV and HCV)	X	As clinically indicated in participants with a history of HBV or HCV infection														

Assessments & Procedures	Screen-ing	Intervention Period (± 3 days)										End-of-Intervention Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day - 28 to First intervention	V1	V2	V3	V4	V5	V6	V7	V8	V9	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13	W15	W17						
		D1	D15	D29	D43	D57	D71	D85	D99	D113						
Hematology	X	X	X	X	X	X		X		X	Q4W	X	X			See Appendix 6 for details on blood tests. Samples must also be drawn prior to study intervention administration and results of selected laboratory tests (see Appendix 6) must be reviewed within 3 days prior to dosing.
Biochemistry	X	X	X	X	X	X		X		X	Q4W	X	X			Biochemistry is listed in Appendix 6. Samples must be drawn prior to dose administration and results of selected laboratory tests (see Appendix 6) must be reviewed within 3 days prior to dosing.
Urinalysis	X	As clinical indicated														Full urinalysis at the Screening visit. If the urinalysis is abnormal, then a culture should be performed.

Assessments & Procedures	Screen-ing	Intervention Period (± 3 days)										End-of-Intervention Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day - 28 to First intervention	V1	V2	V3	V4	V5	V6	V7	V8	V9	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13	W15	W17						
		D1	D15	D29	D43	D57	D71	D85	D99	D113						
β-HCG pregnancy test	X	X		X		X		X		X	Q4W		X	X[c]		β-HCG should be determined from serum at Screening and from a urine or serum sample thereafter. 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. [c] Participants may go to local laboratory to perform pregnancy test. Clinical visit is not required.
T4 and TSH	X				X			X			Q6W		X			

CCI [redacted]

CCI [redacted]
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[redacted]

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Assessments & Procedures	Screen-ing	Intervention Period (± 3 days)										End-of-Intervention Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day - 28 to First intervention	V1	V2	V3	V4	V5	V6	V7	V8	V9	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13	W15	W17						
		D1	D15	D29	D43	D57	D71	D85	D99	D113						
CCI [redacted]																
PK, ADA and CCI																
PK and ADA sampling	See Table 2 for PK and ADA sampling times															
Whole blood for pharmacogenetics		X														Whole blood sample for participants who provide separate informed consent.

Assessments & Procedures	Screening	Intervention Period (± 3 days)										End-of-Intervention Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day -28 to First intervention	V1	V2	V3	V4	V5	V6	V7	V8	V9	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13	W15	W17						
		D1	D15	D29	D43	D57	D71	D85	D99	D113						
CCI [redacted]																

ADA=antidrug antibody, AE=adverse events, CCI [redacted], CT=computed tomography, D=day, ECG=electrocardiogram, CCI [redacted] HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, CCI [redacted] PD= progressive disease, PE=physical examination, PGIC=patient global impression of change, CCI [redacted] T4=free thyroxine, TSH=thyroid-stimulating hormone, V=visit, W=week, W1D1=Week 1 Day 1.

Table 2 Bintrafusp alfa Pharmacokinetic, Immunogenicity Sampling

Bintrafusp alfa Measure	Screening / Baseline Assessments	Treatment Phase (± 3 days)						End-of-Treatment Visit	Safety Follow-up Visit		Notes
		V1	V2	V3	V4	V7					
		W1	W3	W5	W7	W13					
	Day -28 to First Treatment	D1 Pre/End Infusion	D15 Pre/End Infusion	D29 Pre/End Infusion	D43 Pre/End Infusion	D85 Pre/End Infusion	Until Progression Pre/End Infusion	On the Day of or Within 7 Days of Decision	Up to 28 Days (± 5 days) After Last Treatment	12 Weeks (± 2 weeks) After Last Treatment	
Blood sample for PK		X/X	X/-	X/X	X/-	X/-	X/- Q6W up to/including W25, then Q12W	X	X		Samples for PK analysis to be taken before (pre) infusion (as close to the start of the infusion as possible), immediately after the completion of infusion (as close to the completion as possible but no later than 30 minutes post end of infusion). The pre-dose sample should still be drawn even if dosing is ultimately deferred at the study visit. The exact time of each draw must be recorded.
Blood sample for ADA		X/-	X/-	X/-	X/-	X/-	X/- Q6W up to/including W25, then Q12W	X	X		Pre-dose ADA samples to be collected within 4 hours prior to study intervention infusions.

ADA=antidrug antibody, D=days, PK=pharmacokinetics, Q6W=every 6 weeks; Q12w=every 12 weeks; V=visit, W=week.

2 Introduction

Bintrafusp alfa (M7824) is a first-in-class, intravenously (IV) administered bifunctional fusion protein that combines an anti-programmed death-ligand 1 (anti-PD-L1) antibody and the soluble extracellular domain of the human transforming growth factor-β (TGF-β) receptor as a TGF-β neutralizing "trap" into a single molecule. Bintrafusp alfa is the recommended international nonproprietary name for M7824.

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

2.1 Study Rationale

This is a Phase II, multicenter, international, single-arm, open label study to evaluate bintrafusp alfa monotherapy in participants with advanced unresectable cervical cancer with disease progression during or after prior platinum-based chemotherapy.

The majority of studies of systemic anticancer treatments (including chemotherapy and targeted agents) in platinum-experienced cervical cancer patients have resulted in meager clinical response with a reported objective response rates (ORR) ranging from 3% to 10% (Monk 2009). A literature review of studies including almost 2000 patients (see Section 2.2) similarly resulted in a median ORR across studies of 10% and weighted average median progression-free survival (PFS) and overall survival (OS) of only 3.3 and 8.3 months, respectively.

Pembrolizumab is the first checkpoint inhibitor that received accelerated approval from the Food and Drug Administration (FDA) in 2018 for use as a monotherapy for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 1) as determined by an FDA-approved test. While the overall response rates with pembrolizumab (12.2% to 14.3%) are comparable to other treatment options for platinum-experienced cervical cancer patients, the durability of responses for pembrolizumab are noteworthy and have presented immunotherapy as a promising treatment for this disease (see Section 2.2). Notably, the limited response rates leave room for improvement.

A novel agent such as bintrafusp alfa, which targets the tumor microenvironment where it blocks both the cell intrinsic PD-L1/programmed death-1 (PD-1) interaction and the immunosuppressive TGF-β, is hypothesized to be more effective than agents that target only a single pathway (see Section 2.2).

The promising clinical activity of bintrafusp alfa observed in cervical cancer patients of the Phase I Study EMR200647-001 (see Section 2.2) and its manageable safety profile in close to 700 participants with various cancer types (refer to IB) support further investigation of bintrafusp alfa in participants with advanced, unresectable cervical cancer with disease progression during or after prior platinum-containing chemotherapy; see Section 4.2 for more details.

2.2 Background

Globally, cervical cancer is one of the most common and lethal gynecologic cancers. Advanced/metastatic disease is typically treated with chemotherapy, often with poor response rates and durations of response (DOR).

Improved treatment options are needed for patients with advanced cervical cancer:

- Currently, platinum-containing chemotherapy regimen with or without bevacizumab is the standard first-line therapy for patients with metastatic cervical cancer. In patients with locoregionally advanced cervical cancer, concurrent platinum-containing chemotherapy in combination with radiation therapy is recommended (Monk 2007).
- Despite a large series of tested treatment options for patients following standard of care first-line treatment, there is no established consensus for second-line treatment. Treatment options are limited due to low response rates that are typically short-lived and associated with variable toxicities (McLachlan 2017; Monk 2007).

A literature review of clinical studies reporting efficacy outcomes for systemic anticancer treatments in platinum-experienced patients with locally advanced or metastatic cervical cancer led to the identification of 59 relevant publications reporting results on 1,943 patients with platinum-experienced cervical cancer. The majority of studies reported meager response rates with a median reported ORR of 10%. A random-effect model to account for heterogeneity between studies estimated the ORR across all selected publications at 15% (95% CI: 12.4%, 18.2%). In addition to this limited response the weighted average median OS and PFS times were 8.3 and 3.3 months respectively.

In addition to the low response rates, responses were short in duration when they were reported (15 studies): median DORs ranged from 1.6 to 13.9 months (13.9 months duration was reported in a study of temsirolimus with a single partial responder among 33 patients evaluable for response), and 12 studies (80%) reported median durations of responses of 6.2 months or less (Tinker 2013).

Nivolumab was the first PD-1 inhibitor with reported efficacy data in cervical cancer. In Checkmate-358, 19 patients with recurrent and/or metastatic cervical cancer were treated, and an ORR of 26.3% (95% CI: 9.1, 51.2) was observed (Hollebecque 2017). Neither DOR, nor proportion of treated cervical cancer patients naïve to systemic chemotherapy were reported.

Pembrolizumab is the first checkpoint inhibitor that received approval (accelerated) from the FDA in 2018 for use as monotherapy treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1. This approval was based on the interim results from the Phase II KEYNOTE-158 study (Chung 2019):

- Among the 98 patients with previously treated advanced cervical cancer, the ORR was 12.2% (95% CI: 6.5%, 20.4%), median PFS was 2.1 months (95% CI: 2.0, 2.2 months), and median OS was 9.4 months (95% CI: 7.7, 13.1 months).

- Among the 77 patients with PD-L1 positive (CPS ≥ 1), chemotherapy refractory cervical cancer, the ORR was 14.3% (95% CI: 7.4, 24.1). At the time of the publication, median DOR was not reached (range 4.1 to 18.6+ months), and median OS was 11 months (95% CI: 9.1, 14.1).
- In KEYNOTE-158, no responses were observed among the PD-L1 negative patients (CPS < 1, n=15), and 3 patients experienced best overall response as stable disease.

While the overall response rates with pembrolizumab are only comparable to other treatment options for cervical cancer patients (12.2% to 14.3%), the durability of responses are noteworthy and have presented immunotherapy as a promising treatment for this disease.

Recently, molecular characterization of cervical cancer by The Cancer Genome Atlas 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-β1 upregulation by human papilloma virus (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 patients with chemotherapy refractory cervical cancer in Phase I study EMR200647-001. In the Phase I study, a total of 25 patients 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:

- ORR of 24.0% (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 DOR not reached; range 2.3+ to 24.9+ months).
- One additional participant developed a partial response (PR) after initial confirmed disease progression, bringing the total clinical response rate to 28.0% (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 patient with negative tumor PD-L1 expression (via 73-10 assay) had a confirmed PR.

Based on the biological rationale and promising clinical activity of bintrafusp alfa in cervical cancer and manageable safety profile in close to 700 participants with various cancer types (refer to IB), this study is designed to further investigate bintrafusp alfa in participants with advanced, unresectable, cervical cancer with disease progression during or after platinum-containing chemotherapy.

2.3 Benefit/Risk Assessment

At the time of study initiation, bintrafusp alfa demonstrated promising clinical efficacy in a cohort of participants with second-line (2L)+ cervical cancer in the Phase I study EMR200647-001, with a confirmed ORR of 24.0% and total clinical response rate of 28.0% (95% CI: 12.1, 49.4). The median DOR had not been reached by data cutoff - 5 of 6 responses were ongoing, with 1 ongoing response already lasting for > 2 years. These results demonstrate encouraging clinical efficacy of bintrafusp alfa in cervical cancer with favorable response rate and durability compared to historical benchmarks.

Platinum-containing chemotherapy regimen with or without bevacizumab is the standard first-line therapy for patients with metastatic cervical cancer. For patients with advanced unresectable and/or metastatic cervical cancer with disease progression during or after platinum-based chemotherapy there is no established consensus for second-line treatment options due to low response rates, typically short-lived and variable toxicities (Bookman 2000; Muderspach 2001; Schilder 2005; Alberts 2012). Based upon the poor clinical prognosis new treatment options for this patient population are needed, and these patients are included in the eligibility for this study (further rationale included in Section 4.2).

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, MS200647-0008) compared with therapies targeting PD-L1 or TGF-β. The following have been identified as important identified risks for M7824: Immune-related adverse events (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 immune-related adverse events (irAEs) [myositis, myocarditis, encephalitis]), TGF-β inhibition mediated skin reactions, anemia and bleeding adverse events. The overall incidence and severity for irAEs is found to be consistent across bintrafusp alfa studies and similar to the known safety profile of approved anti-PD-L1 agents (Brahmer 2018).

Infusion-related reactions (IRRs) 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. At the time of study initiation, the overall bintrafusp alfa related IRRs were observed to be < 5%, of low-grade (Grade 1/2) severity and not requiring permanent treatment discontinuation.

Dermatologic AEs related to TGF-β-inhibition (including keratoacanthomas [KA] and cutaneous squamous cell cancers) are an important identified risk with bintrafusp alfa not seen with other PD-1/PD-L1 antibodies. These lesions were previously observed in participants with genetic mutations in the TGF-β receptor (i.e., Ferguson-Smith syndrome), and participants treated with the TGF-β-targeting agent fresolimumab (Goudie 2011; Morris 2014). At the time of study initiation, in the Phase I studies, treatment-emergent TGF-β inhibition mediated skin reactions were observed in approximately 11% of participants, and were well-managed with simple excision (or spontaneous resolution) and did not require any participant to discontinue treatment (refer to

IB). The risk of these lesions with bintrafusp alfa was considered manageable, especially in the context of encouraging clinical activity in several tumor types.

CCI

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3 Objectives and Endpoints

Table 3 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate clinical efficacy of bintrafusp alfa based on ORR	• Confirmed objective response according to RECIST 1.1 assessed by an IRC
Secondary	
• To evaluate clinical efficacy of bintrafusp alfa based on DOR	• DOR according to RECIST 1.1 assessed by an IRC
• To evaluate clinical efficacy of bintrafusp alfa based on DRR	• Durable response of at least 6 months according to RECIST 1.1 assessed by an IRC
• To evaluate clinical safety of bintrafusp alfa	• Occurrence of TEAEs and treatment-related AEs including AEs of special interest
• To evaluate clinical efficacy based on PFS	• PFS according to RECIST 1.1 assessed by an IRC
• To evaluate ORR, DOR, DRR, and PFS by Investigator read	• Confirmed objective response, DOR, DRR, and PFS according to RECIST 1.1 assessed by Investigator
• To evaluate clinical efficacy based on OS	• OS
• To characterize the PK profile of bintrafusp alfa	• The concentration observed immediately at the end of infusion (C_{EOI}) of bintrafusp alfa • The concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration [C_{trough}] for multiple dosing) of bintrafusp alfa
• To characterize the immunogenicity of bintrafusp alfa	• Immunogenicity of bintrafusp alfa as measured by ADA assay from Screening through Safety Follow-up visit (up to 28 days after last treatment)
• To evaluate clinical efficacy of bintrafusp alfa according to PD-L1 expression	• Efficacy endpoints by PD-L1 expression in tumor

CCI [redacted]	

ADA=antidrug antibody, AE=adverse event, DOR=duration of response, DRR=durable response rate, HPV=human papilloma virus, ir =immune-related, IRC=Independent Review Committee CCI [redacted] NCI-CTCAE v5.0=National Cancer Institute-Common Terminology Criteria for Adverse Events v5.0, OS=overall survival, ORR=objective response rates, PD-L1=programmed death-ligand 1, PFS=progression-free survival, PK=pharmacokinetic, CCI [redacted], RECIST 1.1=Response Evaluation Criteria in Solid Tumors Version 1.1, TEAE=Treatment-emergent adverse event, CCI [redacted].

4 Study Design

4.1 Overall Design

This is a Phase II, multicenter, international, single-arm study to evaluate bintrafusp alfa monotherapy in participants with advanced unresectable and/or metastatic cervical cancer with disease progression during or after platinum-based chemotherapy. See Section 5.1 and Section 5.2 for more details for the patient population.

The primary objective is to evaluate the clinical efficacy of bintrafusp alfa based on the ORR. The key secondary objectives are safety, DOR, durable response rate (DRR), PFS, and OS. The clinical efficacy of bintrafusp alfa will also be retrospectively evaluated according to PD-L1 expression. CCI [redacted]

The study plans to enroll approximately 135 eligible participants from multiple study sites globally. The Sponsor will monitor enrollment in the study and may make determinations to limit enrollment in certain countries and/or regions in order to obtain a study population representative of global standard of care, including prior bevacizumab treatment and representative enrollment across the participating global regions (for example, asian versus non-asian countries).

The study is intended to enroll at least 15% of participants from China. After reaching completion of the global study enrollment, if the number of participants enrolled in China does not meet the 15% target, enrollment may continue in China to meet local requirement until the target (at least 15%) participants from China is met.

CCI [redacted]

The study includes:

- 28-day Screening period
- Treatment with bintrafusp alfa at a dose of 1200 mg once every 2 weeks until confirmed PD per RECIST 1.1, death, unacceptable toxicity, or study withdrawal.
  - In the case of PD, treatment may continue if the participant's performance status (PS) has remained at least stable, in the opinion of the Investigator, the participant will benefit from continued treatment, and if other criteria are fulfilled as outlined in the protocol (see Section 7.1.3).
  - Participants who have experienced a confirmed complete response (CR) should continue treatment for a maximum of 24 months after confirmation of response (at the discretion of the Investigator). If the Investigator believes that a participant with confirmed CR may benefit from treatment beyond 24 months, it may be permissible to continue treatment after discussion with the Medical Monitor and the Sponsor's Medical Responsible.
  - Patients with SD or PR should continue treatment until disease progression, or any other discontinuation criterion is met.
- Safety Follow-up will continue until 12 weeks after the last dose of bintrafusp alfa. The 12-week Safety Follow-up is allowed to be conducted via telephone calls or patient chart reviews unless there is a medical necessity requiring a clinical visit.
- Long-term Follow-up should be performed every 12 weeks after the Safety Follow-up according to the Schedule of Activities (see Table 1). Long-term Follow-up should be performed by chart reviews or telephone calls.
- Survival Follow-up will continue until the end of study as defined in Section 4.4. After stipulated end of study, Survival Follow-up may continue until the last participant has died or at the discretion of the Sponsor.

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

4.2 Scientific Rationale for Study Design

This study enrolls patients with advanced unresectable and/or metastatic cervical cancer with disease progression during or after platinum-based chemotherapy.

Single-Arm Design

This is a single-arm study for patients who have progressed on prior platinum-containing therapy. Available treatments for this patient population have shown limited activity with low response rates and short DOR with most studies reporting median PFS results < 6 months (Monk 2009).

The primary objective of this study is the confirmed overall response rate assessed by Independent Review Committee (IRC) according to RECIST 1.1, and the key secondary endpoints include DOR, PFS and OS.

Data from a similar patient population with cervical cancer in the Phase I study EMR200647-001 demonstrated that bintrafusp alfa is an active drug with encouraging and durable (> 6 months) clinical responses for these patients. Therefore, this single-arm Phase II study will allow an adequate and more robust assessment of clinical activity in platinum-experienced cervical cancer.

Prior Platinum-Based Therapy

Platinum-containing chemotherapy regimen with or without bevacizumab is the standard first-line therapy for patients with metastatic cervical cancer. For patients with advanced unresectable and/or metastatic cervical cancer with disease progression during or after platinum-based chemotherapy there is no established consensus for second-line treatment options due to low response rates that are typically short-lived with variable toxicities (Marth 2017). To be documented with the informed consent, all patients enrolled in the study must have all available treatment options discussed with them during the Screening period.

Inclusion of Human Immunodeficiency Virus Positive Patients

In the typical pathogenesis of cervical neoplasia, standard Screening and early treatment are effective for detecting and treating pre-cancerous lesions as well as early cancerous growth. Given the natural history of the disease with a long developmental timeline, patients who develop metastatic disease are frequently those who had prolonged periods with limited access to standard medical care. In addition, these patients are also at higher risk for comorbid illnesses, including human immunodeficiency virus (HIV) infection.

Research has suggested that HIV+ cancer patients are more likely to die due to their cancer than HIV-related complications. In addition, though with limited data, PD-1/PD-L1 inhibitors used in cancer patients with HIV were shown to be safe and with noted activity (Spano 2019). This is consistent with an analysis of literature reports, including PD-1/PD-L1 inhibitors as well as cytotoxic T-cell lymphocyte-associated antigen-4 (CTLA-4) blocking agents, from 73 patients showing a manageable safety profile consistent with the agents; activity in multiple tumor types. In addition, 93% of patients with undetectable viral loads maintained undetectable levels during treatment (Cook 2019).

The inclusion criteria in this study incorporate recommendations from recent FDA Guidance on Cancer Clinical Trial Eligibility Criteria (March 2019) that specifies patients with stable, well-controlled HIV should be included in clinical studies. Human immunodeficiency virus testing is not mandatory for study inclusion; a known history of HIV infection should be reported for

verification of HIV-specific inclusion criteria and appropriate safety monitoring. Any patient undergoing HIV testing for the purpose of this study must be appropriately consented as per local regulations.

4.3 Justification for Dose

The recommended Phase II dose (RP2D) for bintrafusp alfa is 1200 mg administered as an IV infusion once every 2 weeks. The selection of RP2D is based on the available clinical data from the Phase I Studies EMR200647-001 and MS200647-0008, including safety/tolerability, pharmacokinetic (PK), and pharmacodynamics (PD-L1 target occupancy in peripheral blood mononuclear cell and TGF-β plasma concentrations), as well as efficacy in 2L non-small cell lung cancer cohorts from the EMR200647-001 study. The selection of RP2D is also supported by population pharmacokinetic (PopPK) and exposure-response modeling and simulation.

