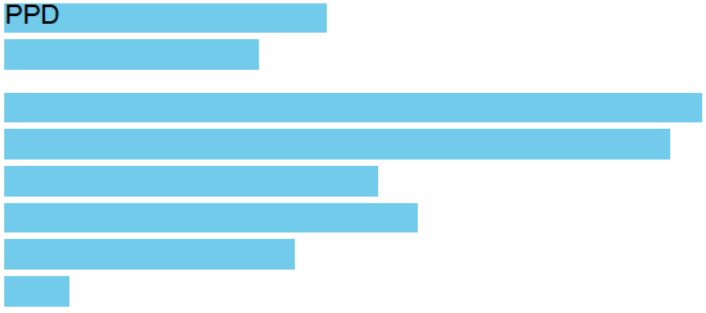
Clinical Study Protocol

Title Page

Clinical Study Protocol Title	Phase I, First-in-Human, Open-Label, Multiple Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M6223 (an Inhibitor of TIGIT) as Single Agent and in Combination with Bintrafusp alfa (anti-PD-L1/ TGFβ Trap) in Participants with Metastatic or Locally Advanced Solid Unresectable Tumors
Study Number:	MS201430_0001
Protocol Version:	01 December 2021/Version 3.0
Merck Compound Number:	M6223
Study Phase:	I
Short Title:	First-In-Human Study of M6223
Coordinating or Principal Investigator:	PPD 

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Regulatory Agency Identifying Numbers:	ClinicalTrials.gov Identifier: NCT04457778 IND: PPD
Keywords:	Immunotherapy, antibody

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	14-Aug-2019
2.0	Protocol Amendment	03-Feb-2021
3.0	Protocol Amendment	01-Dec-2021

Protocol Version 3.0 (01-December-2021)

Overall Rationale for the Amendment

The key purpose of this amendment is to update the risk classification and management of selected risks and adverse events related to bintrafusp alfa, to replace investigation of a Q3W dosing regimen with M6223 in combination with bintrafusp alfa with Q3W dosing of M6223 monotherapy, and to increase the opportunity to obtain paired biopsies.

Section # and Name	Description of Change	Brief Rationale
1.1 (Synopsis) 1.2 (Schema) 1.3 (Schedule of Activities) 3 (Objectives and Endpoints) 4.1 (Overall Design) 4.2 (Scientific Rationale for Study Design) 4.3.2 (Combination with Bintrafusp alfa) 6.1 (Study Interventions) 6.6.1.2.2 (Part 1 B: Dose Escalation of M6223 Combined with Bintrafusp alfa) CCI [redacted] Appendix 8 (Description of the Bayesian Dose Escalation Model)	Removed information and objectives related to the combination of M6223 with bintrafusp alfa at the Q3W dosing schedule in Part 1B of the study.	The M6223 in combination with bintrafusp alfa at the Q3W dosing schedule arm in Part B of the study will not be enrolled due to changes in program strategy.
1.1 (Synopsis) 1.2 (Schema) 1.3 (Schedule of Activities) 3 (Objectives and Endpoints) 4.1 (Overall Design) 5.1 (Inclusion Criteria) CCI [redacted] Appendix 8 (Description of the Bayesian Dose Escalation Model)	Added the additional dosing schedule of M6223 monotherapy Q3W and the corresponding recommended dose for expansion (RDE) cohorts to Part 1A. Specified that paired biopsies at Screening and on treatment are mandatory for participants in the M6223 monotherapy Q3W cohort.	To pursue Q3W dosing as M6223 monotherapy (rather than as combination therapy with bintrafusp alfa).