Refer to the IB for the completed and detailed data and analysis 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 when 67% of all study participants and 67% of the participants from China have died (in case of additional China enrollment after global enrollment completion) whichever occurs last. However, the study ends when each participant was followed up for at least 3 years after the first dose if it occurs earlier. 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.

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 should be taken into consideration 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 his/her parent or guardian will be required in addition to the participant's written consent.

Type of Participant and Disease Characteristics

2. Have a histologically documented advanced unresectable and/or metastatic cervical cancer (squamous cell carcinoma, adenocarcinoma, adenosquamous cell carcinoma) with disease progression during or after the prior platinum-containing chemotherapy:
    a. The prior platinum-containing chemotherapy may be:
        i. A systemic treatment for advanced unresectable, recurrent, persistent or metastatic disease or
        ii. Treatment in the adjuvant or neo-adjuvant setting with disease progression or recurrence within 6 months of completion of platinum-containing chemotherapy.
    b. Participants who previously only received platinum as a radiosensitizer are not eligible.
    c. Participants must be naïve to checkpoint inhibitors (see Section 5.2).
3. Measurable disease outside the central nervous system (CNS) according to RECIST 1.1 at Screening. Evidence of measurable disease outside the CNS must be confirmed by IRC prior to start of treatment. Note: Lesions within the CNS are to be considered as non-target lesions only. Lesions may be considered measurable regardless of prior irradiation. Target lesions should preferably be selected from areas that have not been irradiated, or appear not to have been irradiated. If necessary, target lesion may be selected from areas that have been, or appear to have been irradiated in the opinion of the assessor.
4. Archival tumor tissue sample or newly obtained (preferred) core or excisional biopsy of a tumor lesion is mandatory and collected during the Screening period prior to enrollment. Fine needle aspirates are not acceptable. CCI [redacted] If participant received local therapy (e.g., radiation therapy or chemoradiotherapy) after the archival tissue was taken, a new, acceptable biopsy will be required prior to study entry.
5. Have Eastern Cooperative Oncology Group (ECOG) PS of 0 to 1 at study entry and Day 1 of treatment with bintrafusp alfa.
6. Life expectancy ≥ 12 weeks as judged by the Investigator.
7. Have adequate organ function:
    a. Adequate hematological function defined by absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L, and hemoglobin (Hgb) ≥ 9 g/dL.

b. Adequate hepatic function defined by a total bilirubin level ≤ the upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 1.5 × ULN. For participants with liver involvement in their tumor, AST ≤ 5.0 × ULN, ALT ≤ 5.0 × ULN, and bilirubin ≤ 3.0 × ULN are acceptable.

c. Adequate renal function defined by creatinine ≤ 1.5 × ULN or calculated creatinine clearance (CrCL) ≥ 30 mL/min for participant with creatinine > 1.5× 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:

CrCL = ([140-age] × weight [kg] × [0.85 for females only]) / (72 × creatinine).

d. Adequate coagulation function defined as international normalized ratio (INR) or prothrombin time (PT) ≤ 1.5× ULN unless the participant is receiving anticoagulant therapy and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN unless the participant is receiving anticoagulant therapy.

8. Participants with known HIV infections are in general eligible if the following criteria are met (FDA Guidance on Cancer Clinical Trial Eligibility, March 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 study Medical Monitor.

b. Participants with HIV infection should have no evidence of documented multi-drug 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/µL.

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 study Medical Monitor.

f. If prophylactic antimicrobial drugs are indicated, patient may still be considered eligible upon agreement with the study Medical Monitor.

9. Participants with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infections are in general eligible if the following criteria are met (FDA Guidance on Cancer Clinical Trial Eligibility, March 2019):

a. Patients with serologic evidence of chronic HBV infection must have an HBV viral load below the limit of quantification. If medically indicated, participants infected with HBV must be treated and on a stable dose of antivirals (e.g., entecavir, tenofovir, or lamivudine; adefovir or interferon are not allowed) at study entry and with planned monitoring and management according to appropriate labeling guidance.

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

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

- N**ot** a Woman of childbearing potential (WOCBP)

OR

- If a WOCBP, uses 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.

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 Section 8.2.4.

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

11. 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:

Medical Conditions

1. Participants with active 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 treatment. Note: Lesions in the CNS at baseline must be assessed as non-target lesions only.

2. Has interstitial lung disease OR has had a history of pneumonitis that has required oral or IV steroids

3. 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).

4. Previous malignant disease (other than the target malignancy to be investigated in this study) within the last 3 years, except:

   a. Participants with a history of superficial/noninvasive bladder cancer, or basal or squamous cell carcinoma in situ previously treated with curative intent are NOT excluded.

   b. Endoscopically resected early gastrointestinal (GI) cancers limited to mucosal layer (esophageal, gastric, and colorectal) that are without recurrence in > 1 year are allowed.

   c. Participants with other localized malignancies (e.g., noninvasive breast cancer [ductal carcinoma in situ]) treated with curative intent should be discussed with the Medical Monitor. Further biopsy/evaluations may be required prior to allowing enrollment if there are any concerns of a non-cervical cancer recurrence.

Any questions regarding these criteria should be discussed with Medical Monitor.

5. 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).

6. 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.

7. Known severe hypersensitivity (Grade ≥ 3 National Cancer Institute-Common Terminology Criteria for Adverse Events v5.0 [NCI-CTCAE v5.0]) to investigational product (bintrafusp alfa) or any components in its formulation, any history of anaphylaxis, or recent, within 5 months, history of uncontrollable asthma.

8. Persisting Grade > 1 NCI-CTCAE v5.0 toxicity (except alopecia and vitiligo) related to prior therapy; however, sensory neuropathy Grade ≤ 2 is acceptable.

9. 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 II), or serious cardiac arrhythmia. Participants with history of bleeding diathesis or recent major bleeding events 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-PD-1, anti-PD-L1, anti-PD-L2, anti-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]).

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.

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. Rescreened participants will be assigned a new participant number.

For participants who have abnormal laboratory value at Screening that may correct or are using a prohibited concomitant medication that will be discontinued, or undergoing a prohibited procedure that will be completed, the Screening period may be extended up to 2 weeks upon discussion with the Medical Monitor as long as all Screening parameters will have been collected within 28 days from first study intervention. In other situations when a participant has been screen-failed, the site should contact the Medical Monitor to discuss whether the participant may be rescreened.

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

Table 4 Study Intervention

Study 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 1200 mg over 1 hour (- 10 minutes/+ 20 minutes, i.e., over 50 to 80 minutes) once every 2 weeks.
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.

6.2 Study Intervention(s) Preparation, Handling, CCI , 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 must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the Pharmacy Manual.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) must be stored in a secure, environmentally controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition, and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.

- The dose(s) each participant used during the study.
- The disposition (including return, if applicable) of any unused study intervention(s).
- Dates, quantities, batch numbers, vial numbers, expiry dates, formulations, and the participant numbers.

- The Investigator site will maintain records, which adequately document that participants were provided the doses specified in this protocol, and that all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) must 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) is provided in the Operations Manual.

Bintrafusp alfa should be stored in a refrigerator CCI [redacted] until use. Bintrafusp alfa must not be frozen and should be stored in the original packaging.

Additional instructions for the preparation, handling, storage, and disposal of bintrafusp alfa will be provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

The Sponsor or delegate will assign a unique participant identifier number to participants in chronological order 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. Enrollment will utilize an Interactive Voice/Web Response System.

6.3.2 Blinding

Not applicable.

6.4 Study Intervention Compliance

In this study, participants will receive study intervention at the study site. Well trained medical staff will monitor and perform the study intervention administration. The information of each study intervention administration, including the date, time, and dose of study intervention, will be recorded on the electronic case report forms (eCRFs). The Investigator will make sure that the information entered into the eCRF regarding study intervention administration is accurate for each participant. Any reason for noncompliance should be documented.

Noncompliance is defined as a participant missing > 1 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 4 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 form 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 6.9).
3. Blood transfusions and erythroid growth factors are permitted as clinically indicated.

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

6.5.2 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 or for the treatment of irAEs, specifically:
    - Short-term administration of systemic steroid (i.e., for allergic reactions 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 prednisone per day.
- Prophylactic use of corticosteroids for IRRs is prohibited.
- Concomitant local or regional treatment (radio/chemo-embolization) is prohibited.
- Other systemic anticancer therapy.
- Live vaccines are prohibited. Administration of inactivated vaccines is allowed (e.g., inactivated influenza vaccines).
- Any traditional Chinese medication used as anticancer treatment (regardless of the type of cancer) is prohibited. Traditional Chinese medication for indications other than anticancer treatment, such as supportive care, may be administered at the discretion of the Investigator. List of prohibited Chinese medications is provided in the Appendix 7.
- Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin).

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

6.5.3 Other Interventions

Permitted Procedures

- 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.

Prohibited Procedures

- Major surgery within 4 weeks before the start of the study. Discuss with the Medical Monitor if unplanned major surgery is required on study to plan for timing of re-treatment. Any diagnostic biopsies collected for clinical reasons during the study should be documented as a concomitant procedure including the outcome of available pathology reports.

6.6 Dose Selection and Modification

Participants will receive an IV infusion of bintrafusp alfa at a dose of 1200 mg over 1 hour CCI [redacted] once every 2 weeks as detailed in the SoA (see Table 1).

Dose modification of bintrafusp alfa is not allowed.

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 whatever care they and their physicians agree upon.

6.8 Special Precautions

Any treatment-emergent adverse event (TEAE) that is assessed as potentially 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 correlation 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 6.9.2. Recommended guidance and management for specific irAEs as per published guidelines is provided in Appendix 5.
- Infusion-related reaction (IRR) and hypersensitivity reaction guidance are presented in Section 6.9.1.
- Anemia guidance is presented in Section 6.9.4.
- Potential TGF-β-mediated skin AEs guidance and management are provided in Section 6.9.3.
- For guidance and management of bleeding events, see Section 6.9.5.

General guidance:

- In any case, if ≥ 2 doses are missed due to AE, the Medical Monitor should be consulted
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks is an indication for permanent treatment discontinuation (except for use of steroids as hormone substitution)
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0 to 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 Appendix 5:

Grade 4 treatment-related TEAEs

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

- Endocrinopathies that have been controlled by hormone replacement
- 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
- If alternative explanation is identified for Grade 4 non-tumor bleeding.

See Appendix 5 for guidance on specific Grade 4 irAEs, as most require permanent treatment discontinuation.

Grade 3 treatment-related TEAE

1. Participants with any severe or Grade 3 treatment-related adverse reactions that recur should be permanently discontinued. Exceptions may be considered for the following after discussion with Medical Monitor:
    - Transient Grade 3 flu-like symptoms or fever that is controlled with medical management

- Transient Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to ≤ Grade 1 or baseline
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumors
- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis
- Grade 3 Hgb decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor use
- 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)
- Keratoacanthoma (KA) and cutaneous squamous cell carcinoma (cSCC)
- 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. See Appendix 5 for guidance on specific Grade 3 irAEs as many require permanent treatment discontinuation, including pneumonitis and nephritis.
   - AST or ALT > 5 times ULN or total bilirubin greater than 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 ≥ 50% relative to baseline and lasts for at least 1 week.

3. Persistent Grade 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0 to 1 within 12 weeks after dose of treatment.

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 (refer to Appendix 5). Toxicity grading is assigned based on NCI-CTCAE v5.0.

6.9 Management of Adverse Events of Special Interest

Adverse events of special interest (AESI) are serious or nonserious AEs specific to the known mechanism of action of the study intervention that are of clinical interest.

For this study, AESIs include the following:

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

6.9.1 Infusion-related Reactions Including Immediate Hypersensitivity

Infusion-related reactions including immediate 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 during the infusion of pharmacologic or biologic agents or any event occurring during or within 1 day of study intervention administration. They are identified based on a list of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and criteria on the timely relationship to an infusion. Events are divided into reactions versus signs and symptoms:

- Reactions are 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 are 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

Premedication prior to bintrafusp alfa administration for the first 2 infusions is optional and at the discretion of the Investigator. If an Investigator chooses to administer premedications, premedication with an antihistamine and with paracetamol (acetaminophen) (e.g., 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to each dose of bintrafusp alfa is recommended.

If Grade ≥ 2 infusion reaction(s) are seen during the first 2 infusions, premedication should be continued/implemented for future infusions.

An assessment for possible IRR should be triggered based upon the development of specific symptoms within 24 hours of an infusion.

Management of symptoms should follow the guidelines shown in **Error! Reference source not found.**.

Table 5 Treatment Modification of Bintrafusp alfa for Symptoms of Infusion-related Reactions Including Immediate Hypersensitivity

NCI-CTCAE v5.0 Grade	Treatment Modification
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator.
Grade 2 – moderate • 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.	• 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.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the infusion of study intervention-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 • Restart the medication taking out the drug that is the cause of IRRs from the next scheduled visit
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.	

In the event of a Grade 2 IRR that does not improve or worsens after implementation of the treatment modifications indicated in Table 5 (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 or ranitidine), 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 IV 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 (NSAID), e.g., ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each IV infusion.

6.9.2 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 per published guidelines as provided in Appendix 5. These recommendations are in accordance with the joint American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines (Brahmer 2018) and National Comprehensive Cancer Network (NCCN 2018) guidelines.

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

- For Grade 1 immune-related pneumonitis: continue treatment. If clinically indicated, monitor participants weekly or more frequently as needed with history, physical examination, and pulse oximetry. If symptoms appear and/or changes in the physical examination are noted, treat as Grade 2.
- For myositis: in case of management with rituximab, treatment should be discontinued.

For organ/system specific management guidelines, see the guideline tables in Appendix 5.

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

6.9.3 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 SoA (see Table 1). Baseline skin assessments include a detailed medical history of genetic or iatrogenic skin conditions, skin type, significant UV exposure/sun damage of skin, geographical location, and occupational or environmental exposure to radiation or chemicals.

Skin AEs appear to be related to both mechanisms of bintrafusp alfa; anti-PD-L1 and anti-TGF-β:

1. Immune-related skin AEs possibly mediated by PD-L1 inhibition (e.g. rash or maculo-papular rash, distributed typically on trunk and uniformly on limbs). Just as immune-related AEs to other organs (see Section 6.9.2), immune related AEs affecting the skin are important identified risks for bintrafusp alfa and AESI.

   Immune-related skin AEs should be managed according to the recommended guidance and management for specific irAEs as per published guidelines (refer to Appendix 5). Treatment

typically include use of emollients, non-sedating antihistamines for pruritus, targeted use of potent topical steroids to most inflamed lesions; oral corticosteroids in highly symptomatic case.

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

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 study Medical Monitor, as needed, for management of TGF-β inhibition mediated skin reactions.

6.9.4 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 Hgb values at least 9 g/dL; routine blood test parameters are required in the SoA (see Table 1)
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 6.

Table 6 Evaluation Guidance of Suspected Anemia Adverse Events

Baseline Anemia Evaluation (Prior to Transfusion, if feasible)	
CBC with differential (e.g., Hgb, hematocrit, MCV, reticulocytes counts, ANC). Peripheral blood smear for cell morphological assessment. Complete metabolic panel including liver panel-LFTs, bilirubin, LDH, renal function, and other chemistries if indicated: 1. Coagulation factors (PT, PTT, INR) 2. Urinalysis including culture 3. Iron panel (TIBC, ferritin, Fe) 4. Serum folate, B12 values 5. TSH/hormonal panel 6. Fecal-occult blood testing 7. Erythropoietin.	
Further Recommendation Based on Suspected Etiology (in Addition to Baseline Anemia Testing)	
Unknown etiology, suspect possible hemolysis	Coombs test, fibrinogen, haptoglobin, d-dimer. Consider hematology consultation. Consider blood transfusion at clinical discretion.
Unknown etiology, suspect possible bleeding	Consider blood transfusion at clinical discretion. Consider surgical/interventional radiology consultation. Consider imaging, as clinically indicated (e.g., FAST scan, CT scan, MRI, angiography). Consider endoscopy (upper/lower).
Unknown etiology despite above work-up	Hematology consultation. Consider bone marrow aspiration/morphologic evaluation.
ANC=absolute neutrophil count, CBC=complete blood count, CT=computed tomography, FAST=Focused assessment with sonography for trauma, Hgb=hemoglobin, INR=international normalized ratio, LDH=lactate dehydrogenase, LFT=liver function test, MCV=mean corpuscular volume, MRI=magnetic resonance imaging, PT=prothrombin time, PTT=partial thromboplastin time, TIBC=total iron binding capacity, TSH=thyroid-stimulating hormone.	

6.9.5 Bleeding Events

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

6.9.5.1 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 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.

6.9.5.2 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.

6.9.6 Other Potential Risks

6.9.6.1 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.

6.9.6.2 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 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.

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 7.1.2.1).

- A participant may discontinue from the study intervention at any time at his/her own request (i.e., withdrawal of consent), and without giving a reason.
- Occurrence of an exclusion criterion, 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 Section 6.8 and 6.9 for TEAEs and AESIs that require treatment discontinuation).
- Confirmed PD per RECIST 1.1, 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).
- Unacceptable toxicity.
- Some TEAEs and AESIs require withdrawal from treatment. See Section 6.8 and 6.9 for additional details.
- Drug must not be given to a known pregnant participant (refer to Appendix 3).
- Use of a prohibited concomitant drug, as defined in Section 6.5.2, where the predefined consequence is withdrawal from the study intervention.

The SoA specifies the data to collect at study intervention discontinuation and follow-up and any additional evaluations that need to be completed.

In case of discontinuation from the study intervention:

- The day of End-of-Treatment will correspond to the day of withdrawal (or within 7 days).
- An attempt should be made to perform all assessments scheduled for the End-of-Treatment visit if possible. If not possible, the most clinically relevant assessments and appropriate eCRFs for the End-of-Treatment visit should be prioritized as feasible.
- Participants will be asked to continue Safety and Survival Follow-up, which includes the collection of data on survival, patient-reported outcome (PRO) questionnaires, and subsequent

anticancer therapy. 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.

7.1.1 Temporary Discontinuation

See Sections 6.8 and 6.9 for guidance on temporary discontinuation from study intervention.

7.1.2 Rechallenge

7.1.2.1 Reinitiation

One reinitiating course of treatment at the same dose and schedule and treatment duration up to 24 months is allowed at the discretion of the Investigator and agreement of the Medical Responsible for:

- Participants who are experiencing 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.

OR

- Participants who are discontinued due to an AE that is subsequently well managed or resolved 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 SoA (see Table 1). Participants who reinitiate treatment should stay on study and should be treated and monitored according the SoA for the rest of the study.

Prior to reinitiation, the Investigator will need to confirm that the benefit of reinitiating treatment outweighs any risk involved, such as that which led to initial treatment discontinuation. For participants with only stable disease 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 trial 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 treatment. 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/CCI [redacted] 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 SoA 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 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with bintrafusp alfa.

7.1.3.2 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 SoA. 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 metastasis, participants may continue study interventions after the local treatment of the brain lesions provided that the above criteria are met in addition to the following:

- Tumor assessment showing disease progression has been performed and was documented according to RECIST 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, 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 his/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 SoA. The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need 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 must 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 study site 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) where applicable locally and 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 should be documented in the participant's medical record.

- If the participant continues to be unreachable, she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA.
- No protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All 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 SoA.
- A maximum of 119 mL of blood will be collected in any 1-month (first month) period from each participant in the study, including all sample types.

8.1 Efficacy Assessments and Procedures

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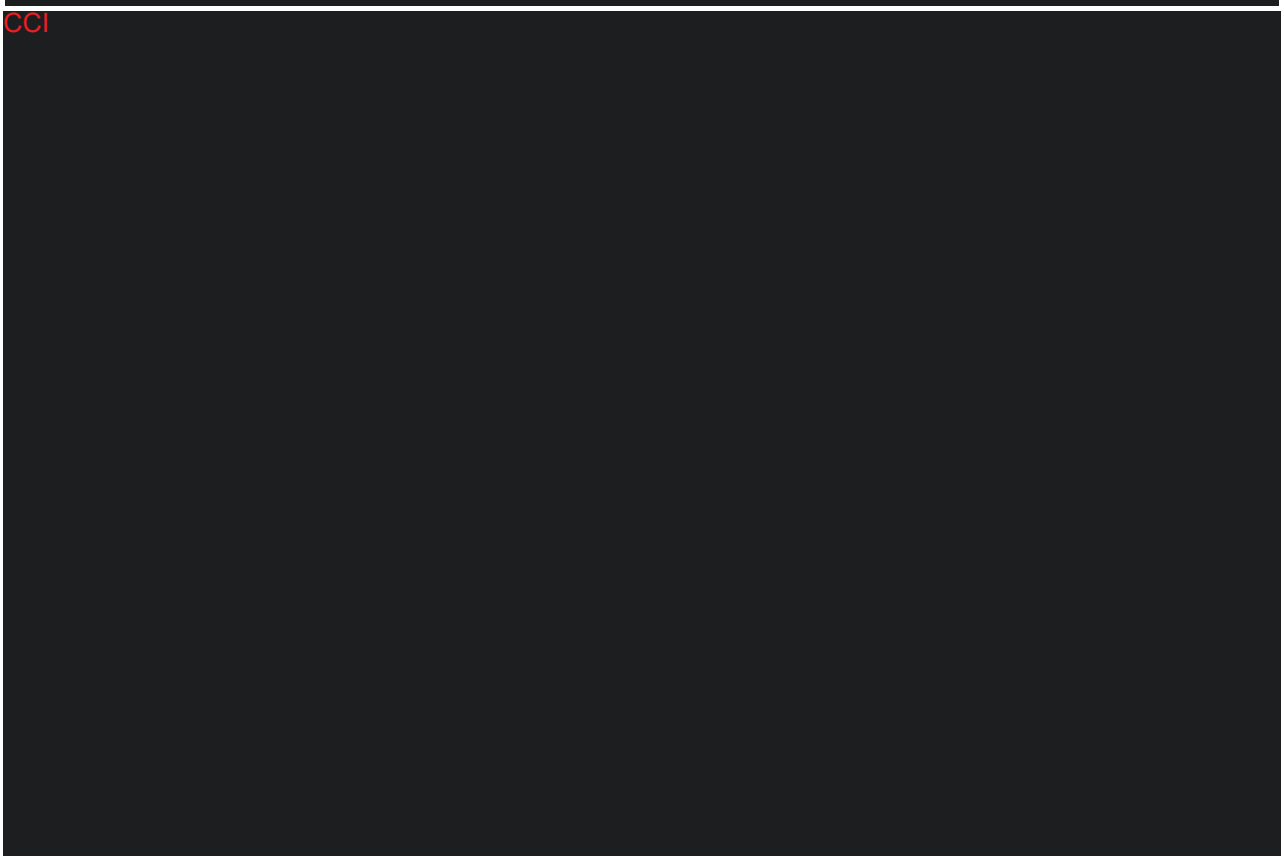

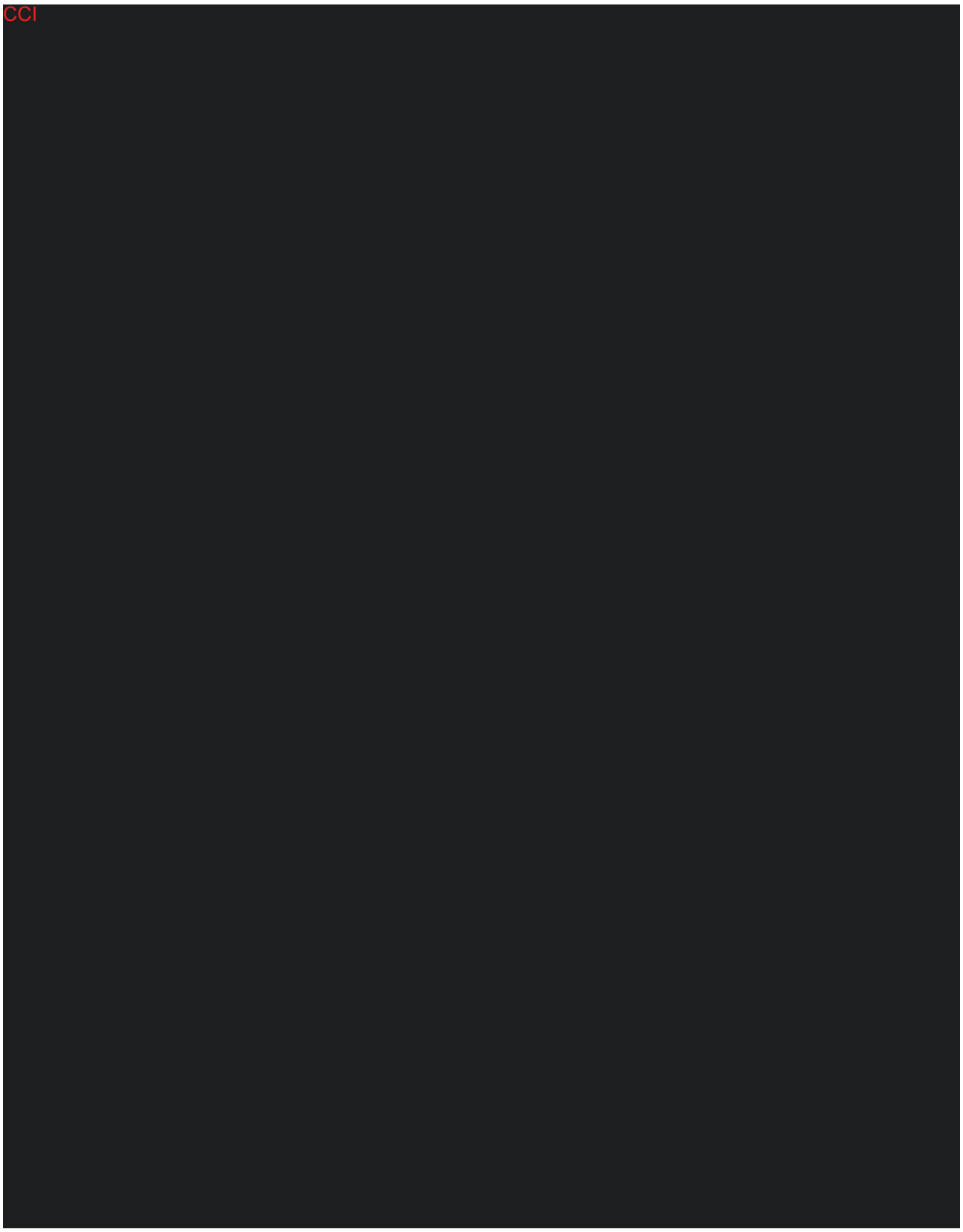

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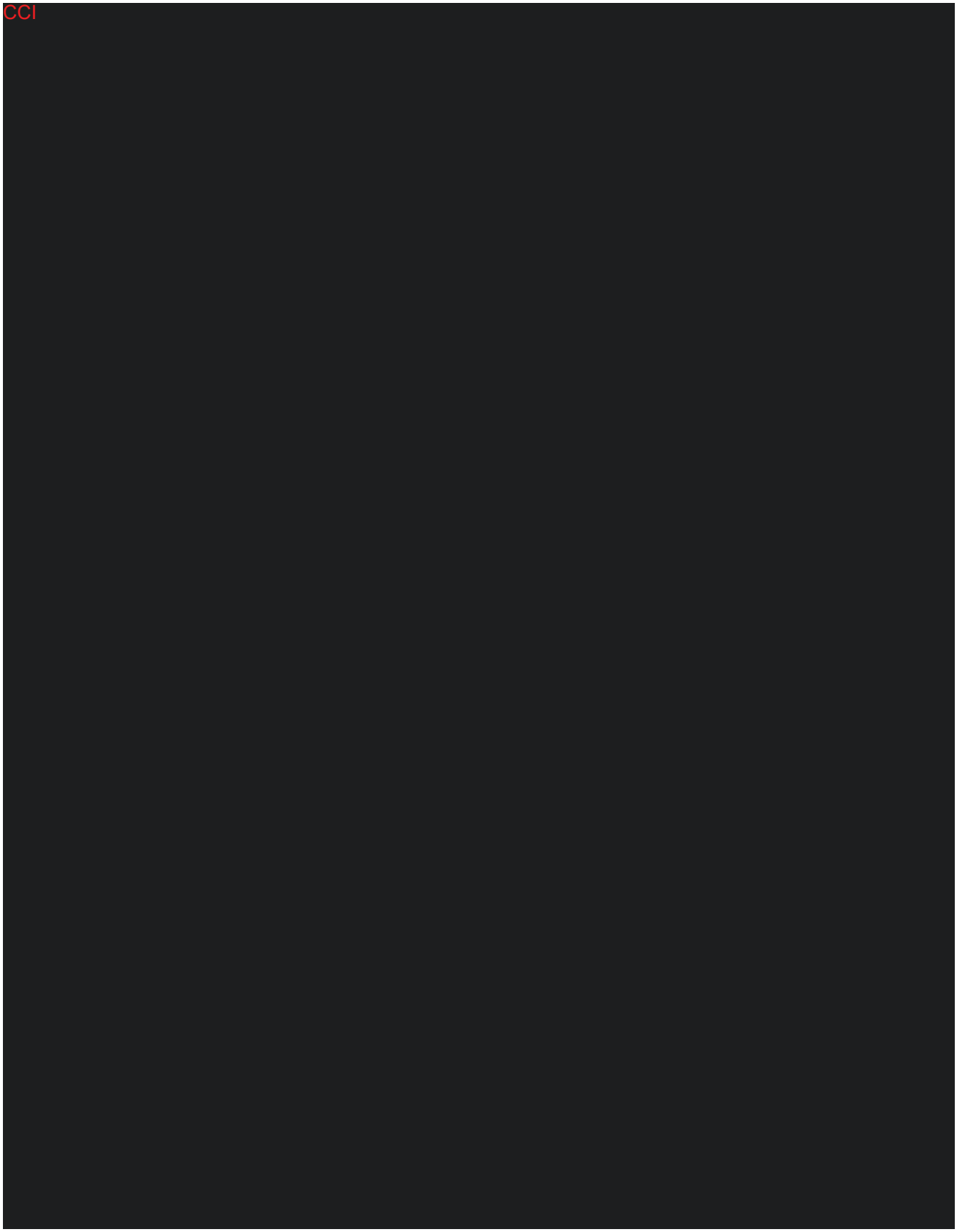

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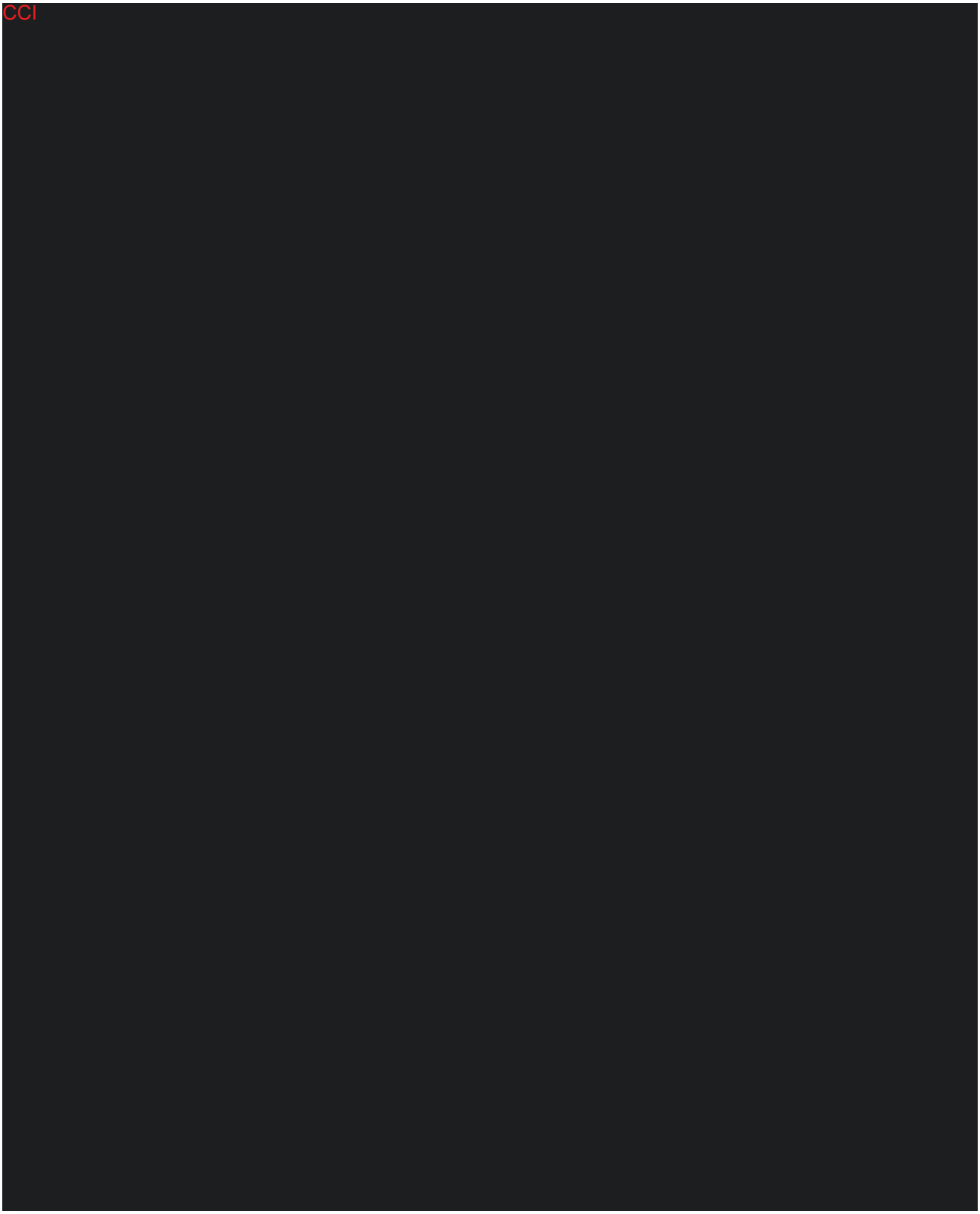

8.2 Safety Assessments and Procedures

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 (ECGs), 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 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information).

The safety assessments will be performed according to the SoA (Table 1). Periodic evaluations of the study data will be conducted by the study team to ensure safety and the validity and scientific merit of the study (see Section 8.2.4).

Ongoing events at the 12-week Safety Follow-up visit should continue to be monitored and documented until resolution or resolution with sequelae. All serious adverse events (SAEs) ongoing at the End-of-Treatment visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

If a liver function test (LFT) 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.

8.2.1 Physical Examinations

- Vital signs, physical examinations, and ECOG PS will be conducted at Screening and at subsequent visits as indicated in the SoA (Table 1). These should be documented in the eCRF.
- A complete physical examination at Screening will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- 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 should 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 seated or 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 should 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 will be measured with a pulse oximeter and recorded in the eCRF.

8.2.3 Electrocardiograms

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

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 6 at the time points listed in the SoA (Table 1). All samples should 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 must receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study must be forwarded to the Sponsor or designated organization.

The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must 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 SoA (Table 1), 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 in Screening or while on study, a site must consent the participant for HIV testing as per local standard guidance.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and a SAE are in Appendix 4.

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

The AE reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the 28-day Safety Follow-up visit, defined as 28 days (± 5 days) after the last study intervention administration. After this visit, all SAEs and nonserious treatment-related AEs should be documented until the last Safety Follow-up visit, defined as 12 weeks (± 2 weeks) after the last study intervention. Ongoing events at the 12-week Safety Follow-up visit should continue to be monitored and documented until resolution or resolution with sequelae, unless the participant is documented as “lost to follow-up”.

Any SAE assessed as related to study intervention must be recorded and reported, as indicated in Appendix 4, whenever it occurs, irrespective of the time elapsed since the last administration of study intervention.

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

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the participant’s condition will be recorded as AEs, regardless if reported by the participant or observed by the Investigator.

Complete, accurate, and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs must be additionally documented and reported using the appropriate SAE Report Form as specified in Appendix 4.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

Adverse events are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) and are assessed for their outcome at the 28-day Safety Follow-up visit.

All SAEs ongoing at the 28-day Safety Follow-up 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. Further information on follow-up procedures is given in Appendix 4 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reports).

Monitoring of Specific Adverse Events

If monitoring is warranted for certain treatment-related TEAEs for safety issues, the treating physician or Investigator is requested to follow the participant during the post-treatment long-term follow-up phase until the end of study period or the participant is "lost to follow-up" and report the management and outcome of AEs to the Sponsor.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must report SAEs (particularly deaths) in accordance with applicable site-specific requirements to the IRB that approved the study.

In accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and the Japanese ministerial ordinance on GCP, the Sponsor/designee will immediately inform all the study Investigators and the Heads of the study sites 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. In line with respective applicable regulations, the Sponsor/designee will immediately inform all the study Investigators and the Heads of the study sites of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). In addition, per applicable regulations, the Sponsor/designee will inform the study Investigators and the Heads of the study sites of all SAEs that were reported to the Health Authorities. In accordance with the Japanese regulatory requirements concerning safety reporting, the Investigator should place copies of the Safety Reports in the Investigator Site File. The Head of the study site should also maintain copies of Safety Reports appropriately. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IRB/IEC and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IRB/IEC of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

8.3.5 Pregnancy

Only pregnancies the Investigator considers to be related to the study intervention (e.g., resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) must be recorded in the AE page/section of the eCRF for pregnancies in female participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Appendix 4, section on Reporting Serious Adverse Events.

Investigators must actively follow-up, document, and report on the outcome of all these pregnancies, even if the participants are withdrawn from the study.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains an event and the Parent-Child/Fetus AE Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 8.3.1, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a participant occurring during the study, the participant must be discontinued from study intervention. The Sponsor/designee must be notified without delay and the participant must be followed as indicated above.

8.4 Treatment of Overdose

For this study, any dose of bintrafusp alfa greater than 2 times (i.e., > 2400 mg) of the planned dose administered within a 24-hour time period will be considered an overdose.

Of note: In the dose-escalation study (EMR200647-001), participants safely received up to 30 mg/kg bintrafusp alfa every 2 weeks (including those with doses > 2400 mg) with no observed maximum tolerated dose (refer to the IB). Safety at significantly higher doses has not been clinically evaluated.

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

Even if it not associated with an AE or a SAE, any overdose is recorded in the CRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 4, section on Reporting Serious Adverse Events.

If an AE occurs resulting from an overdose, it should follow SAE reporting criteria as indicated in Appendix 4.

8.5 Pharmacokinetics

- 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 SoA. 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 quantification of bintrafusp alfa in serum will be performed using a validated immunoassay assay 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 shipment 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.

Pharmacokinetic (PK) and antidrug antibody (ADA) samples will be collected according to the bintrafusp alfa PK, Immunogenicity Sampling (Table 2). Pharmacokinetic 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 7). Individual as well as mean concentration-time plots will be depicted.

The following PK parameters will be calculated, when appropriate.

Table 7 Pharmacokinetic Parameters

Symbol	Definition
C_{EOI}	The concentration observed immediately at the end of infusion.
C_{trough}	The concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing).