Section # and Name	Description of Change	Brief Rationale
1.1 (Synopsis) 4.3.1 (Monotherapy Dose Escalation M6223) 6.6.1.2.1 (M6223 Monotherapy Dose Escalation)	Clarified the highest dose in the M6223 monotherapy Q3W regimen.	Changes made to more clearly align with description of dose escalation procedure elsewhere throughout protocol.
1.3 (Schedule of Activities)	In Table 2, added hematological assessment in M6223 monotherapy Q3W, Cycle 2 Day 15. Corrected the time of EOI ECG assessment and EOI and post infusion PK in Table 5 (from C2D8 to C2D1). Clarified that physical examinations do not need to be repeated on Cycle 1 Day 1 if they were performed within 3 days prior to Day 1. Clarified in Table 1 that biopsies in C2D1 are obtained predose.	To ensure adequate safety monitoring for anemia in the M6223 monotherapy Q3W regimen. To correct the error that EOI ECG assessment and EOI and post infusion PK was to be carried out on C2D8, a noninfusion day, instead of C2D1. To avoid misunderstanding of the timing of physical examinations in Cycle 1. To provide clearer wording and ensure consistency between Table 1, Table 2, and Table 3, as all biopsies were obtained predose since the protocol inception.
4.4 (End of Study Definition)	Clarified definition of end of study. The end of the study is defined as the date of the last participant having finished 12 months of treatment and 90-day safety follow-up.	To provide clearer wording about the definition of end of study.
1.2 (Schema) 4.1 (Overall Design) CCI [redacted] 6.6.1.4 (Safety Monitoring Committee)	Added backfill cohort to the Schema. Updated number of participants in the backfill cohort to up to 8 at M6223 monotherapy dose levels 900 mg and 1600 mg and allow to continue with recruitment after dose escalation completed. Added that the SMC will convene after all participants in the backfill cohort have completed the DLT observation period.	To ensure adequate number of paired biopsies for meaningful exploratory biomarker analysis. To ensure that the full data from participants in the backfill cohort are analyzed by the SMC.
2.2 (Background)	Updated clinical data and status of the bintrafusp alfa development program.	To include additional safety data and recent changes in the bintrafusp alfa program that are relevant to the M6223 FIH study.
2.3.2 (Benefit/Risk Assessment of Bintrafusp alfa) 6.9.1 (Adverse Events of Special Interest) 6.9.1.4 (Adverse Events of Special Interest for Bintrafusp Alfa) 6.9.2 (Additional Identified and Potential Risks)	Updated categorization of risks related to bintrafusp alfa, added anemia and bleeding adverse events as risks, and updated risks of TGFβ inhibition mediated skin reactions and impaired wound healing. Updated information on risk and mitigations measures.	These changes were made to align with bintrafusp alfa IB v7.0 (05-Apr-21) and the ongoing bintrafusp alfa program.

Section # and Name	Description of Change	Brief Rationale
6.6.2 (Dose Modifications) 6.8.5 (Anemia) 6.9.1.4.2 (Anemia)	Updated management of risk of anemia, which is an AE associated with bintrafusp alfa, including dose reductions of bintrafusp alfa.	These changes are based on safety finding presented in the bintrafusp alfa IB v7.0 (05-Apr-21) and mitigation activities generally applied in the ongoing bintrafusp alfa program.
6.6.2 (Dose Modifications) 6.9.1.4.3 (Bleeding Adverse Events) 6.9.3 (Adverse Drug Reactions Requiring Treatment Discontinuation)	Updated management of risk of bleeding, which is an AE associated with bintrafusp alfa, including dose reductions of bintrafusp alfa.	These changes are based on safety finding presented in the bintrafusp alfa IB version 7.0 (05-Apr-21) and mitigation activities generally applied in the ongoing BA program.
6.8.4 (TGFβ Inhibition Mediated Skin Reactions) 6.9.1.4.1 (TGFβ Inhibition Mediated Skin Reactions)	Updated management of AE associated with TGFβ inhibition mediated skin reactions, which is an AE associated with bintrafusp alfa.	Based on safety finding presented in the bintrafusp alfa IB version 7.0 (05-Apr-21) and mitigation activities generally applied in the ongoing bintrafusp alfa program.
6.8 (Special Precautions) 6.9 (Management of Adverse Events of Special Interest, Identified and Potential Risks, and Adverse Drug Reactions)	Relocated some subsections in Section 6.8 (Special Precautions) to Section 6.9 (Management of Adverse Events of Special Interest, Identified and Potential Risks, and Adverse Drug Reactions).	To provide a clearer, more appropriate, organization of content across higher level sections.
8.3.4 (Regulatory Reporting Requirements for Serious Adverse Events) Appendix 4 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting)	Clarified reporting requirements for the Investigator as well as reporting through an Electronic Data Capture (EDC) system.	To provide clearer guidance to the Investigator regarding reporting requirements.
Appendix 12 (Sponsor Signature Page)	Changed Medical Responsible.	To update with the current Medical Responsible.
Throughout	Made minor editorial and document formatting revisions, including renumbering of Sections and Tables.	These changes are minor; therefore, they have not been summarized.