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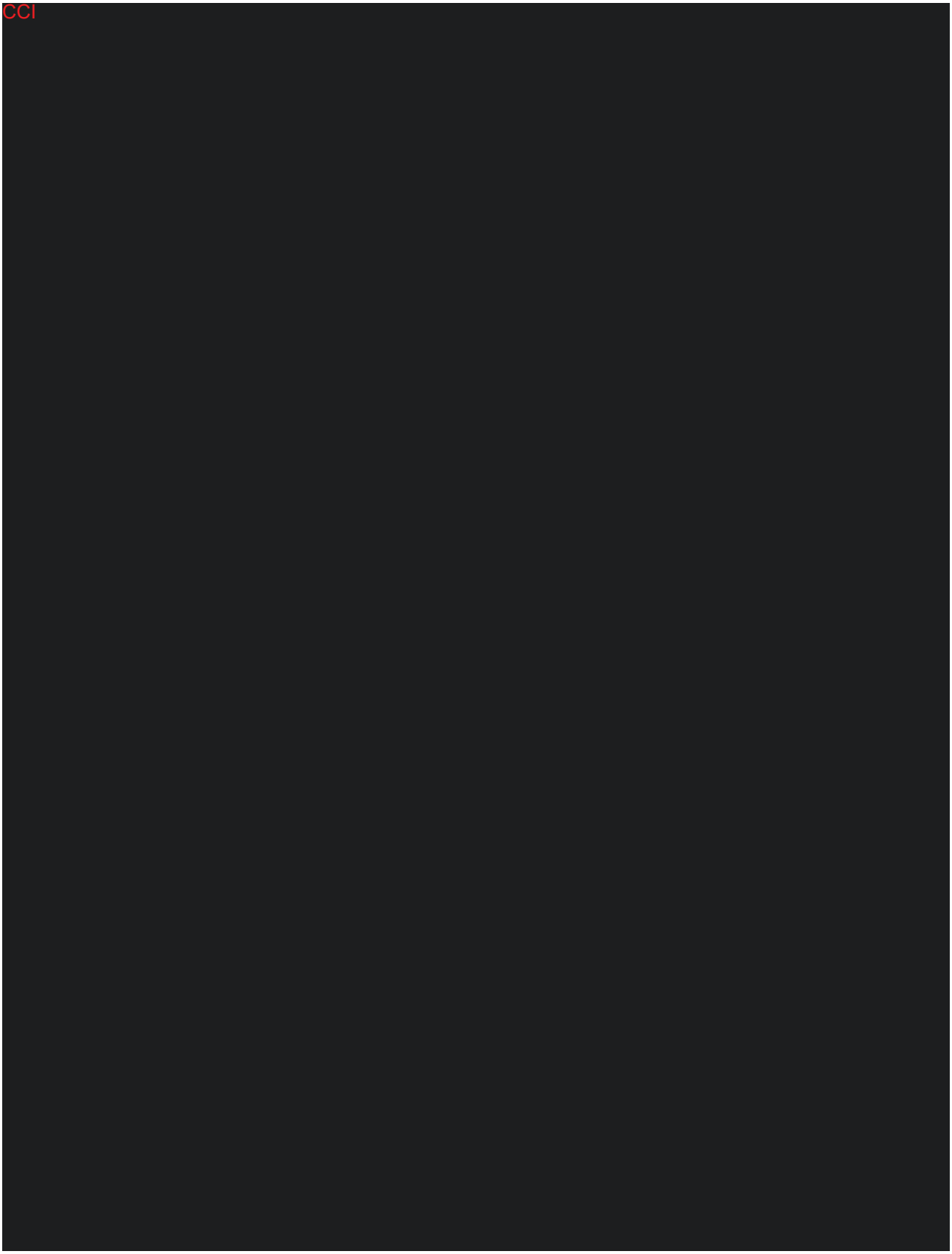

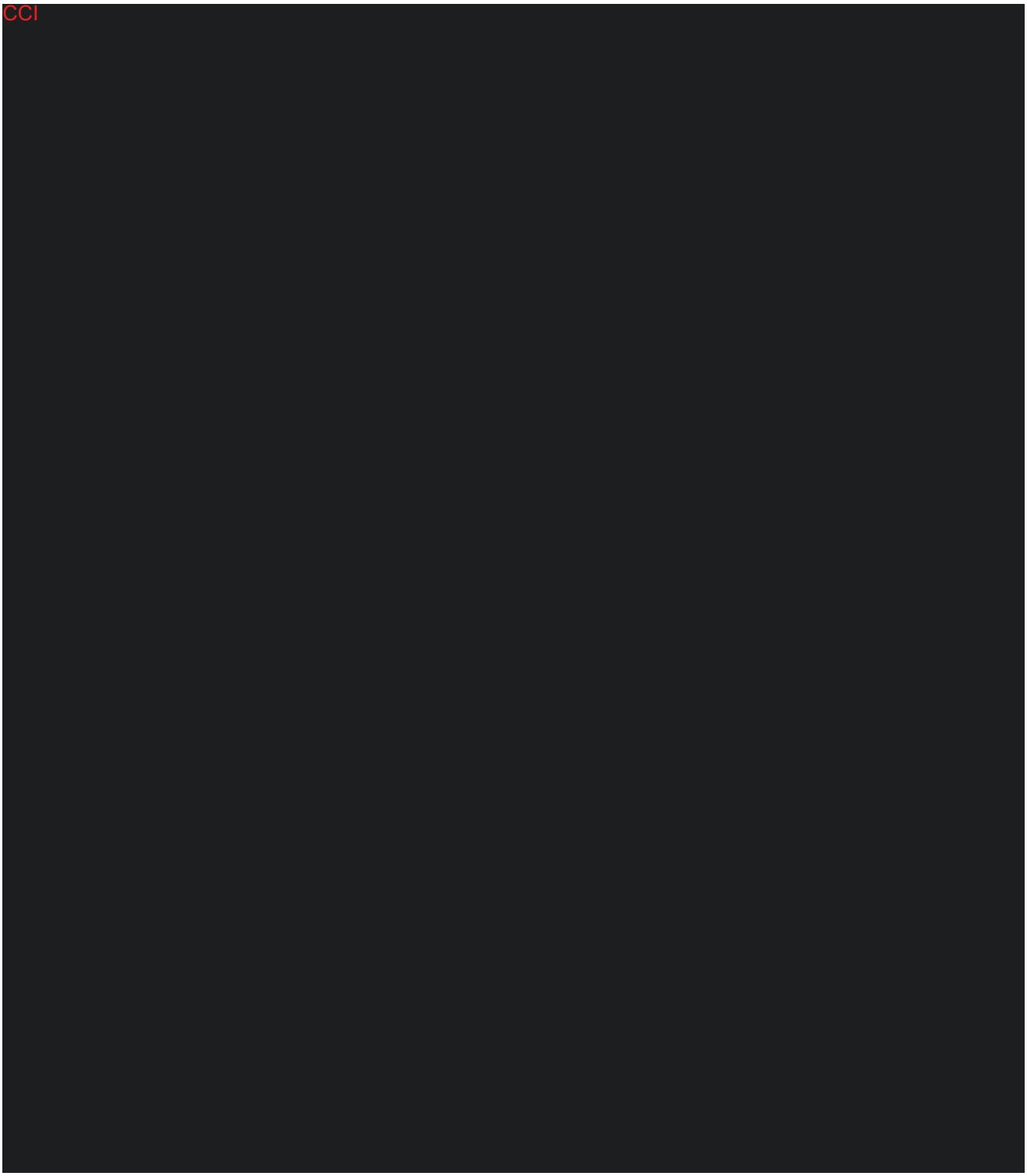

8.9 Health Economics

Not applicable.

8.10 Immunogenicity Assessments

Whole blood samples of approximately 5 mL will be collected for the detection of antibodies against bintrafusp alfa in serum, as specified in the bintrafusp alfa Pharmacokinetic, Immunogenicity Sampling (Table 2). Samples will be collected prior to any bintrafusp alfa administration on the same study day. Collection times are specified in the SoA.

The detection of antibodies to bintrafusp alfa will be performed using a validated immunoassay assay method with tiered testing of Screening, confirmatory, and titration. Confirmed positive antibodies may be tested for the presence of neutralizing antibodies and may be further characterized.

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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.

9 Statistical Considerations

9.1 Statistical Hypotheses

The study aims to estimate the ORR with a sufficient level of precision and that the associated 95% confidence interval is above a minimal threshold of 15%.

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9.3 Populations for Analyses

The analyses populations are specified below. The final decision to exclude participants from any analysis population will be made and documented during a data review meeting prior to database lock.

The analysis will be performed on approximately 135 patients globally. China participants (whether enrolled before or after the completion of the global enrollment) may be analyzed separately per local regulatory requirements, and follow the same definition as Section 4.1.

For purposes of analysis, the analysis populations are defined in Table 11.

Table 11 Analysis Populations

Screening (SCR)	All participants, who provided informed consent, regardless of the participant's study intervention status in the study.
Safety (SAF)/ Full Analysis Set (FAS)	All participants, who were administered at least 1 infusion of bintrafusp alfa. The primary analysis population for efficacy and CCI analyses is the Full Analysis Set. The primary analysis population for all analyses of safety and health-related quality of life is the Safety population.
Pharmacokinetic (PK)	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.
Immunogenicity Analysis Set (IMM)	All participants who were administered at least 1 infusion of bintrafusp alfa and have at least one valid ADA result. All ADA analyses will be based on this analysis set.

9.4 Statistical Analyses

Full details of all planned analyses will be described in the study integrated analysis plan (IAP). Major modifications of planned analyses will be reflected in a protocol amendment or in the CSR.

In general, continuous variables will be summarized using number (n), mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. Proportions are calculated based on the number of participants in the analysis set of interest, unless otherwise specified in the IAP.

Data collected after reinitiation of treatment will be summarized according to the specifications in the IAP.

9.4.1 Efficacy Analyses

Analysis of efficacy variables will also be performed on subgroup of interest as listed in Table 3, including but not restricted to PD-L1 expression.

Statistical analysis methods for primary and key secondary efficacy endpoints are summarized in Table 12. Further details will be specified in the IAP.

Table 12 Statistical Analysis Methods for Efficacy Analysis

Endpoint	Statistical Analysis Methods
Primary	
Confirmed objective response according to RECIST 1.1 assessed by IRC	The ORR will be determined as the proportion of participants with a confirmed objective response of PR or CR. Confirmation of the response according to RECIST 1.1 will be required no sooner than 4 weeks after the initial documentation of CR or PR. The response at each scheduled tumor assessment and the overall response will be listed for each participant. The number and proportion of overall response (defined as CR + PR) will be tabulated The 95% CI for the ORR will be calculated using the Clopper-Pearson method.
Key Secondary	
DOR assessed by an IRC	DOR is defined as the time from first documentation of a confirmed objective response (CR or PR) according to RECIST 1.1 to the date of first documentation of objective response of disease progression (PD) or death due to any cause, whichever occurs first. The censoring rules for DOR are as described below for PFS. Kaplan-Meier estimates will be provided; Median DOR and the 95% confidence interval for the median will be calculated according to Brookmeyer and Crowley (Brookmeyer 1982); Swimmer plots will be provided.
Durable response assessed by an IRC	A durable response is defined as an objective response (CR or PR) according to RECIST 1.1, determined by IRC, with a duration of at least 6 months. Participants for whom the DOR is censored will be treated as failures (successes) in the analysis of durable response if the censored DOR is below (at least) 6 and 12 months. The DRR is defined as the percentage of participants with durable response. The 95% CI for the DRR will be calculated using the Clopper-Pearson method.
PFS according to RECIST 1.1 assessed by an IRC	PFS according to RECIST 1.1, is defined as the time from first administration of study intervention until date of the first documentation of PD or death due to any cause in the absence of documented PD, whichever occurs first. PFS data will be censored on the date of the last adequate tumor assessment for participants who do not have an event (PD or death), for participants who start new anticancer treatment prior to an event, or for participants with an event after 2 or more missing tumor assessments. Participants who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored on the date of first administration of study intervention unless death occurred on or before the time of the second planned tumor assessment, in which case the death will be considered an event. Kaplan-Meier estimates will be provided; Median PFS and the 95% confidence interval for the median will be calculated according to Brookmeyer and Crowley (Brookmeyer 1982)
Overall survival	Overall survival is defined as the time from first administration of study intervention to the date of death due to any cause. Participants last known to be alive will be censored at date of last contact. Kaplan-Meier estimates will be provided; Median OS and the 95% confidence interval for the median will be calculated according to Brookmeyer and Crowley (Brookmeyer 1982)
Confirmed Objective response, DOR, DRR, and PFS according to RECIST 1.1 assessed by Investigator	Definition and analyses to be performed on the efficacy endpoints as assessed by Investigator will be similar to the endpoints as assessed by IRC, see above

Endpoint	Statistical Analysis Methods
CR= complete response, DOR= duration of response, DRR= durable response rate, IRC= Independent Review Committee, ORR= objective response rates, PFS= progression-free survival, PR= partial response, RECIST 1.1= Response Evaluation Criteria in Solid Tumors Version 1.1.	

9.4.2 Safety Analyses

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

Safety endpoints include AEs, AESIs, clinical laboratory assessments, vital signs, physical examination, and ECOG PS as described in Section 8.2.

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

Treatment-emergent adverse events are those events with onset dates occurring during the on-treatment period or if the worsening of an event is during the on-treatment period. The incidence of TEAEs, regardless of attribution, and TEAEs defined as possibly related to bintrafusp alfa will be summarized by MedDRA preferred term and System Organ Class (SOC) and described in terms of intensity and relationship to bintrafusp alfa. Any AEs with an onset or worsening date after the on-treatment period will be reported separately.

See Table 13 for analysis methods. The specifics for analysis will be defined in the IAP and finalized before database lock.

Table 13 Safety Endpoints and Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary Occurrence of TEAEs and treatment-related AEs	The Safety Analysis Set will include all participants who receive at least one dose of study intervention and will be based on all safety analysis reporting outcomes like AEs, clinically relevant bioscience (AESIs) and laboratory tests outcomes. The safety endpoints will be tabulated using descriptive statistics. • Participants will be analyzed according to the actual treatment they receive. • The safety endpoints will be analyzed using descriptive statistics. • The incidence of TEAEs, SAEs, treatment-related AEs, and AESIs, irAEs will be summarized by Preferred Term and System Organ Class for each treatment arm, and 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). 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.

Endpoint	Statistical Analysis Methods
AE=adverse event; AESI=adverse event of special interest; ECG=electrocardiogram; IAP=Integrated Analysis Plan; irAE=immune-related adverse event; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; SAE=serious adverse event; TEAE=treatment-emergent adverse event.	

9.4.3 Other Analyses

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

Serum concentrations of bintrafusp alfa will be determined by a validated method at the times listed in the SoA (see Table 1).

- Details on the PK, immunogenicity, CCI [redacted] will be specified in the IAP finalized before database lock. The PopPK analysis and exposure-response may be performed using combined data from several bintrafusp alfa clinical studies and will be specified in a separate IAP. PopPK, exposure response and CCI [redacted] analyses will be presented separately from the main CSR.
- Details on the PK analyses (C_{EOI} and C_{trough}) will be specified in the IAP finalized before database lock.

ADA/Immunogenicity

Samples for ADA assessments will be collected as per the SoA.

The immunogenicity testing strategy is in accordance with current regulatory guidance documents and industry best practices.

A validated method to detect ADAs in the presence of drug in human serum will be applied. The ADA titers of positive samples will be determined. Positive samples may be further evaluated for neutralizing capability. Individual participants will be categorized across all valid ADA results as ever-positive versus never-positive. ADA ever-positive participants will be further categorized as pre-existing, including treatment boosted, versus treatment emergent. ADA treatment-emergent participants will be further subdivided into transient positive and persistent positive.

Individual participants may be categorized across all valid neutralizing antibody results as ever-positive versus never-positive. Neutralizing antibody ever-positive participants may be further categorized as pre-existing versus treatment-emergent. Neutralizing antibody treatment-emergent participants may be further subdivided into transient positive and persistent positive.

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

CCI [redacted]

9.4.4 Sequence of Analyses

The planned efficacy analyses are specified below. Details of all planned analyses will be defined in the IAP:

- The interim analysis on objective response will be performed C[redacted] months after 81 participants have been enrolled. At the same time, the analysis of durable response of at least 6 months will be performed to support the ORR data and confirm that the responses are durable.
- The primary analysis on objective response will be performed 12 months after the accrual of the last planned global participant. At the same time, the analysis of durable response of at least 6 months will be performed to support the ORR data and confirm that the responses are durable. The analysis of DOR and PFS will be performed as well to support efficacy assessment of bintrafusp alfa.
- CCI [redacted]
- A separate analysis of key endpoints of ORR, DOR and OS may be performed in the subgroup of Chinese participants per local regulatory requirements once the cutoff criteria mentioned above are met for this subgroup (i.e., 12 months after accrual of the last Chinese participant for ORR, DOR and PFS and once at least 67% of Chinese participants have died for OS, respectively).
- If the study continues beyond 67% of the participants died (either globally or in the additional China enrollment), subsequent analyses may be performed.

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11 Appendices

Appendix 1 Abbreviations

2L	second-line
ADA	antidrug antibody
ADA	antidrug antibody
AEs	adverse events
AESIs	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-PD-L1	anti-programmed death-ligand 1
ART	antiretroviral therapy
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
CBC	complete blood count
C_{EOI}	concentration observed immediately at the end of infusion
CI	confidence interval
CNS	central nervous system
CPS	Combined Positive Score
CR	complete response
CrCL	creatinine clearance
CROs	contract research organizations
CSR	Clinical Study Report
cSCC	cutaneous squamous cell carcinoma
CT	computed tomography
CTLA-4	cytotoxic T-cell lymphocyte-associated antigen-4
C_{trough}	concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing)
D	day
DNA	deoxyribonucleic acid
DOR	duration of response
DRR	durable response rate

ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report forms
EORTC	European Organisation for Research and Treatment of Cancer
EQ	EuroQol
EQ-5D-5L	EuroQol 5-dimension
FAS	Full Analysis Set
FDA	Food and Drug Administration
FT4	free thyroxine
GCP	Good Clinical Practice
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HPV	human papilloma virus
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
ir	immune-related
irAEs	immune-related adverse events
IRB	Independent Review Board
IRC	Independent Review Committee
IRR	infusion-related reactions
IV	intravenous
KA	keratoacanthoma
LDH	lactate dehydrogenase
LFT	liver function test

MedDRA	Medical Dictionary for Regulatory Activities
CCI [redacted]	
N	number of participants
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSAID	nonsteroidal anti-inflammatory drug
ORR	objective response rates
OS	overall survival
PAI-1	plasminogen activator inhibitor-1
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
CCI [redacted]	
PK	pharmacokinetic
PopPK	population pharmacokinetic
PR	partial response
CCI [redacted]	[redacted]
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
QLQ-C30	Quality-of-Life-Core 30 questionnaire
QLQ-CX24	Quality-of-Life Questionnaire Cervical Cancer module
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	ribonucleic acid
RP2D	recommended Phase II dose
SAE	serious adverse event
SD	stable disease

SoA	summary of activities
SUSARs	suspected unexpected serious adverse reactions
TEAEs	treatment-emergent adverse event
TGF-β	transforming growth factor-β
CCI [redacted]	[redacted]
TSH	thyroid-stimulating hormone
TTP	thrombotic thrombocytopenic purpura
ULN	upper limit of normal
V	visit
VAS	visual analog scale
W	week
W1D1	Week 1 Day 1
W3	week 3
WOCBP	woman of childbearing potential
β-HCG	β-human chorionic gonadotropin

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 his/her legally-authorized representative (where allowed by local laws and regulations) and answer all questions on the study.
- Participants must 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 GCP; local regulations; 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 must 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. All participant records or datasets transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor must 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, who will be required to give consent for their data to be used, as specified in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

The Coordinating 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 and EudraCT.

This study requires a significant logistic and administrative structure for its efficient execution. Details of structures and associated procedures will be defined in a separate Investigator Site File.

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.

Participant 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 adverse events (AEs) and serious adverse events (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).

Details of structures and associated procedures will be defined in a separate Integrated Project Management Plan.

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 Good Clinical Practice (GCP) Guidelines
- The Japanese ministerial ordinance on GCP
- Applicable laws and regulations.

The Investigator must 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 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 committees will be involved in the study: IRC

Independent Radiology (Review) Committee (IRC)

The IRC will be composed of a minimum of 3 members. The role of the IRC will be to review radiographic image findings for the determination of the best overall response (objective response) and date of disease progression for each participant. In addition, the IRC will review radiographic imaging findings for each patient to confirm presence of measurable disease per RECIST 1.1 prior

to inclusion in the study. The full membership, mandate, and processes of the IRC will be detailed in the IRC 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

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

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 eCRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the eCRF. Details for managing eCRFs are in the Operations Manual.

For PRO data (e.g., quality of life and pain assessments), ePRO will be used. Paper collection can be used only when electronic collection is not readily available. Phone interview of PRO data collection will also be utilized at 12-week Safety Follow-up visit.

The Investigator will maintain accurate documentation (source data) that supports the information in the eCRF.

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. PDF files of the eCRFs will be downloaded from the system by the Investigators at study completion. Details will be outlined in Data Management documents and procedures.

Study monitors will perform ongoing source data verification to confirm that data in the eCRF 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.

Data recorded on printed or electronic eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator or 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 the SIV training materials and online study modules.

Study and Site Start and Closure

Study Start

- The study start date is the date when the clinical study will be open for recruitment.
- The first act of recruitment is the first date that the first ICF is signed. This 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 contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 3 Contraception

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

Woman of Childbearing Potential (WOCBP)

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

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

A WOCBP is **not**:

1. Premenarchal

2. A premenopausal female with 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 (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.

A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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 (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation

- Oral
- Intravaginal*
- Transdermal*
- Injectable*
- Progestogen-only hormone contraception associated with inhibition of ovulation
- Oral
- Injectable*
- Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence 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 (LAM) 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

Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the NCI-CTCAE, v5.0 (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 should 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.

Investigators must also systematically assess the causal relationship of AEs to study intervention (including any other non-study interventions, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study intervention include, but may not be limited to, temporal relationship between the AE and the study intervention, known side effects of study intervention, medical history, concomitant medication, course of the underlying disease, and study procedures.

Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study intervention discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia or increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important (e.g., new cancer). Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g., an overnight stay to facilitate intravenous therapy) are not considered SAEs. 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.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are not to be considered AEs.

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) should not be reported as an (S)AE, unless the participant's general condition is more severe than expected for the participant's condition and/or unless the outcome is fatal within the adverse event reporting period, as defined in Section 8.3.2.

Adverse Events of Special Interest

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

Other Adverse Events to be Reported Following a Specialized Procedure

Not applicable.

Recording and Follow-up of AE and/or SAE

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented.

Specific guidance is in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

Reporting Serious Adverse Events

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee using the electronic SAE report form in the Electronic Data Capture (EDC) system.

Reporting of SAEs using a paper report form is required as a back-up method only for an EDC system failure. Names, addresses, and telephone and fax numbers will be included on the paper form. All information from the paper form must be transcribed into the electronic form as soon as the system becomes available.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, an electronic SAE report form must be completed immediately thereafter.

Relevant pages from the eCRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

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

Appendix 5 The Recommendations for irAE Management

This appendix provides recommendations to the Investigators for the management of irAEs. The contents are based on the NCCN irAE management guidelines (in Accordance with the Joint American Society of Clinical Oncology Clinical Practice Guidelines and National Comprehensive Cancer Network, Brahmer JR, 2018) and FDA recommendations to require permanent treatment discontinuation for G4 irAEs (unless otherwise indicated in the tables below). Differences with ASCO/NCCN irAE management guidelines as recommended by the FDA are shown in bold and underlined text in the tables below. Critical instructions include the requirement that treatment must be permanently discontinued for the following Grade 4 irAE toxicities: Rash/inflammatory dermatitis, nephritis, autoimmune hemolytic anemia, hemolytic uremic syndrome, aplastic anemia, immune thrombocytopenia, acquired TTP, and in certain circumstances, lymphopenia.

Table of Tables

Table A1 Management of Skin irAEs in Patients Treated With ICPis

1.0 Skin Toxicities	
1.1 Rash/inflammatory dermatitis	
Definition: Erythema multiforme minor (a targetoid reaction in the skin and mucous membranes usually triggered by infections, such as herpes simplex viruses, but can be associated with an immune-related drug eruption and if progresses to erythema multiforme major, it and can be a harbinger of SCAR, such as SJS), lichenoid (resembling the flat-topped, polygonal, and sometimes scaly or hypertrophic lesions of lichen-planus), eczematous (inflammatory dermatitis characterized by pruritic, erythematous, scaly, or crusted papules or plaques on the skin, which is vulnerable to superinfection, psoriasiform [resembling the well-demarcated, erythematous, and scaly papules and plaques of psoriasis], morbilliform [a nonpustular, nonbullous measles-like exanthematous rash of the skin often referred to as “maculopapular”] and without systemic symptoms or laboratory abnormalities, excluding occasional isolated peripheral eosinophilia, palmoplantar erythrodysesthesia [hand-foot syndrome; redness, numbness, burning, itching, and superficial desquamation of the palms and soles], neutrophilic dermatoses [e.g., Sweet syndrome], and others)	
Diagnostic work-up	
Pertinent history and physical examination Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease or unrelated primary skin disorder If needed, a biologic checkup, including a blood cell count and liver and kidney tests Directed serologic studies if an autoimmune condition is suspected, such as lupus or dermatomyositis: a screening antinuclear antibody test, SS-A/Anti-Ro, SS-B/Anti-La if predominantly photodistributed/photosensitivity, antihistone, double-stranded DNA, and other relevant serologies. Consider expanding serologic studies or diagnostic work-up if other autoimmune conditions are considered based on signs, symptoms Skin biopsy Consider clinical monitoring with use of serial clinical photography Review full list of patient medications to rule out other drug-induced cause for photosensitivity	
Grading	Management
Grading according to CTCAE is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration	
G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic	Continue ICPi Treat with topical emollients and/or mild-moderate potency topical corticosteroids Counsel patients to avoid skin irritants and sun exposure
G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis	Consider holding ICPi and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to Grade 1 Consider initiating prednisone (or equivalent) at dosing 1 mg/kg, tapering over at least 4 weeks In addition, treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids
G3: As G2 but with failure to respond to indicated interventions for a G2 dermatitis	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids Initiate (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks
G4: All severe rashes unmanageable with prior interventions and intolerable	**Permanently discontinue ICPi** Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves

	Monitor closely for progression to severe cutaneous adverse reaction Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology
1.2 Bullous dermatoses	
Definition: Including bullous pemphigoid or other autoimmune bullous dermatoses, bullous drug reaction Diagnostic work-up Physical examination Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease If needed, a biologic checkup, including a blood cell count, liver, and kidney tests; consider serum antibody tests to rule out bullous pemphigoid or, under the guidance of dermatology, sending patient serum for indirect immunofluorescent testing to rule out other autoimmune blistering diseases Referral to dermatology for blisters that are not explained by infectious or transient other causes (e.g., herpes simplex, herpes zoster, bullous impetigo, bullous insect bite, friction or pressure blister) Consider skin biopsy (both hematoxylin and eosin evaluation of lesional skin and direct immunofluorescence evaluation of perilesional skin)	
Grading	Management
G1: Asymptomatic, blisters covering < 10% BSA and no associated erythema	If blisters are < 10% BSA, asymptomatic, and noninflammatory (such as the case with friction blisters or pressure blisters), cessation of ICPi is not necessary, and only observation and/or local wound care is warranted. When symptomatic bullae or erosions, which are deroofed vesicles or bullae, are observed on the skin or mucosal surfaces, the cutaneous irAE is by definition considered at least G2 See G2 management recommendations
G2: Blistering that affects quality of life and requires intervention based on diagnosis not meeting criteria for Grade > 2 Blisters covering 10%-30% BSA	Hold ICPi therapy and consult with dermatology for work-up and to determine appropriateness of resuming Attention given to general local wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions, which are left over on the skin after the blister has popped or if the roof of the blister easily sloughs off Counsel patients to avoid skin irritants and overexposure to sun, wear protective clothing, use sunscreens Work-up for autoimmune bullous disease as aboveInitiate Class 1 high-potency topical corticosteroid (e.g., clobetasol, betamethasone or equivalent) and reassess every 3 days for progression or improvement Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg dosing and taper over at least 4 weeks Monitor patients with G2 irAEs closely for progression to involvement of greater BSA and/or mucous membrane involvement. Consider following patients closely using serial photography Primer on monitoring for complicated cutaneous adverse drug reactions:
	Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx,

	odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements
	Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN
G3: Skin sloughing covering > 30% BSA with associated pain and limiting self-care ADL	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab, as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.
G4: Blisters covering > 30% BSA with associated fluid or electrolyte abnormalities	Permanently discontinue ICPi Admit patient immediately and place under supervision of a dermatologist Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg with tapering over at least 4 weeks when the toxicity resolves If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.
1.3 SCARs, including SJS, TEN, acute generalized exanthematous pustulosis, and DRESS/DIHS	
Definition: Severe changes in either structure or functions of skin, the appendages or the mucous membranes due to a drug Diagnostic work-up	
Total body skin examination with attention to examining all mucous membranes as well as complete review of systems Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease. A biologic checkup, including a CBC with differential test, and liver and kidney function tests, including urinalysis, in addition to the blood work; if the patient is febrile, blood cultures should be considered as well. Skin biopsies to assess for full-thickness epidermal necrosis, as is seen in SJS/TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses or other drug reactions, such as acute generalized exanthematous pustulosis.	

Consider following patients closely using serial clinical photography.

If mucous membrane involvement or blistering is observed on the skin, consider early admission to a burn center for further monitoring and management Primer on monitoring for complicated cutaneous adverse drug reactions:

Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements.

Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (e.g., pemphigus) and SJS/TEN.

Grading	Management
All Grades	In cases of suspected SJS or any mucous membrane involvement, discontinue ICPi treatment and monitor closely for improvement, regardless of grade
G1: NA	For SCARs, there is no G1 category; if lower BSA is involved with bullae or erosions, there should remain a high concern that this reaction will progress to G3 or G4
G2: Morbilliform ("maculopapular") exanthem covering 10%-30% BSA with systemic symptoms, lymphadenopathy, or facial swelling	Hold ICPi and monitor patients closely every 3 days with G2 irAEs for progression to involvement of greater BSA and/or mucous membrane involvement Consider following patients closely using serial photography Initiate therapy with topical emollients, oral antihistamines, and medium- to high-strength topical corticosteroids Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks
G3: Skin sloughing covering < 10% BSA with mucosal involvement associated signs (e.g., erythema, purpura, epidermal detachment, mucous membrane detachment)	Hold ICPi therapy and consult with dermatology Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum Administer IV (methyl)prednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks Admit to burn and/or consult wound services with attention to supportive care, including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (e.g., ophthalmology; ear, nose, and throat; urology; gynecology; etc., as appropriate)
G4: Skin erythema and blistering/sloughing covering ≥ 10% to > 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (e.g.,	Permanently discontinue ICPi Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services Consider further consultations based on management of mucosal surfaces

liver function test elevations in the setting of DRESS/DIHS)	(e.g., ophthalmology; urology; gynecology; ear, nose, and throat surgery; etc.) Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal IVIG or cyclosporine may also be considered in severe or corticosteroid-unresponsive cases Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations
Additional considerations: The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immunodirected toxicity Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS/DIHS All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate	

Abbreviations: ADL, activities of daily living; AE, adverse event; BSA, body surface area; CBC, complete blood count; CTCAE, Common Terminology Criteria for Adverse Events; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; G, Grade; ICPi, immune checkpoint inhibitor; ICU, intensive care unit; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; NA, not applicable; SCAR, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; TENS, toxic epidermal necrolysis.

Table A2 Management of GI irAEs in Patients Treated With ICPis

2.0 GI Toxicities	
2.1 Colitis	
Definition: A disorder characterized by inflammation of the colon Diagnostic work-up	
G2 Work-up of blood (CBC, comprehensive metabolic panel, TSH, ESR, CRP), stool (culture, Clostridium difficile, parasite, CMV or other viral etiology, ova and parasite) should be performed Consider testing for lactoferrin (for patient stratification to determine who needs more urgent endoscopy) and calprotectin (to follow-up on disease activity) Screening laboratories (HIV, hepatitis A and B, and blood quantiferon for TB) to prepare patients to start infliximab should be routinely done in patients at high risk for those infections and appropriately selected patients based on infectious disease expert's evaluation Imaging (e.g., CT scan of abdomen and pelvis and GI endoscopy with biopsy) should be considered as there is evidence showing that the presence of ulceration in the colon can predict a corticosteroid refractory course, which may require early infliximab Consider repeating endoscopy for patients who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring can be considered when clinically indicated and when planning to resume therapy	
G3-4 All the work-up listed for G2 (blood, stool, imaging, and scope with biopsy) should be completed immediately Consider repeating endoscopy for patients who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring should only be considered when clinically indicated and when planning to resume ICPi	
Grading (based on CTCAE for diarrhea, as most often used clinically)	Management
All patients	Counsel all patients to be aware of and inform their health care provider immediately if they experience: Abdominal pain, nausea, cramping, blood or mucus in stool or changes in bowel habits, fever, abdominal distention, obstipation, constipation For G2 or higher, consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less; concurrent immunosuppressant maintenance therapy should be considered only if clinically indicated in individual cases
G1: Increase of fewer than four stools per day over baseline; mild increase in ostomy output compared with baseline	Continue ICPi; alternatively, ICPi may be held temporarily and resumed if toxicity does not exceed G1 Monitor for dehydration and recommend dietary changes Facilitate expedited phone contact with patient/caregiver May obtain gastroenterology consult for prolonged G1 cases
G2: Increase of four to six stools per day over baseline; moderate increase in ostomy output compared with baseline	Should hold ICPi temporarily until patient's symptoms recover to G1; can consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less Concurrent immunosuppressant maintenance therapy (10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases May also include supportive care with medications such as Imodium if infection has been ruled out Should consult with gastroenterology for G2 or higher

2.0 GI Toxicities	
	Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent When symptoms improve to G1 or less, taper corticosteroids over at least 4-6 weeks before resuming treatment, although resuming treatment while on low-dose corticosteroid may also be an option after an evaluation of the risks and benefits EGD/colonoscopy, endoscopy evaluation should be highly recommended for cases Grade ≥ 2 to stratify patients for early treatment with infliximab based on the endoscopic findings and to determine the safety of resuming PD-1, PD-L1 therapy Stool inflammatory markers can be considered (lactoferrin and calprotectin) in cases of G2 or higher to differentiate functional versus inflammatory diarrhea, and use calprotectin to monitor treatment response if provider prefers Repeat colonoscopy is optional for cases of G2 or higher for disease activity monitoring to achieve complete remission, especially if there is a plan to resume ICPi
G3: Increase of seven or more stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL	Should consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less. Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent) Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance If symptoms persist ≥ 3-5 days or recur after improvement, consider administering IV corticosteroid or noncorticosteroid (e.g., infliximab) Consider colonoscopy in cases where patients have been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (i.e., CMV colitis) and for those who are anti-TNF or corticosteroid refractory
G4: Life-threatening consequences; urgent intervention indicated	Permanently discontinue treatment Should admit patient when clinically indicated; patients managed as outpatients should be very closely monitored Administer 1-2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks Consider early infliximab 5-10 mg/kg if symptoms refractory to corticosteroid within 2-3 days Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections
Additional considerations The use of vedolizumab (not approved in Japan) may be considered in patients refractory to infliximab and/or contraindicated to TNF-a blocker. The decision should be made on an individual basis from gastroenterology and oncology evaluation. This is based on case series showing promising results Patients with hepatitis and irAE colitis are rare, and management should include permanently discontinuing ICPi and offering other immunosuppressant agents that work systemically for both conditions Currently, enteritis alone as the cause of diarrhea is uncommon and requires small bowel biopsy as the evaluation tool. It may be managed similar as colitis, including corticosteroid and/or infliximab, etc.	

2.0 GI Toxicities	
2.2 Hepatitis	
Definition: A disorder characterized by a viral pathologic process involving the liver parenchyma Diagnostic work-up Monitor patient for abnormal liver blood tests: AST, ALT, and bilirubin prior to each infusion and/or weekly if G1 liver function test elevations. No treatment is recommended for G1 liver function test abnormality For G2 or higher: Work-up for other causes of elevated liver enzymes should be tested, viral hepatitis, alcohol history, iron study, thromboembolic event, liver ultrasound, cross-sectional imaging for potential liver metastasis from primary malignancy. If suspicion for primary autoimmune hepatitis is high, can consider ANAs, antismooth muscle antibodies, antineutrophil cytoplasmic antibodies. If patients with elevated alkaline phosphatase alone, g-glutamyl transferase should be tested. For isolated elevation of transaminases, consider checking CK for other etiologies	
Grading	Management
All patients	Counsel all patients to be aware of and inform their health care provider immediately if they experience: Yellowing of skin or whites of the eyes Severe nausea or vomiting Pain on the right side of the abdomen Drowsiness Dark urine (tea colored) Bleeding or bruising more easily than normal Feeling less hungry than usual
G1: Asymptomatic (AST or ALT > ULN to 3.0 x ULN and/or total bilirubin > ULN to 1.5 x ULN)	Continue ICPi with close monitoring; consider alternate etiologies Monitor laboratories one to two times weekly Manage with supportive care for symptom control
G2: Asymptomatic (AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN)	Hold ICPi temporarily and resume if recover to G1 or less on prednisone ≤ 10 mg/d For Grade 2 hepatic toxicity with symptoms, may administer corticosteroid 0.5-1 mg/kg/d prednisone or equivalent if the abnormal elevation persists with significant clinical symptoms in 3-5 days Increase frequency of monitoring to every 3 days Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of idiosyncratic liver failure (Note: No clear evidence shows the liver toxicity from infliximab from other studies) In follow-up, may resume ICPi treatment followed by taper only when symptoms improve to G1 or less and corticosteroid ≤ 10 mg/d; taper over at least 1 month Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs
G3: Symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis (AST or ALT 5-20 x ULN and/or total bilirubin 3-10x3 ULN)	Permanently discontinue ICPi Immediately start corticosteroid 1-2 mg/kg methylprednisolone or equivalent If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using azathioprine should test for thiopurine methyltransferase deficiency) Laboratories at daily or every other day; consider inpatient monitoring for patients with AST/ALT > 8 x ULN and/or elevated TB 3 x ULN Increase frequency of monitoring to every 1-2 days

2.0 GI Toxicities	
	Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of liver failure (Note: No clear evidence shows that the liver toxicity from infliximab from other studies); alternatives include non–TNF-a agents as systemic immunosuppressants If no improvement is achieved with corticosteroids or for patients on combination therapy with a novel agent, with standard chemotherapy, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis Corticosteroid taper can be attempted around 4-6 weeks; re-escalate if needed; optimal duration unclear
G4: Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma; AST or ALT > 20 x ULN and/or total bilirubin > 10 x ULN)	Permanently discontinue ICPi Administer 2 mg/kg/d methylprednisolone equivalents If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil Monitor laboratories daily; consider inpatient monitoring Avoid the use of infliximab in the situation of immune-mediated hepatitis Hepatology consult if no improvement was achieved with corticosteroid Corticosteroid taper can be attempted around 4-6 weeks when symptoms improve to G1 or less; re-escalate if needed; optimal duration unclear Consider transfer to tertiary care facility if necessary
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations is moderate.	

*not approved in Japan.

Abbreviations: ADL, activities of daily living; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CBC, complete blood count, CK, creatine kinase; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-cell lymphocyte-4; EGD, esophagogastroduodenoscopy; ESR, erythrocyte sedimentation rate; G, Grade; GI, gastrointestinal; HIV, human immunodeficiency virus; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; PD-1; programmed death 1; PD-L1, programmed death ligand 1; TB, tuberculosis; TNF, tumor necrosis factor; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

Table A3 Management of Lung irAEs in Patients Treated With ICPis

3.0 Lung Toxicities	
3.1 Pneumonitis	
Definition: Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging) No symptomatic, pathologic, or radiographic features are pathognomonic for pneumonitis Diagnostic work-up Should include the following: CXR, CT, pulse oximetry For G2 or higher, may include the following infectious work-up: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity	
Grading	Management
G1: Asymptomatic, confined to one lobe of the lung or < 25% of lung parenchyma, clinical or diagnostic observations only	Continue ICPi If clinically indicated. Monitor participants weekly or more frequently as needed with history, physical examination and pulse oximetry; may also offer CXR. May offer one repeat CT scan in 3-4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks If symptoms appear and/or changes in the physical exam are noted, treat as G2
G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL	Hold ICPi until resolution to G1 or less Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks Consider bronchoscopy with BAL Consider empirical antibiotics Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; no clinical improvement after 48-72 hours of prednisone, treat as G3
G3: Severe symptoms, hospitalization required, involves all lung lobes or 50% of lung parenchyma, limiting self-care ADL, oxygen indicated G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation)	Permanently discontinue ICPi Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks Pulmonary and infectious disease consults if necessary Bronchoscopy with BAL ± transbronchial biopsy Patients should be hospitalized for further management
Additional considerations GI and Pneumocystis prophylaxis with PPI and Bactrim may be offered to patients on prolonged corticosteroid use (> 12 weeks), according to institutional guidelines Consider calcium and vitamin D supplementation with prolonged corticosteroid use The role of prophylactic fluconazole with prolonged corticosteroid use (> 12 weeks) remains unclear, and physicians should proceed according to institutional guidelines Bronchoscopy + biopsy; if clinical picture is consistent with pneumonitis, no need for biopsy All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ADL, activities of daily living; BAL, bronchoalveolar lavage; CT, computed tomography; CXR, chest x-ray; DLCO, diffusing capacity of lung for carbon monoxide; G, Grade; GI, gastrointestinal; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; PPI, proton pump inhibitor.

Table A4 Management of Endocrine irAEs in Patients Treated With ICPis

4.0 Endocrine Toxicity	
Counsel patients to inform their health care provider immediately if they experience any changes in their health since their last visit, especially any of the following:	
Headaches that will not go away or unusual headache patterns Vision changes Rapid heartbeat Increased sweating Extreme tiredness or weakness Muscle aches Weight gain or weight loss Dizziness or fainting Feeling more hungry or thirsty than usual Hair loss Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness Feeling cold Constipation Voice gets deeper Urinating more often than usual Nausea or vomiting Abdominal pain	
4.1 Thyroid	
4.1.1 Primary hypothyroidism	
Definition: Elevated TSH, normal or low FT4 Diagnostic work-up TSH and FT4 every 4-6 weeks as part of routine clinical monitoring on therapy or for case detection in symptomatic patients	
Grading	Management
G1: TSH < 10 mIU/L and asymptomatic G2: Moderate symptoms; able to perform ADL; TSH persistently > 10 mIU/L	Should continue ICPi with close follow-up and monitoring of TSH, FT4 May hold ICPi until symptoms resolve to baseline Consider endocrine consultation Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist > 10 mIU/L (measured 4 weeks apart) Monitor TSH every 6-8 weeks while titrating hormone replacement to normal TSH FT4 can be used in the short-term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low Once adequately treated, should monitor thyroid function (at least TSH) every 6 weeks while on active ICPi therapy or as needed for symptoms to ensure appropriate replacement; repeat testing annually or as indicated by symptoms once stable
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate supplementation Endocrine consultation

4.0 Endocrine Toxicity	
	May admit for IV therapy if signs of myxedema (bradycardia, hypothermia) Thyroid supplementation and reassessment as in G2
Additional considerations For patients without risk factors, full replacement can be estimated with an ideal body weight–based dose of approximately 1.6 µg/kg/d For elderly or fragile patients with multiple comorbidities, consider titrating up from low dose, starting at 25-50 mg Extreme elevations of TSH can be seen in the recovery phase of thyroiditis and can be watched in asymptomatic patients to determine whether there is recovery to normal within 3-4 weeks Under guidance of endocrinology, consider tapering hormone replacement and retesting in patients with a history of thyroiditis (initial thyrotoxic phase) Adrenal dysfunction, if present, must always be replaced before thyroid hormone therapy is initiated	
4.1.2 Hyperthyroidism	
Definition: Suppressed TSH and high normal or elevated FT4 and/or triiodothyronine Diagnostic work-up Monitor TSH, FT4 every 4-6 weeks from the start of therapy or as needed for case detection in symptomatic patients Consider TSH receptor antibodies if there are clinical features and suspicion of Grave disease (e.g., ophthalmopathy) Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch transition to hypothyroidism in patients with thyroiditis and hyperthyroidism	
Grading	**Management**
G1: Asymptomatic or mild symptoms	Can continue ICPi with close follow-up and monitoring of TSH, FT4 every 2-3 weeks until it is clear whether there will be persistent hyperthyroidism (see below) or hypothyroidism (see 4.1.1) Consider holding ICPi until symptoms return to baseline Consider endocrine consultation b-Blocker (e.g., atenolol, propranolol) for symptomatic relief Hydration and supportive care Corticosteroids are not usually required to shorten duration For persistent hyperthyroidism (> 6 weeks) or clinical suspicion, work-up for Graves disease (TSI or TRAb) and consider thionamide (methimazole or PTU) Refer to endocrinology for Graves disease
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate therapy Endocrine consultation b-Blocker (e.g., atenolol, propranolol) for symptomatic relief For severe symptoms or concern for thyroid storm, hospitalize patient and initiate prednisone 1-2 mg/kg/d or equivalent tapered over 1-2 weeks; consider also use of SSKI or thionamide (methimazole or PTU).
Additional considerations Thyroiditis is transient and resolves in a couple of weeks to primary hypothyroidism or normal. Hypothyroidism can be treated as above. Graves' disease is generally persistent and is due to increased thyroid hormone production that can be treated with antithyroid medical therapy. Physical examination findings of ophthalmopathy or thyroid bruit are diagnostic of Graves and should prompt early endocrine referral.	