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

Phase I, First-in-Human, Open-Label, Multiple Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M6223 (an Inhibitor of TIGIT) as Single Agent and in Combination with Bintrafusp alfa (Anti-Programmed Death Ligand 1 [anti-PD-L1]/TGFβ Trap) in Participants with Metastatic or Locally Advanced Solid Unresectable Tumors.

Short Title:

First-in-human study of M6223.

Rationale:

The administration of M6223 as monotherapy escalation or combined escalation with bintrafusp alfa to participants who have histologically or cytologically proven locally advanced or advanced solid malignancies and who are refractory to or have progressed under standard treatment and have no other treatment options known to confer clinical benefit, is proposed based on the following information:

- M6223 is a monoclonal antibody binding to TIGIT and blocking its interactions with its ligands CD112 and CD155, thereby inhibiting TIGIT-related immunosuppressive pathway
- M6223 can also interrupt the interaction of TIGIT with the co-stimulatory receptor CD226, leading to increased CD226 dimerization and co-stimulatory signaling
- Preclinical models demonstrated that M6223 has antitumor activity and confers immunologic memory to tumor rechallenge in mice who survived the initial tumor exposure
- The pharmacodynamics (Pd) of M6223 were preclinically demonstrated by investigation of tumor-infiltrating leukocytes: M6223 treatment was associated with the significantly increasing ratio of the expression of CD226 to TIGIT on infiltrated T cells and natural killer (NK) cells, and increased the ratio of CD8+ T cells to Tregs in the tumor
- Clinical experience with this class of agents described in the literature suggests an acceptable safety profile as single agent and no excess toxicity in combination with programmed death-1 (PD-1)-targeting immune checkpoint inhibitors. Furthermore, initial evidence of clinical antitumor activity of TIGIT antibodies in solid tumors in monotherapy and in combination with anti-PD-1 has been provided
- The antitumor effects of M6223 were synergistically enhanced by co-administration of M6223 with bintrafusp alfa in syngeneic tumor models in TIGIT knock-in mice. Additionally, bintrafusp alfa is differentiated from other agents with anti-programmed death ligand 1 (PD-L1) activity that are already under development in combination with an anti-TIGIT because it targets both PD-1/(L1) and TGFβ immune suppressive pathways.

Objectives and Endpoints:

Objectives	Endpoints
PRIMARY	
To determine safety and tolerability and (if observed) the maximum tolerated doses (MTD) of M6223 as a single agent (Part 1A) for both the Q2W and Q3W regimens and of M6223 combined with bintrafusp alfa (Part 1B) for the Q2W regimen in participants with advanced solid tumors who are refractory to or have progressed under standard treatment and have no other treatment options known to confer clinical benefit.	Occurrence of DLTs during the first 4 weeks (Day 1 to Day 28) of study intervention. Occurrence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events. Incidence, nature, and severity of TEAEs and deaths, including cause of death, from Screening up to the 30 days Safety Follow-up Visit. Changes (from start of treatment until 30 days after end of treatment) in clinical laboratory measures from baseline, safety ECGs measures, vital signs, ECOG performance status.
To determine the recommended doses of M6223 monotherapy (Part 1A) for both the Q2W and Q3W regimens and of M6223 combined with bintrafusp alfa (Part 1B) for the Q2W regimen for further exploratory clinical development.	Primary endpoints (see above) and available data for secondary and exploratory endpoints (see below).
SECONDARY	
To characterize the PK profile of M6223 when given alone (Part 1A) or when combined with bintrafusp alfa (Part 1B).	PK parameters of M6223 in terms of AUC_{0-t}, $AUC_{0-\infty}$, AUC_T, C_{max}, C_{trough}, t_{max}, $t_{1/2}$ and λ_z (Part 1A and Part 1B) on Day 1 of Treatment of Cycle 1, 2 and 4 from time zero to 14 (Q2W) or 21 (Q3W) days postdose.
To characterize the PK of bintrafusp alfa in combination with M6223 (Part 1B) by sparse sampling.	PK parameters of bintrafusp alfa in terms of C_{max} and C_{trough} on Day 1 of Treatment of Cycle 1 and 4 from time zero to 14 days postdose.
To characterize immunogenicity of M6223 when given alone and immunogenicity of M6223 and bintrafusp alfa when given in combination and its relationship to drug exposure.	Immunogenicity of M6223 (Part 1A and Part 1B) and bintrafusp alfa (Part 1B), as measured by anti-drug antibody (ADA) assays, from predose of Cycle 1 Day 1 through 30 days safety follow-up Visit.
To characterize the relationship between exposure and QT interval of M6223 alone and in combination with bintrafusp alfa.	QT interval from Cycle 1 to Cycle 7.
To characterize preliminary clinical activity parameters of M6223 in monotherapy (Part 1A) and in combination with bintrafusp alfa (Part 1B) using RECIST v1.1.	OR, DOR, time to response, disease control (DC), progression-free survival (PFS) using RECIST v1.1, per Investigator, and overall survival (OS).