4.0 Endocrine Toxicity	
4.2 Adrenal – primary adrenal insufficiency	
Definition: Adrenal gland failure leading to low morning cortisol, high morning ACTH, as well as hyponatremia and hyperkalemia with orthostasis and volume depletion due to loss of aldosterone	
Diagnostic work-up for patients in whom adrenal insufficiency is suspected: Evaluate ACTH (AM), cortisol level (AM) Basic metabolic panel (Na, K, CO_2, glucose) Consider ACTH stimulation test for indeterminate results If primary adrenal insufficiency (high ACTH, low cortisol) is found biochemically: Evaluate for precipitating cause of crisis such as infection Perform an adrenal CT for metastasis/hemorrhage	
Grading	Management
G1: Asymptomatic or mild symptoms	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Replacement therapy with prednisone (5-10 mg daily) or hydrocortisone (10-20 mg orally every morning, 5-10 mg orally in early afternoon) May require fludrocortisone (0.1 mg/d) for mineralocorticoid replacement in primary adrenal insufficiency Titrate dose up or down as symptoms dictate
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Initiate outpatient treatment at two to three times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg in the morning, and 10-20 mg in the afternoon) to manage acute symptoms. Taper stress-dose corticosteroids down to maintenance doses over 5-10 days Maintenance therapy as in G1.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormone Endocrine consultation See in clinic or, for after hours, make an emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation hydrocortisone 100 mg or dexamethasone 4 mg (if the diagnosis is not clear and stimulation testing will be needed) Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge Maintenance therapy as in G1
Additional considerations Primary and secondary adrenal insufficiency can be distinguished by the relationship between ACTH and cortisol. If the ACTH is low with low cortisol, then management is as per 4.3.	

4.0 Endocrine Toxicity	
Patients on corticosteroids for management of other conditions will have low morning cortisol as a result of iatrogenic, secondary adrenal insufficiency. ACTH will also be low in these patients. A diagnosis of adrenal insufficiency is challenging to make in these situations (see next section on hypophysitis). Emergent therapy for someone with suspected adrenal insufficiency is best done with dexamethasone as a stimulation test can still be performed. If the diagnosis is already confirmed, can use hydrocortisone 100 mg. All patients need education on stress dosing and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS. Endocrine consultation prior to surgery or any procedure for stress-dose planning.	
4.3 Pituitary - hypophysitis	
Definition: Inflammation of the pituitary with varying effects on hormone function. Most commonly presenting with central adrenal insufficiency. May also have central hypothyroidism, diabetes insipidus, and hypogonadism. Diagnostic work-up Diagnosis: Low ACTH with a low cortisol. Low or normal TSH with a low FT4. Hypernatremia and volume depletion with diabetes insipidus. Low testosterone or estradiol with low LH and FSH. Testing: Evaluate ACTH, cortisol (AM), TSH, FT4, electrolytes Consider evaluating LH, FSH, and testosterone levels in males or estrogen in premenopausal females with fatigue, loss of libido, and mood changes Consider MRI of the brain with or without contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities ± new severe headaches or complaints of vision changes	
Grading	Management
G1: Asymptomatic or mild symptoms	Consider holding ICPi until patient is stabilized on replacement hormones Endocrine consultation Hormonal supplementation as in G1
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormones Endocrine consultation Hormonal supplementation as in G1 Consider initial pulse dose therapy with prednisone 1-2 mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks
Additional considerations Be aware of the need to start corticosteroids first when planning hormone replacement therapy for multiple deficiencies All patients need instruction on doubling doses for illness (stress dosing) and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS Corticosteroid use can cause isolated central adrenal insufficiency Work-up cannot be done with a simple AM cortisol in a patient on corticosteroids for other conditions Laboratory confirmation of adrenal insufficiency should not be attempted until treatment with corticosteroids for other disease is ready to be discontinued. For long-term exposure, consult endocrinology for recovery and weaning protocol using hydrocortisone.	
4.4 Diabetes	
Definition: T2DM is a combination of insulin resistance and insufficiency that may require oral or insulin therapy. It may be new onset or exacerbated during therapy for nonimmunologic reasons, such as corticosteroid exposure. Autoimmune T1DM results from islet cell destruction and is often acute onset, with ketosis and an insulin requirement Diagnostic work-up Monitor patients for hyperglycemia or other signs and symptoms of new or worsening DM, including measuring glucose at baseline and with each treatment cycle during induction for 12 weeks, then every 3-6 weeks thereafter. To guide the work-up in new-onset hyperglycemia, clinicians should consider a patient's medical background, exposure history, and risk factors for each subtype of DM.	

4.0 Endocrine Toxicity	
Laboratory evaluation in suspected T1DM should include testing for ketosis in urine and an assessment of the anion gap on a metabolic panel. Anti–glutamic acid decarboxylase, anti–islet cell, or anti–insulin antibodies are highly specific for autoimmune diabetes. Insulin and C-peptide levels can also assist in the diagnosis.	
Grading	Management
G1: Asymptomatic or mild symptoms; fasting glucose value > ULN (160 mg/dL); fasting glucose value > ULN (8.9 mmol/L); no evidence of ketosis or laboratory evidence of T1DM	Can continue ICPi with close clinical follow-up and laboratory evaluation May initiate oral therapy for those with new-onset T2DM Screen for T1DM if appropriate, for example, acute onset with prior normal values or clinical concern for ketosis
G2: Moderate symptoms, able to perform ADL, fasting glucose value > 160-250 mg/dL; fasting glucose value > 8.9-13.9 mmol/L, ketosis or evidence of T1DM at any glucose level	May hold ICPi until glucose control is obtained Titrate oral therapy or add insulin for worsening control in T2DM Should administer insulin for T1DM (or as default therapy if there is confusion about type) Urgent endocrine consultation for any patient with T1DM; in the absence of endocrinology, internal medicine may suffice Consider admission for T1DM if early outpatient evaluation is not available or signs of ketoacidosis are present
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL G3: > 250-500 mg/dL (> 13.9-27.8 mmol/L) G4: > 500 mg/dL (> 27.8 mmol/L)	Hold ICPi until glucose control is obtained on therapy with reduction of toxicity to G1 or less Urgent endocrine consultation for all patients Initiate insulin therapy for all patients Admit for inpatient management: Concerns for developing DKA, Symptomatic patients regardless of diabetes type, New-onset T1DM unable to see endocrinology
Additional considerations Insulin therapy can be used as the default in any case with hyperglycemia Long-acting therapy alone is not usually sufficient for T1DM, where half of daily requirements are usually given in divided doses as prandial coverage and half as long acting. Insulin doses will be lower in T1DM because of preserved sensitivity (total daily requirement can be estimated at 0.3-0.4 units/kg/d). In T2DM, sliding-scale coverage with meals over a few days provides data to estimate a patient's daily requirements and can be used to more rapidly titrate basal needs. All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ACTH, adrenocorticotropic hormone; ADL, activities of daily living; CT, computed tomography; DKA, diabetic ketoacidosis; DM, diabetes mellitus; EMS, emergency medical services; FSH, follicle-stimulating hormone; FT4, free thyroxine; G, Grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; LH, luteinizing hormone; MRI, magnetic resonance imaging; PTU, propylthiouracil; 2L, second-line; SSKI, potassium iodide; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TRAb, thyroid-stimulating hormone receptor antibody; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin; ULN, upper limit of normal.

Table A5 Management of Musculoskeletal irAEs in Patients Treated With ICPis

5.0 Musculoskeletal Toxicities	
5.1 Inflammatory arthritis	
Definition: A disorder characterized by inflammation of the joints Clinical symptoms: Joint pain accompanied by joint swelling; inflammatory symptoms, such as stiffness after inactivity or in the morning, lasting > 30 minutes to 1 hour; improvement of symptoms with NSAIDs or corticosteroids but not with opioids or other pain medications may also be suggestive of inflammatory arthritis.	
Diagnostic work-up G1 Complete rheumatologic history and examination of all peripheral joints for tenderness, swelling, and range of motion; examination of the spine Consider plain x-ray/imaging to exclude metastases and evaluate joint damage (erosions), if appropriate Consider autoimmune blood panel including ANA, RF, and anti-CCP, and anti-inflammatory markers (ESR and CRP) if symptoms persist; if symptoms are suggestive of reactive arthritis or affect the spine, consider HLA B27 testing G2 Complete history and examination as above; laboratory tests as above Consider US ± MRI of affected joints if clinically indicated (e.g., persistent arthritis unresponsive to treatment, suspicion for differential diagnoses such as metastatic lesions or septic arthritis) Consider early referral to a rheumatologist, if there is joint swelling (synovitis) or if symptoms of arthralgia persist > 4 weeks G3-4 As for G2 Seek rheumatologist advice and review Monitoring: Patients with inflammatory arthritis should be monitored with serial rheumatologic examinations, including inflammatory markers, every 4-6 weeks after treatment is instituted.	
Grading	Management
All Grades	Clinicians should follow reports of new joint pain to determine whether inflammatory arthritis is present; question whether symptom new since receiving ICPi
G1: Mild pain with inflammation, erythema, or joint swelling	Continue ICPi Initiate analgesia with acetaminophen and/or NSAIDs
G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling, limiting instrumental ADL	Hold ICPi and resume upon symptom control and on prednisone ≤ 10 mg/d Escalate analgesia and consider higher doses of NSAIDS as needed If inadequately controlled, initiate prednisone or prednisolone 10-20 mg/d or equivalent for 4-6 weeks If improvement, slow taper according to response during the next 4-6 weeks; if no improvement after initial 4-6 weeks, treat as G3 If unable to lower corticosteroid dose to < 10 mg/d after 3 months, consider DMARD Consider intra-articular corticosteroid injections for large joints Referral to rheumatology
G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL	For G3: Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to G1 or less For G4: permanently discontinue ICPi Initiate oral prednisone 0.5-1 mg/kg If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD

5.0 Musculoskeletal Toxicities	
	Synthetic: methotrexate, leflunomide Biologic: consider anticytokine therapy such as TNF-a or IL-6 receptor inhibitors. (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis.) Test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment Referral to rheumatology.
Additional considerations Early recognition is critical to avoid erosive joint damage. Corticosteroids can be used as part of initial therapy in inflammatory arthritis, but due to likely prolonged treatment requirements, physicians should consider starting corticosteroid-sparing agents earlier than one would with other irAEs Oligoarthritis can be treated early on with intra-articular corticosteroids; consider early referral. Consider PCP prophylaxis for patients treated with high dose of corticosteroids for 12 weeks, as per local guidelines.	
5.2 Myositis	
Definition: A disorder characterized by muscle inflammation with weakness and elevated muscle enzymes (CK). Muscle pain can be present in severe cases. Can be life-threatening if respiratory muscles or myocardium are involved Diagnostic work-up Complete rheumatologic and neurologic history regarding differential diagnosis; rheumatologic and neurologic examination, including muscle strength; and examination of the skin for findings suggestive of dermatomyositis. Muscle weakness is more typical of myositis than pain. Consider pre-existing conditions that can cause similar symptoms. Blood testing to evaluate muscle inflammation CK, transaminases (AST, ALT), LDH, and aldolase can also be elevated Troponin to evaluate myocardial involvement and other cardiac testing, such as echocardiogram, as needed Inflammatory markers (ESR and CRP) Consider EMG, imaging (MRI), and/or biopsy on an individual basis when diagnosis is uncertain and overlap with neurologic syndromes, such as myasthenia gravis, is suspected Consider paraneoplastic autoantibody testing for myositis and neurologic conditions, such as myasthenia gravis Monitoring: CK, ESR, CRP	
G1: Complete examination and laboratory work-up as above G2: Complete history and examination as above; autoimmune myositis blood panel; EMG, MRI of affected joints Early referral to a rheumatologist or neurologist G3-4: As for G2 Urgent referral to a rheumatologist or neurologist	
Grading	Management
G1: Mild weakness with or without pain	Continue ICPi If CK is elevated and patient has muscle weakness, may offer oral corticosteroids, and treat as G2 Offer analgesia with acetaminophen or NSAIDs if there are no contraindications
G2: Moderate weakness with or without pain, limiting age-appropriate instrumental ADL	Hold ICPi temporarily and may resume upon symptom control, if CK is normal and prednisone dose 10 mg; if worsens, treat as per G3 NSAIDs as needed Referral to rheumatologist or neurologist If CK is elevated three times or more), initiate prednisone or equivalent at 0.5-1 mg/kg

5.0 Musculoskeletal Toxicities	
	May require permanent discontinuation of ICPi in most patients with G2 symptoms and objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy)
G3-4: Severe weakness with or without pain, limiting self-care ADL	For G3: Hold ICPi until G1 or less and permanently discontinue if any evidence of myocardial involvement For G4: permanently discontinue ICPi Consider hospitalization for severe weakness Referral to rheumatologist or neurologist Initiate prednisone 1 mg/kg or equivalent. Consider 1-2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia) Consider plasmapheresis Consider IVIG therapy Consider other immunosuppressant therapy, such as methotrexate, azathioprine, or mycophenolate mofetil, if symptoms and CK levels do not improve or worsen after 4-6 weeks; rituximab is used in primary myositis but caution is advised given its long biologic duration In case of management with rituximab, ICPi treatment should be discontinued
Additional considerations: Caution is advised with rechallenging	
5.3 Polymyalgia-like syndrome	
Definition: Characterized by marked pain and stiffness in proximal upper and/or lower extremities and no signs of true muscle inflammation such as CK elevation or EMG findings of myositis. No true muscle weakness, difficulty in active motion related to pain Diagnostic work-up	
G1 Complete rheumatologic history regarding differential diagnosis and examination of all joints and skin Check for symptoms of temporal arteritis, such as headache or visual disturbances; refer to ophthalmologist if present, and consider temporal artery biopsy ANA, RF, anti-CCP CK to evaluate differential diagnosis of myositis Inflammatory markers (ESR, CRP) Monitoring: ESR, CRP	
G2: Complete history and examination as above; autoimmune tests as required for differential diagnosis; early referral to a rheumatologist G3-4: As for G2; see rheumatologist advice and review	
Grading	Management
G1: Mild stiffness and pain	Continue ICPi Initiate analgesia with acetaminophen and/or NSAIDs if there are no contraindications
G2: Moderate stiffness and pain, limiting age-appropriate instrumental ADL	Consider holding ICPi and resuming upon symptom control, prednisolone < 10 mg; if worsens, treat as per G3 Initiate prednisone 20 mg/d or equivalent; if symptoms improve, start to taper dose after 3-4 weeks If no improvement or need for higher dosages after 4 weeks, escalate to G3 Consider referral to rheumatology

5.0 Musculoskeletal Toxicities	
G3-4: Severe stiffness and pain, limiting self-care ADL	For G3: Hold ICPi and may resume, in consultation with rheumatology, if recover to G1 or less; however, note that cases of toxicity returning upon rechallenge have been reported. ICPi should be permanently discontinued in such cases For G4: permanently discontinue ICPi Referral to rheumatology Should initiate prednisone 20 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a corticosteroid-sparing agent such as methotrexate or IL-6 inhibition with tocilizumab (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis or GI metastases). Consider admission for pain control
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ADL, activities of daily living; ALT, alanine aminotransferase; ANA, antinuclear antibodies; AST, aspartate aminotransferase; CCP, citrullinated protein antibody; CK, creatine kinase; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; EMG, electromyography; ESR, erythrocyte sedimentation rate; G, Grade; HLA, human leukocyte antigen; ICPi, immune checkpoint inhibitor; IL, interleukin; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging, NSAID, nonsteroidal anti-inflammatory drug; PCP, Pneumocystis pneumonia; RF, rheumatoid factor; TB, tuberculosis; TNF, tumor necrosis factor.

Table A6 Management of Renal irAEs in Patients Treated With ICPis

6.0 Renal Toxicities	
Nephritis and renal dysfunction: diagnosis and monitoring For any suspected immune-mediated adverse reactions, exclude other causes Monitor patients for elevated serum creatinine prior to every dose Routine urinalysis is not necessary, other than to rule out UTIs, etc.; nephrology may consider further If no potential alternative cause of AKI identified, then one should forego biopsy and proceed directly with immunosuppressive therapy Swift treatment of autoimmune component important	
6.1 Nephritis	
Definition: Inflammation of the kidney affecting the structure	
Grading	Management
G1: Creatinine level increase > ULN - 1.5 x ULN	Consider temporarily holding ICPi, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status) and baseline renal function. A change that is still < 1.5 ULN could be meaningful
G2: Creatinine > 1.5 - 3.0 x baseline; > 1.5 - 3.0 x ULN	Hold ICPi Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc.); if other etiologies ruled out, administer 0.5-1 mg/kg/d prednisone equivalents If worsening or no improvement: 1 to 2 mg/kg/d prednisone equivalents and permanently discontinue treatment If improved to G1 or less, taper corticosteroids over 4-6 weeks If no recurrence of chronic renal insufficiency, discuss resumption of ICPI with patient after taking into account the risks and benefits.
G3: Creatinine > 3.0 x baseline; > 3.0 - 6.0 x ULN	Permanently discontinue ICPi
G4: Life-threatening consequences; dialysis indicated; > 6.0 x ULN	Permanently discontinue ICPi Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc.) Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent)
Additional considerations Monitor creatinine weekly Reflex kidney biopsy should be discouraged until corticosteroid treatment has been attempted	
6.2 Symptomatic nephritis: follow-up	
Grading	Management
G1	Improved to baseline, resume routine creatinine monitoring
G2	If improved to G1, taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring If elevations persist > 7 days or worsen and no other cause found, treat as G3
G3	If improved to G1, taper corticosteroids over at least 4 weeks

6.0 Renal Toxicities	
	If elevations persist 3-5 days or worsen, consider additional immunosuppression (e.g., mycophenolate)
G4	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist 2-3 days or worsen, consider additional immunosuppression (e.g., mycophenolate)
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: AKI, acute kidney injury; G, Grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; ULN, upper limit of normal; UTI, urinary tract infection.