Overall Design:

This is a First-in-Human open-label, multicenter, Phase I study designed to determine the safety, tolerability, pharmacokinetics (PK), Pd, and preliminary antitumor activity of M6223 as monotherapy (Part 1A) and in combination with bintrafusp alfa (Part 1B).

Number of Participants:

This is a dose-escalation study and the total sample size will depend on the number of cohorts to be evaluated and cannot be predefined. It is expected that approximately 17 to 26 participants will be enrolled in Part 1A Q2W (based on 6-7 dose levels planned). In the Q3W regimen, it is expected that 1 dose level will be tested in 2 cohorts (approximately 6 participants). In addition to the planned dose levels, up to 8 participants will be enrolled in the M6223 monotherapy Q2W backfill

cohort with mandatory paired biopsies to collect a sufficient number of tumor samples for a meaningful Pd characterization of M6223 effect on tumor microenvironment.

The total sample size for Part 1A is expected to be 40.

For Part 1B, the combination escalation, it is expected that about 3 dose levels will need to be tested in the Q2W regimen and the estimated sample size for this including the recommended dose for expansion (RDE) confirmation will be 12 to 15 participants.

Study Intervention Groups and Duration:

The target population of Part 1 is participants who have histologically or cytologically proven locally advanced or advanced solid malignancies and who are refractory to or have progressed under standard treatment and have no other treatment options known to confer clinical benefit. In each part of the study, study intervention will be administered in sequential cohorts investigating M6223 or M6223 combined with bintrafusp alfa at dose levels as guided by the Safety Monitoring Committee (SMC).

Part 1A: Monotherapy dose escalation with M6223

M6223 monotherapy dose escalation will start at a dose of 10 mg M6223 intravenous (IV) every 2 weeks (Q2W). Dose escalation of M6223 (Part 1A) will proceed according to the recommendation of the SMC to at least 1600 mg, unless the MTD has been reached earlier or there is excess of PK nonlinearity, or the SMC recommends to stop further dose escalation following review of safety, tolerability, PK and Pd results. Depending on the observed toxicity profile and available PK and Pd, a dose regimen different to or dose(s) higher/lower than the prespecified doses may be tested. Decision making by the SMC will be supported by a Bayesian 2-parameter logistic regression model.

Testing of a Q3W regimen is also planned. The SMC will recommend the M6223 dose(s) to be tested in Part 1A for the Q3W regimen considering the safety, PK and Pd data available from the Q2W regimen. The starting dose of M6223 for the Q3W regimen will not be more than 50% higher than the highest M6223 Q2W tested and considered acceptable by the SMC at this time. The SMC may decide to test additional cohorts at the same or other (lower or higher) doses in the Q3W regimen depending on the safety, PK and Pd observed. Paired biopsies are mandatory for participants in the Q3W regimen.

Backfill Cohort

Additional up to 8 participants with mandatory paired (at Screening and on treatment) biopsies will be enrolled at 900 mg Q2W M6223 and 1600 mg Q2W M6223 to evaluate the functional Pd effect of M6223 in the tumor microenvironment and PK/Pd relationship to inform the selection of the potential RDE(s).

Part 1B: Dose escalation of M6223 in combination with Bintrafusp alfa

The SMC will recommend the starting dose of M6223 for Part 1B for the Q2W regimen, which cannot be higher than the highest tolerable dose of M6223 in Part 1A of the study at the time

Part 1B is started. Part 1B can only start after safety data of at least 2 different dose levels of Part 1A are available. Part 1A may still be ongoing when Part 1B is started.

The SMC may decide to test additional cohorts at the same or other (lower or higher) doses in the Q2W combination regimen depending on the safety, PK and Pd observed.

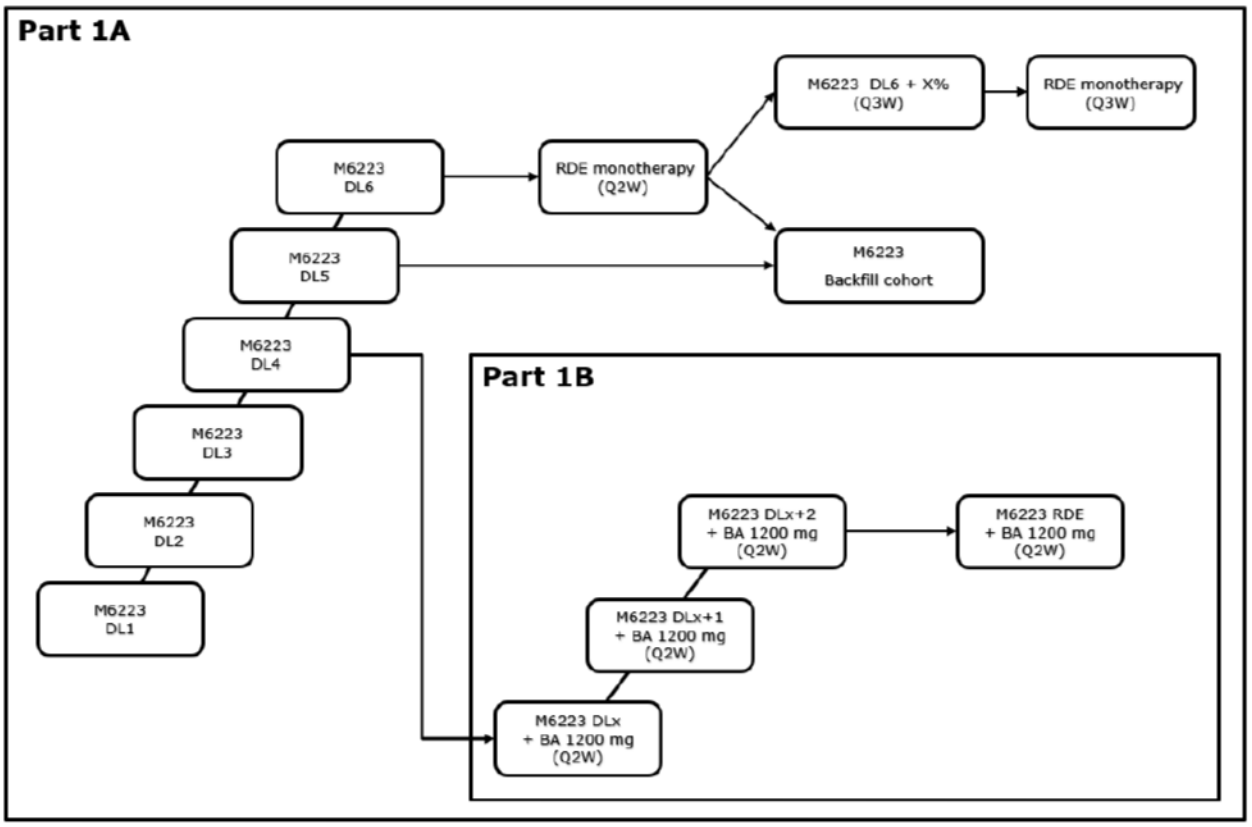
The study will include a screening period of up to 28 days, a treatment period consisting of administrations of M6223 either as single agent (Part 1A) or combined with bintrafusp alfa (Part 1B), End of Treatment (EoT) Visit up to 7 days after the decision to stop study intervention, and a Safety Follow-up period including a visit at 30 ± 5 days and at 90 ± 2 weeks (as a phone call) after the last M6223 or bintrafusp alfa administration as applicable. The EoT Visit should take place within 7 days after last study intervention (M6223 or bintrafusp alfa) but before the start of subsequent anticancer treatment. During long-term follow-up, participants will be followed every 3 months for documentation of subsequent anticancer therapy until end of study.

Involvement of Special Committee(s):