Table A7 Management of Nervous System irAEs in Patients Treated With ICPis

7.0 Nervous System Toxicities	
7.1 Myasthenia gravis	
Definition: Fatigable or fluctuating muscle weakness, generally more proximal than distal. Frequently has ocular and/or bulbar involvement (ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, dysarthria, facial muscle weakness). May have neck and/or respiratory muscle weakness. (Note: May occur with myositis and/or myocarditis). Respiratory symptoms may require evaluation to rule out pneumonitis, myocarditis. Miller Fisher variant of Guillain-Barré syndrome (ophthalmoparesis) and the oculobulbar myositis (ptosis, ophthalmoparesis, dysphagia, neck and respiratory weakness) with ICPi may have overlapping symptoms.	
Diagnostic work-up AChR and antistriated muscle antibodies in blood; if AChR antibodies are negative, consider muscle specific kinase and lipoprotein-related 4 antibodies in blood Pulmonary function assessment with NIF and VC CPK, aldolase, ESR, CRP for possible concurrent myositis Consider MRI of brain and/or spine, depending on symptoms to rule out CNS involvement by disease or alternate diagnosis If respiratory insufficiency or elevated CPK, troponin T, perform cardiac examination with ECG and TTE for possible concomitant myocarditis Neurologic consultation Electrodiagnositic studies, including neuromuscular junction testing with repetitive stimulation and/or jitter studies, NCS to exclude neuropathy, and needle EMG to evaluate for myositis	
Grading	Management
All grades	All grades warrant work-up and intervention given potential for progressive myasthenia gravis to lead to respiratory compromise
No G1	
G2: Some symptoms interfering with ADL MGFA severity class 1 (ocular symptoms and findings only) and MGFA severity class 2 (mild generalized weakness)	Hold ICPi and may resume in G2 patients (MGFA 1 and 2) only if symptoms resolve Should consult neurology Pyridostigmine starting at 30 mg orally three times a day and gradually increase to maximum of 120 mg orally four times a day as tolerated and based on symptoms Administer corticosteroids (prednisone, 1-1.5 mg/kg orally daily) if symptoms G2; wean based on symptom improvement
G3-4: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms, or MGFA severity class 3-4 moderate to severe generalized weakness to myasthenic crisis	Permanently discontinue ICPi Admit patient, may need ICU-level monitoring Neurology consult Continue corticosteroids and initiate IVIG 2 g/kg IV over 5 days (0.4 g/kg/d) or plasmapheresis for 5 days Frequent pulmonary function assessment Daily neurologic review
Additional considerations Avoid medications that can worsen myasthenia: β-blockers, IV magnesium, fluoroquinolones, aminoglycosides, and macrolides Initially a 5-day course of plasmapheresis or a 2 g/kg course of IVIG over 5 days 1-2 mg/kg methylprednisolone daily, wean based on symptom improvement Pyridostigmine, wean based on improvement ICPi-associated myasthenia gravis may be monophasic, and additional corticosteroid-sparing agents may not be required	

7.0 Nervous System Toxicities	
7.2 Guillain-Barré syndrome	
Definition: Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. Often starts with sensory symptoms/neuropathic pain localized to lower back and thighs. May involve extremities (typically ascending weakness but not always), facial, respiratory, and bulbar and oculomotor nerves. May have dysregulation of autonomic nerves.	
Diagnostic work-up Neurologic consultation MRI of spine with or without contrast (rule out compressive lesion and evaluate for nerve root enhancement/thickening) Lumbar puncture: CSF typically has elevated protein and often elevated WBCs; even though this is not typically seen in classic Guillain-Barré syndrome, cytology should be sent with any CSF sample from a patient with cancer. Serum antibody tests for Guillain-Barré syndrome variants (GQ1b for Miller Fisher variant a/w ataxia and ophthalmoplegia) Electrodiagnostic studies to evaluate polyneuropathy Pulmonary function testing (NIF/VC) Frequent neurochecks	
Grading	Management
All grades	Warrant work-up and intervention given potential for progressive Guillain-Barré syndrome to lead to respiratory compromise Note: There is no G1 toxicity
G1: Mild, none	NA
G2: Moderate, some interference with ADL, symptoms concerning to patient	Discontinue ICPi
G3-4: Severe, limiting self-care and aids warranted, weakness, limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms	Permanently discontinue ICPi. Admission to inpatient unit with capability of rapid transfer to ICU-level monitoring Start IVIG (0.4 g/kg/d for 5 days for a total dose of 2 g/kg) or plasmapheresis. Corticosteroids are usually not recommended for idiopathic Guillain-Barré syndrome; however, in ICPi-related forms, a trial is reasonable (methylprednisolone 2-4 mg/kg/d), followed by slow corticosteroid taper Pulse corticosteroid dosing (methylprednisolone 1 g/d for 5 days) may also be considered for G3-4 along with IVIG or plasmapheresis Frequent neurochecks and pulmonary function monitoring Monitor for concurrent autonomic dysfunction Nonopioid management of neuropathic pain Treatment of constipation/ileus
Additional considerations Slow prednisone taper after corticosteroid pulse plus IVIG or plasmapheresis May require repeat IVIG courses Caution with rechallenging for severe cases	
7.3 Peripheral neuropathy	
Definition: Can present as asymmetric or symmetric sensory, motor, or sensory motor deficit. Focal mononeuropathies, including cranial neuropathies (e.g., facial neuropathies/Bell palsy) may be present. Numbness and paresthesias may be painful or painless. Hypo- or areflexia or sensory ataxia may be present.	
Diagnostic work-up G1 Screen for reversible neuropathy causes: diabetic screen, B12, folate, TSH, HIV, consider serum protein electrophoresis, and other vasculitic and autoimmune screen Neurologic consultation	

7.0 Nervous System Toxicities	
Consider MRI of spine with or without contrast G2: in addition to above MRI spine advised/MRI of brain if cranial nerve Consider EMG/NCS Consider neurology consultation G3-4: go to Guillain-Barré syndrome algorithm	
Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate	Low threshold to hold ICPi and monitor symptoms for a week If to continue, monitor very closely for any symptom progression
G2: Moderate, some interference with ADL, symptoms concerning to patient (i.e., pain but no weakness or gait limitation)	Hold ICPi and resume once return to G1 Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild) Neurontin, pregabalin, or duloxetine for pain
G3-4: Severe, limiting self-care and aids warranted, weakness limiting walking or respiratory problems (i.e., leg weakness, foot drop, rapidly ascending sensory changes) Severe may be Guillain-Barré syndrome and should be managed as such	Permanently discontinue ICPi Admit patient Neurologic consultation Initiate IV methylprednisolone 2-4 mg/kg and proceed as per Guillain-Barré syndrome management
7.4 Autonomic neuropathy	
Definition: Nerves that control involuntary bodily functions are damaged. This may affect blood pressure, temperature control, digestion, bladder function, and sexual function. A case of severe enteric neuropathy with ICPi has been reported. Can present with GI difficulties such as new severe constipation, nausea, urinary problems, sexual difficulties, sweating abnormalities, sluggish pupil reaction, and orthostatic hypertension.	
Diagnostic work-up An evaluation by neurologist or relevant specialist, depending on organ system, with testing that may include Screening for other causes of autonomic dysfunction: diabetic screen, adrenal insufficiency, HIV, paraproteinemia, amyloidosis, botulism; consider chronic diseases such as Parkinson and other autoimmune screening AM orthostatic vitals Consider electrodiagnostic studies to evaluate for concurrent polyneuropathy Consider paraneoplastic Lambert-Eaton myasthenic syndrome, antineutrophil cytoplasmic antibodies, and ganglionic AChR antibody testing	
Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient	Low threshold to hold ICPi and monitor symptoms for a week; if to continue, monitor very closely for any symptom progression
G2: Moderate, some interference with ADL, symptoms concerning to patient	Hold ICPi and resume once return to G1 Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild) Neurologic consultation
G3-4: Severe, limiting self-care and aids warranted	Permanently discontinue ICPi Admit patient Initiate methylprednisolone 1 g daily for 3 days followed by oral corticosteroid taper Neurologic consultation
7.5 Aseptic meningitis	
Definition: may present with headache, photophobia, and neck stiffness; often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis). Diagnostic work-up MRI of brain with or without contrast + pituitary protocol AM cortisol, ACTH to rule out adrenal insufficiency	

7.0 Nervous System Toxicities	
Consider lumbar puncture: measure opening pressure; check cell count and protein glucose; and perform Gram stain, culture, PCR for HSV, and other viral PCRs depending on suspicion, cytology May see elevated WBC count with normal glucose, normal culture, and Gram stain; may see reactive lymphocytes or histiocytes on cytology	
Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (i.e., pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, consider empirical antiviral (IV acyclovir) and antibacterial therapy until CSF results Once bacterial and viral infection are negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg or IV methylprednisolone 1 mg/kg if moderate/severe symptoms
7.6 Encephalitis	
Definition: As for aseptic meningitis, need to exclude infectious causes, especially viral (i.e., HSV). Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality	
Diagnostic work-up Neurologic consultation MRI of brain with or without contrast may reveal T2/fluid-attenuated inversion recovery changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal Lumbar puncture: check cell count and protein glucose and perform Gram stain, culture, PCR for HSV and other viral PCRs depending on suspicion, cytology, oligoclonal bands, autoimmune encephalopathy, and paraneoplastic panels. May see elevated WBC count with lymphocytic predominance and/or elevated protein EEG to evaluate for subclinical seizures Blood: metabolic, CBC, ESR, CRP, ANCA (if suspect vasculitic process), thyroid panel including TPO and thyroglobulin Rule out concurrent anemia/thrombocytopenia, which can present with severe headaches and confusion	
Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (i.e., pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits As above for aseptic meningitis suggest concurrent IV acyclovir until PCR results obtained and negative Trial of methylprednisolone 1-2 mg/kg If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids methylprednisolone 1 g IV daily for 3-5 days plus IVIG 2 g/kg over 5 days If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab or plasmapheresis in consultation with neurology.
7.7 Transverse myelitis	
Definition: Acute or subacute weakness or sensory changes bilateral, often with increased deep tendon reflexes	
Diagnostic work-up Neurologic consultation MRI of spine (with thin axial cuts through the region of suspected abnormality) and MRI of brain Lumbar puncture: cell count, protein, glucose, oligoclonal bands, viral PCRs, cytology, onconeural antibodies Blood: B12, HIV, RPR, ANA, Ro/La, TSH, aquaporin-4 IgG Evaluation for urinary retention, constipation	

7.0 Nervous System Toxicities	
Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (i.e., pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Permanently discontinue ICPi Methylprednisolone 2 mg/kg Strongly consider higher doses of 1 g/d for 3-5 days Strongly consider IVIG
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: AChR, acetylcholine receptor; ACTH, adrenocorticotropic hormone; ADL, activities of daily living; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; CBC, complete blood count; CNS, central nervous system; CPK, creatine phosphokinase; CRP, C-reactive protein; CSF, cerebrospinal fluid; ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyography; ESR, erythrocyte sedimentation rate; G, Grade; GI, gastrointestinal; HIV, human immunodeficiency virus; HSV, herpes simplex virus; ICPi, immune checkpoint inhibitor; ICU, intensive care unit; IgG, immunoglobulin G; IV, intravenous; IVIG, intravenous immunoglobulin; irAE, immune-related adverse event; MGFA, Myasthenia Gravis Foundation of America; MRI, magnetic resonance imaging; NA, not applicable; NCS, nerve conduction study; NIF, negative inspiratory force; PCR, polymerase chain reaction; RPR, rapid plasma reagin, TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; TTE, transthoracic echocardiogram; VC, vital capacity; WBC, white blood cell count.

Table A8 Management of Hematologic irAEs in Patients Treated With ICPis

8.0 Hematologic Toxicities	
8.1 Autoimmune hemolytic anemia	
Definition: A condition in which RBCs are destroyed and removed from the blood stream before their normal lifespan is over. Symptoms include weakness, paleness, jaundice, dark-colored urine, fever, inability to do physical activity, and heart murmur.	
Diagnostic work-up History and physical examination (with special consideration of history of new drugs and insect, spider, or snake bites) Blood chemistry, CBC with evidence of anemia, macrocytosis, evidence of hemolysis on peripheral smear; LDH, haptoglobin, bilirubin, reticulocyte count, free Hgb DIC panel, which could include PTNIR infectious causes Autoimmune serology Paroxysmal nocturnal hemoglobinuria screening Direct and indirect bilirubin; LDH; direct agglutinin test; and if no obvious cause, bone marrow analysis, cytogenetic analysis to evaluate for myelodysplastic syndromes Evaluation for viral/bacterial (mycoplasma, etc.) causes of hemolysis studies Protein electrophoresis, cryoglobulin analysis Work-up for bone marrow failure syndrome if refractory, including B12, folate, copper, parvovirus, FE, thyroid, infection Glucose-6-phosphate dehydrogenase Evaluation of common drug causes (ribavirin, rifampin, dapsone, interferon, cephalosporins, penicillins, NSAIDs, quinine/quinidine, fludarabine, ciprofloxacin, lorazepam, diclofenac, etc.) Assessment of methemoglobinemia	
Grading	Management
G1: Hgb < LLN to 10.0 g/dL; < LLN to 6.2 mmol/L; < LLN to 100 g/L	Continue ICPi with close clinical follow-up and laboratory evaluation
G2: Hgb < 10.0 to 8.0 g/dL; < 6.2to4.9mmol/L; < 100 to 80 g/L	Hold ICPi and strongly consider permanent discontinuation Administer 0.5-1 mg/kg/d prednisone equivalents
G3: Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated	Permanently discontinue ICPi Should use clinical judgment and consider admitting the patient Hematology consult Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms/speed of development) If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue ICPi treatment Consider RBC transfusion per existing guidelines; do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return a patient to a safe Hgb range (7-8 g/dL in stable, noncardiac inpatients) Should offer patients supplementation with folic acid 1 mg once daily
G4: Life-threatening consequences, urgent intervention indicated	Permanently discontinue ICPi Admit patient Hematology consult IV prednisone corticosteroids 1-2 mg/kg/d

8.0 Hematologic Toxicities	
	If no improvement or if worsening while on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, cyclosporin A, and mycophenolate mofetil RBC transfusion per existing guidelines; discuss with blood bank team prior to transfusions that a patient with possible ICPi serious AE is in house.
Additional considerations: Monitor Hgb levels on a weekly basis until the corticosteroid tapering process is complete; thereafter, less-frequent testing is needed	
8.2 Acquired TTP	
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities, and neurologic abnormalities, such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.	
Diagnostic work-up History with specific questions related to drug exposure (e.g., chemotherapy, sirolimus, tacrolimus, opana ER antibiotics, quinine) Physical examination, peripheral smear ADAMTS13 activity level and inhibitor titer LDH, haptoglobin, reticulocyte count, bilirubin, urinalysis to rule out other causes PT, activated PTT, fibrinogen Blood group and antibody screen, direct antiglobulin test, CMV serology Consider CT/MRI brain, echocardiogram, ECG Viral studies Note: This disorder is usually associated with a severe drop in platelets and hemolysis/anemia precipitously	
Grading	Management
All grades	The first step in the management of TTP is a high index of suspicion for the diagnosis and timely recognition; hematology consult should immediately be called, as delay in identification is associated with increased mortality/morbidity. Initially, the patient should be stabilized and any critical organ dysfunction stabilized
G1: Evidence of RBC destruction (schistocytosis) without anemia, renal insufficiency, or thrombocytopenia clinically G2: Evidence of RBC destruction (schistocytosis) without clinical consequence with G2 anemia and thrombocytopenia	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting ICPi therapy Hematology consult Administer 0.5-1 mg/kg/d prednisone
G3: Laboratory findings with clinical consequences (G3 thrombocytopenia, anemia, renal insufficiency > 2) G4: Life-threatening consequences (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	For G3: Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting ICPi therapy For G4: permanently discontinue ICPi Hematology consult In conjunction with hematology, initiate PEX according to existing guidelines with further PEX dependent on clinical progress Administer methylprednisolone 1 g IV daily for 3 days, with the first dose typically administered immediately after the first PEX May offer rituximab In case of management with rituximab, ICPi treatment will be discontinued

8.0 Hematologic Toxicities	
8.3 Hemolytic uremic syndrome	
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia. Signs and symptoms of hemolytic uremic syndrome can include: Bloody diarrhea Decreased urination or blood in the urine Abdominal pain, vomiting, and occasionally fever Pallor Small, unexplained bruises or bleeding from the nose and mouth Fatigue and irritability Confusion or seizures High blood pressure Swelling of the face, hands, feet, or entire body	
Diagnostic work-up History and physical examination (special consideration for new history of high-risk drugs, hypertension, or cardiac causes) CBC with indices Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis. Serum creatinine ADAMTS13 (to rule out TTP) Homocysteine/methylmalonic acid Complement testing C3, C4, CH50 (complement inhibitory antibodies for suspected familial) Evaluate reticulocyte count and mean corpuscular volume Evaluation of infectious cause, including screening for EBV, CMV, HHV6 Evaluation for nutritional causes of macrocytosis (B12 and folate) Pancreatic enzymes Evaluation for diarrheal causes, shiga toxin, Escherichia coli 0157, etc. Direct antibody test (Coombs test), haptoglobin, LDH, and other etiologies of anemia Evaluation for common drugs causing hemolysis (tacrolimus, cyclosporine, sirolimus, etc.) Evaluation for concurrent confusion	
Grading	Management
G1-2: Evidence of RBC destruction (schistocytosis) without clinical consequences of anemia, thrombocytopenia Grade 2 G3: Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae) G4: Life-threatening consequences (e.g., CNS thrombosis/ embolism or renal failure)	For G1 and G2: Continue ICPi with close clinical follow-up and laboratory evaluation Supportive care For G3 and G4: Permanently discontinue ICPi Begin therapy with eculizumab therapy 900 mg weekly for four doses, 1,200 mg week 5, then 1,200 mg every 2 weeks Red blood transfusion according to existing guidelines
8.4 Aplastic anemia	
Definition: Condition in which the body stops producing enough new blood cells	
Diagnostic work-up History and physical examination (close attention to medications, exposure to radiation, toxins, recent viral infections) CBC, smear, reticulocyte count Viral studies, including CMV, HHV6, EBV, parvovirus Nutritional assessments including B12, folate, iron, copper, ceruloplasmin, vitamin D Serum LDH, renal function Work-up for infectious causes Identify marrow hypo/aplasia Bone marrow biopsy and aspirate analysis Peripheral blood analysis, including neutrophil count, proportion of GPI-negative cells by flow for PNH Flow cytometry to evaluate loss of GPI-anchored proteins	

8.0 Hematologic Toxicities	
Type and screen patient for transfusions and notify blood bank that all transfusions need to be irradiated and filtered	
Grading	Management
G1: Nonsevere, < 0.5 polymorphonuclear cells x 10^9/L hypocellular marrow, with marrow cellularity < 25%, peripheral platelet count > 20,000, reticulocyte count < 20,000	Hold ICPi and provide growth factor support and close clinical follow-up, and laboratory evaluation Supportive transfusions as per local guidelines
G2: Severe, hypocellular marrow < 25% and two of the following: ANC < 500, peripheral platelet < 20,000, and reticulocyte < 20,000	Hold ICPi and provide growth factor support and close clinical laboratory evaluations daily Administer ATG + cyclosporine; HLA typing and evaluation for bone marrow transplantation if patient is candidate; all blood products should be irradiated and filtered Supportive care with granulocyte colony-stimulating factor may be added in addition
G3-4: Very severe, ANC > 200, platelet count > 20,000, reticulocyte count > 20,000, plus hypocellular marrow > 25%	For G3: Hold ICPi and monitor weekly for improvement; if not resolved, discontinue treatment until AE has reverted to G1 For G4: permanently discontinue ICPi Hematology consult, growth factor support Horse ATG plus cyclosporine If no response, repeat immunosuppression with rabbit ATG plus cyclosporine, cyclophosphamide For refractory patients, consider eltrombopag plus supportive care
8.5 Lymphopenia	
Definition: An abnormally low level of lymphocytes in PB; for adults, counts of < 1,500/mm^3	
Diagnostic work-up History and physical examination (special attention for lymphocyte-depleting therapy such as fludarabine, ATG, corticosteroids, cytotoxic chemotherapy, radiation exposure, etc., as well as history of autoimmune disease, family history of autoimmune disease) Evaluation of nutritional state as cause Spleen size CBC with differential, peripheral smear and reticulocyte counts CXR for evaluation of presence of thymoma Bacterial cultures and evaluation for infection (fungal, viral, bacterial specifically CMV/HIV)	
Grading	Management
G1-2: 500-1,000 PB lymphocyte count G3: 250-499 PB lymphocyte count G4: < 250 PB lymphocyte count	Continue ICPi for G1 to G2 For G3 single laboratory values out of normal range without any clinical correlates, hold treatment until resolution to G1 For G4, for single laboratory values out of normal range without any clinical correlates, permanent treatment discontinuation is not required. Treatment should be held until the etiology is determined. Permanent treatment discontinuation will only be required, if lymphopenia is considered of immune related in nature, no clear alternative explanation exists for the event, and grade 4 lymphopenia does not resolve within 14 days. If the event is not considered immune related and resolves to G $\leqslant$ 1 restarting treatment may be considered. Check CBC weekly for monitoring, initiation of CMV screening Consider holding ICPi

8.0 Hematologic Toxicities	
	Initiate *Mycobacterium avium* complex prophylaxis and *Pneumocystis jirovecii* prophylaxis, CMV screening. HIV/hepatitis screening if not already done May consider EBV testing if evidence of lymphadenopathy/hepatitis, fevers, hemolysis consistent with lymphoproliferative disease.
8.6 Immune thrombocytopenia	
Definition: An autoimmune disorder characterized by immunologic destruction of otherwise normal platelets	
Diagnostic work-up History and physical examination (special attention for lymphocyte-depleting therapy, such as fludarabine, ATG, corticosteroids, cytotoxic therapy) Family history of autoimmunity or personal history of autoimmune disease History of viral illness CBC Peripheral blood smear, reticulocyte count Bone marrow evaluation only if abnormalities in the above test results and further investigation is necessary for a diagnosis Patients with newly diagnosed immune thrombocytopenia should undergo testing for HIV, hepatitis C virus, hepatitis B virus, and Helicobacter pylori Direct antigen test should be checked to rule out concurrent Evan syndrome Nutritional evaluation Bone marrow evaluation if other cell lines affected and concern for aplastic anemia	
Grading	Management
G1: Platelet count < 100/μL G2: Platelet count < 75/μL	Continue ICPi with close clinical follow-up and laboratory evaluation Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1 Administer prednisone 1 mg/kg/d (dosage range, 0.5-2 mg/kg/d) orally for 2-4 weeks after which time this medication should be tapered over 4-6 weeks to the lowest effective dose IVIG may be used in conjunction with corticosteroids if a more-rapid increase in platelet count is required.
G3: Platelet count < 50/μL	Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1
G4: Platelet count < 25/μL	Permanently discontinue ICPi Hematology consult Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue treatment IVIG used with corticosteroids when a more-rapid increase in platelet count is required If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary If previous treatment with corticosteroids and/or IVIG unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more-potent immunosuppression (From American Society of Hematology guideline on immune thrombocytopenia; consult for further details)

8.0 Hematologic Toxicities	
8.7 Acquired hemophilia	
Definition: Disorder caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors	
Diagnostic work-up Full blood count to assess platelet number, fibrinogen, PT, PTT, INR; the typical finding in patients with acquired hemophilia A is a prolonged activated PTT with a normal PT MRI, CT, and ultrasonography may be indicated to localize, quantify, and serially monitor the location and response of bleeding Medication review to assess for alternative causes Determination of Bethesda unit level of inhibitor	
Grading	Management
G1: Mild, 5%-40% of normal factor activity in blood, 0.05-0.4 IU/mL of whole blood	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits Administer 0.5-1 mg/kg/d prednisone Transfusion support as required Treatment of bleeding disorders with hematology consult
G2: Moderate, 1%-5% of normal factor activity in blood, 0.01- 0.05 IU/mL of whole blood	Hematology consult Administration of factor replacement (choice based on Bethesda unit of titer) Administer 1 mg/kg/d prednisone ± rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d); choice of rituximab v cyclophosphamide is patient specific and should be done with assistance of hematology consult; prednisone, rituximab, and cyclophosphamide should be given for at least 5 weeks Factors should be provided to increase level during bleeding episodes, with choice of factor based on presence or absence of inhibitor
G3-4: Severe, < 1% of normal factor activity in blood, < 0.01 IU/mL of whole blood	Permanently discontinue ICPi Admit patient Hematology consult Administration of factor replacement, choice based on Bethesda unit level of inhibitor Bypassing agents may be used (factor VII, factor VIII inhibitor bypass activity); caution should be taken in the elderly and those with coronary artery disease Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) ± rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d). Transfusion support as required for bleeding If worsening or no improvement add cyclosporine or immunosuppression/immunoadsorption
Additional considerations: The American Heart Association requires specialist clinical and laboratory expertise. Consult and/or transfer to a specialist center is often appropriate. If consultation with or transfer to a hemophilia center is not immediately possible, then investigation and treatment should be initiated while a liaison is being established. All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: AE, adverse event; ANC, absolute neutrophil count; ATG, antithymocyte globulin; CBC, complete blood count; CMV, cytomegalovirus; CNS, central nervous system; CT, computed tomography; CXR, chest x-ray; DIC, disseminated intravascular coagulation; EBV, Epstein-Barr virus; ECG, electrocardiogram; ER, extended release; FE, ferritin; G, Grade; GPI, glycosylphosphatidylinositol; Hgb, hemoglobin; HHV6, human herpesvirus 6; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; ICPi, immune checkpoint inhibitor; INR, international normalized ratio; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; LLN, lower limit of normal; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; PB, peripheral blood; PEX, plasma ex-change; PNH, paroxysmal nocturnal hemoglobinuria; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell count; TTP, thrombotic thrombocytopenic purpura.

Table A9 Management of Cardiovascular irAEs in Patients Treated With ICPis

9.0 Cardiovascular Toxicities	
9.1 Myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis	
Definition: Signs and symptoms may include chest pain, arrhythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion, fatigue	
Diagnostic work-up At baseline ECG Consider troponin, especially in patient treated with combination immune therapies Upon signs/symptoms (consider cardiology consult) ECG Troponin BNP Echocardiogram CXR Additional testing to be guided by cardiology and may include Stress test Cardiac catherization Cardiac MRI	
Grading	Management
G1: Abnormal cardiac biomarker testing, including abnormal ECG G2: Abnormal screening tests with mild symptoms G3: Moderately abnormal testing or symptoms with mild activity G4: Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions	All grades warrant work-up and intervention given potential for cardiac compromise Consider the following: For G1: Hold ICPi For G2, G3, and G4: Permanently discontinue ICPi For G1-G4: High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms) Admit patient, cardiology consultation Immediate transfer to a coronary care unit for patients with elevated troponin or conduction abnormalities In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin
Qualifying statement: Treatment recommendations are based on anecdotal evidence and the life-threatening nature of cardiovascular complications. The appropriateness of rechallenging remains unknown. Note that infliximab has been associated with heart failure and is contraindicated at high doses in patients with moderate-severe heart failure.	
9.2 Venous thromboembolism	
Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream. Clinical signs and symptoms are variable and may include pain, swelling, increased skin vein visibility, erythema, and cyanosis accompanied by unexplained fever for DVT and dyspnea, pleuritic pain, cough, wheezing, or hemoptysis for PE	
Diagnostic work-up Evaluation of signs and symptoms of PE or DVT may include Clinical prediction rule to stratify patients with suspected venous thromboembolism Venous ultrasound for suspected DVT CTPA for suspected PE Can also consider D-dimer for low-risk patients based on risk stratification by clinical prediction rule for DVT/PE when CT or Doppler are not available or appropriate Ventilation/perfusion scan is also an option when CTPA is not appropriate Consider other testing, including ECG, CXR, BNP and troponin levels, and arterial blood gas	

9.0 Cardiovascular Toxicities	
Grading	Management
G1: Venous thrombosis (e.g., superficial thrombosis)	Continue ICPi Warm compress Clinical surveillance
G2: Venous thrombosis (e.g., uncomplicated DVT), medical intervention indicated G3: Thrombosis (e.g., uncomplicated PE [venous], nonembolic cardiac mural [arterial] thrombus), medical intervention indicated	Hold ICPi until AE reverts back to G1 or less. If reverts to G2, use benefit-risk assessment for ICPi continuation Consider consult from cardiology or other relevant specialties LMWH is suggested over VKA, dabigatran, rivaroxaban apixaban, or edoxaban for initial and long-term treatment IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term
G4: Life-threatening (e.g., PE, cerebrovascular event, arterial insufficiency), hemodynamic or neurologic instability, urgent intervention indicated	Permanently discontinue ICPi Admit patient and management according to CHEST, ACC, and/or AHA guidelines and with guidance from cardiology Respiratory and hemodynamic support LMWH is suggested over VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial and long-term treatment IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term Further clinical management as indicated based on symptoms
Additional considerations While it may be impossible to determine the etiology of thromboembolic disease in patients with advanced cancer and the role, if any, that ICPi treatment plays, it is reasonable to remove the potential inciting agents given the severity and life-threatening potential of G4 complications. Clinicians are to use clinical judgment and take into account the risks and benefits when deciding whether to discontinue ICPi treatment. Anticoagulant therapy duration should continue for a minimum of 9-12 months to indefinitely in the setting of active cancer unless patient is asymptomatic, doing well, or in remission. All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: BNP, brain natriuretic peptide; CT, computed tomography; CTPA, computed tomography pulmonary angiography; CXR, chest x-ray; DVT, deep vein thrombosis; ECG, electrocardiogram; G, Grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; LMWH, low-molecular-weight heparin; MRI, magnetic resonance imaging; PE, pulmonary embolism; VKA, vitamin K agonist.

Table A10 Management of Ocular irAEs in Patients Treated With ICPis

10.0 Ocular Toxicities	
Counsel all patients to inform their health care provider immediately if they experience any of the following ocular symptoms Blurred vision Change in color vision Photophobia Distortion Scotomas Visual field changes Double vision Tenderness Pain with eye movement Eyelid swelling Proptosis	
Evaluation, under the guidance of ophthalmology Check vision in each eye separately Color vision Red reflex Pupil size, shape, and reactivity Fundoscopic examination Inspection of anterior part of eye with penlight	
Prior conditions Exclude patients with history of active uveitis History of recurrent uveitis requiring systemic immunosuppression or continuous local therapy Additional considerations Ocular irAEs are many times seen in the context of other organ irAEs High level of clinical suspicion as symptoms may not always be associated with severity Best to treat after ophthalmologist eye examination	
10.1 Uveitis/iritis	
Definition: Inflammation of the middle layer of the eye Diagnostic work-up: as per above	
Grading	Management
G1: Asymptomatic	Continue ICPi Refer to ophthalmology within 1 week Artificial tears
G2: Medical intervention required, anterior uveitis	Hold ICPi temporarily until after ophthalmology consult Urgent ophthalmology referral Topical corticosteroids, cycloplegic agents, systemic corticosteroids May resume ICPi treatment once off systemic corticosteroids, which are purely indicated for ocular adverse effects or once corticosteroids for other concurrent systemic irAEs are reduced to ≤ 10 mg; continued topical/ocular corticosteroids are permitted when resuming therapy to manage and minimize local toxicity Re-treat after return to G1 or less
G3: Posterior or panuveitis	Permanently discontinue ICPi Urgent ophthalmology referral. Systemic corticosteroids and intravitreal/periocular/topical corticosteroids
G4: 20/200 or worse	Permanently discontinue ICPi Emergent ophthalmology referral

10.0 Ocular Toxicities	
	Systemic corticosteroids (IV prednisone 1-2 mg/kg or methylprednisolone 0.8-1.6 mg/kg) and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion
Additional considerations: Consider use of infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment	
10.2 Episcleritis	
Definition: Inflammatory condition affecting the episcleral tissue between the conjunctiva and the sclera that occurs in the absence of an infection Diagnostic work-up: As per 10.0	
Grading	Management
G1: Asymptomatic	Continue ICPi Refer to ophthalmology within 1 week Artificial tears
G2: Vision 20/40 or better	Hold ICPi therapy temporarily until after ophthalmology consult Urgent ophthalmology referral Topical corticosteroids, cycloplegic agents, systemic corticosteroids
G3: Symptomatic and vision worse than 20/40	Permanently discontinue ICPi Urgent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents
G4: 20/200 or worse	Permanently discontinue ICPi Emergent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents
Additional considerations: Consider use of infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment	
10.3 Blepharitis	
Definition: Inflammation of the eyelid that affects the eyelashes or tear production Diagnostic work-up: As per 10.0	
Grading	Management
No formal grading system	Warm compresses and lubrication drops Continue therapy unless persistent and serious
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ICPi, immune checkpoint inhibitor; G, Grade; irAE, immune-related adverse event; IV, intravenous, TNF, tumor necrosis factor.

Appendix 6 Clinical Laboratory Tests

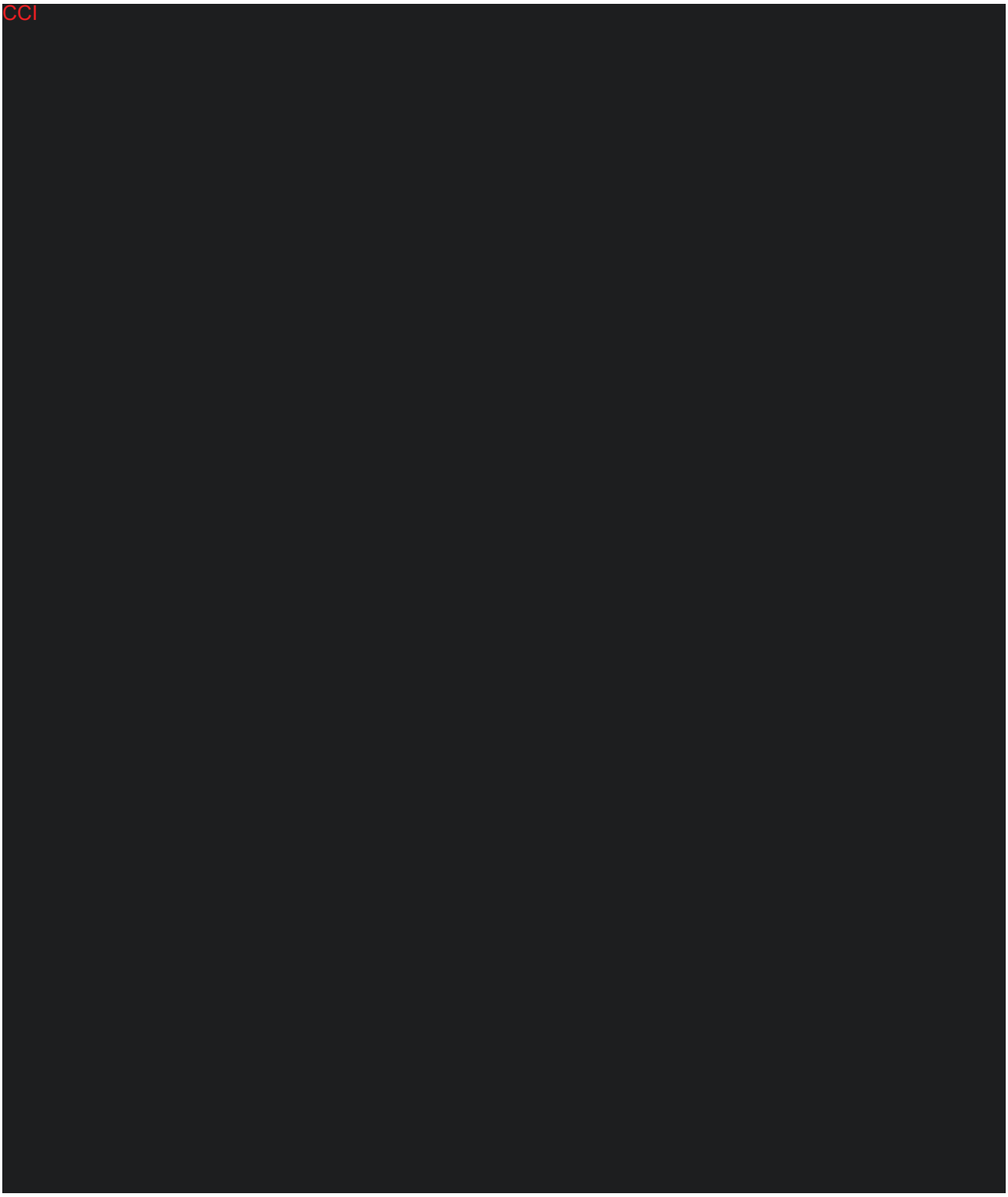
Laboratory Assessments	Parameters			
Hematology	Platelet count[d]		Mean Corpuscular Volume (MCV)	White blood cell (WBC) Count with Differential[d]: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Reticulocytes (%)		Mean corpuscular hemoglobin concentration (MCHC)	
	Hemoglobin[d]		Mean corpuscular hemoglobin (MCH)	
	Hematocrit		Activated partial thromboplastin time (aPTT)[a]	
	Red blood cell count[d]		Prothrombin time[a]	
	Absolute lymphocyte count[d]		International normalized ratio (INR)[a]	
	Absolute neutrophil count[d]			
Biochemistry	Blood Urea Nitrogen/Total urea	Potassium	Aspartate Aminotransferase[d]	Bilirubin (total, indirect/direct)[d]
	Creatinine[d]	Sodium	Alanine Aminotransferase[d]	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Tuberculin skin test, QuantiFERON-TB-Gold, or T-SPOT (for patients with active tuberculosis [as defined in Exclusion Criteria #5, Section 5.2], perform at baseline and as clinically indicated)
	Lipase	Chloride	Albumin	
	C-reactive protein	Amylase		
Full Urinalysis	Dipstick plus microscopic evaluation. Dipstick, including physical appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen, as locally available			
Other Tests	• FSH and estradiol (as needed if **not** a WOCBP only) • Serum or highly sensitive urine human chorionic gonadotropin (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]			

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

[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).

[c] Not required for all patients. Testing required for patients with known history of HIV.

[d] Results must be reviewed by the Investigator within 3 days prior to dosing.



Appendix 9 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

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

Definitions

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

Measurable Disease

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

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

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

Non-measurable Disease

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

Bone lesions:

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

considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

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

Target Lesions

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

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

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline

sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

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

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

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

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

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

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

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

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

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

RESPONSE CRITERIA

Evaluation of Target Lesions

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

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

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

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

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

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at Baseline should have their actual measurements recorded at each

subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at Baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

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

Evaluation of Non-target Lesions

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

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

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

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

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

When the participant has only non-measurable disease. This circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concept applies here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing participants for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the participant should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

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

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

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

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

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

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

Evaluation of Best Overall Response

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

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

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

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

Note:

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

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

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

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

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

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

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In non-randomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure the responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies. However, in all other circumstances, i.e., in randomized studies (Phase II or III) or studies where SD or progression are the primary endpoints,

confirmation of response is not required since it will not add value to the interpretation of the study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

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

Duration of Overall Response

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

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

Duration of Stable Disease

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

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

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

Appendix 10 Protocol Amendment History

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

Protocol Version 2.0 (23-June-2020)

This amendment was 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 protocol was amended to incorporate the main changes to specify and enroll a more homogeneous population (inclusion criterion #2), add contingency plan for the possibility of continued enrollment in China to meet local requirements (if needed), and to reflect the change in patient interview approach to exit interviews only, therewith incorporating regulatory feedback obtained.

Section # and Name	Description of Change	Brief Rationale
Title Page 6.1 Study Intervention(s) Administration, Table 4 Study Intervention 7.3 Lost to Follow-Up 8 Study Assessments and Procedures 8.5 Pharmacokinetics CCI [redacted] 8.10 Immunogenicity Assessments 9.4.3 Other Analyses Appendix 2 Study Governance Appendix 10 Protocol Amendment History	Added text or modified the previous text.	To update wording to be consistent with current Sponsor protocol template (version 14).
1.1 Synopsis 1.2 Schema 4.1 Overall Design 4.4 End of Study Definition CCI [redacted] 9.3 Populations for Analyses	Description of study sample size includes allowance for further enrollment in China if the final global enrollment does not achieve the intended 15% of participants enrolled in China.	This allowance for additional enrollment in China beyond the end of global enrollment (if needed) is intended to satisfy local regulatory requirements.
1.2 Schema 4.1 Overall Design	Added details about the enrollment in the study and determinations to limit enrollment in certain countries and/or regions.	To obtain a study population representative of global standard of care, including prior bevicuzimab treatment, and representative enrollment across the participating global regions.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities and throughout the protocol, as applicable	CCI	
	Updated note for CCI) and blood sample for ADA.	To update the collection time to within 4 hours prior to study intervention infusion.
CCI Appendix 2 Study Governance	CCI	
4.4 End of Study Definition	Description of end of study includes allowance for further enrollment in China.	This allowance for additional enrollment in China beyond the end of global enrollment (if needed) is intended to satisfy local regulatory requirements.
5.1 Inclusion Criterion #2	The patient population for enrollment was modified to specify patients with prior platinum as adjuvant or neo-adjuvant treatment should have disease progression or recurrence within 6 months. Also, patients who previously only received platinum as a radiosensitizer are not eligible.	This change is intended to provide a more homogeneous patient population and incorporates regulatory feedback received for this study.
5.1 Inclusion Criterion #9a	Added text as per the FDA guidance document & American Gastroenterological Association (AGA) guidance for HIV/HBV/HCV.	To clarify the treatment of participants infected with HBV at study entry.
5.4 Screen Failures	Added information about the Screening period extension.	To clarify that the Screening extension will be allowed as long as all Screening parameters will have been collected within 28 days from first study intervention.
6.9.2 Immune-related Adverse Events 6.9.3 Skin Adverse Events	Added definition of which AEs are considered AESIs.	To provide clarification for the Investigator.
CCI	Added details about definition of SD.	To provide clarification on the SD criteria that measurements must meet.
8.2.2 Vital Signs	Updated vital signs measurements.	To add seated position.
9.3 Populations for Analyses	Updated Table 11 Analysis Populations.	To replace ITT with FAS.

Section # and Name	Description of Change	Brief Rationale
9.4.4 Sequence of Analyses	Adjustment for the estimation of the timelines for the final analysis and additional analyses for the potential to continue enrollment to achieve the desired 15% of study population enrolled in China.	This allowance for additional enrollment in China beyond the end of global enrollment (if needed) is intended to satisfy local regulatory requirements.
Appendix 2 Study Governance	Added additional text or modified the previous text.	Modifications based on changes to protocol template version 14 and updates based on regional requirements.
Appendix 9 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1	Addition of RECIST 1.1 as an Appendix.	For consistency across the development program.
Appendix 12 Coordinating Investigator Signature Page Title page	Updated to be consistent with the current information.	Administrative update.
Throughout the protocol	Minor editorial and formatting revisions; correction of minor typographical errors.	To make minor revisions for correctness, readability, consistency of language across the bintrafusp alfa development program, and for compliance with current Sponsor guidelines.

Appendix 11 Sponsor Signature Page

Study Title:	A Phase II, Multicenter, Open Label Study of Bintrafusp alfa (M7824) Monotherapy in Participants with Advanced, Unresectable Cervical Cancer with Disease Progression During or After Platinum-Containing Chemotherapy
Regulatory Agency Identifying Numbers:	CCI [redacted], EudraCT: 2019-003583-40
Clinical Study Protocol Version:	22 June 2021/Version 3.0

I approve the design of the clinical study:

_____ _____

Signature Date of Signature

PPD [redacted]

Appendix 12 Coordinating Investigator Signature Page

Study Title:	A Phase II, Multicenter, Open Label Study of Bintrafusp alfa (M7824) Monotherapy in Participants with Advanced, Unresectable Cervical Cancer with Disease Progression During or After Platinum-Containing Chemotherapy
Regulatory Agency Identifying Numbers:	CCI [redacted] EudraCT: 2019-003583-40
Clinical Study Protocol Version:	22 June 2021/Version 3.0
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 applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

PPD

Appendix 13 Principal Investigator Signature Page

Study Title:	A Phase II, Multicenter, Open Label Study of Bintrafusp alfa (M7824) Monotherapy in Participants with Advanced, Unresectable Cervical Cancer with Disease Progression During or After Platinum-Containing Chemotherapy
Regulatory Agency Identifying Numbers:	CCI [redacted], EudraCT: 2019-003583-40
Clinical Study Protocol Version:	22 June 2021/Version 3.0
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: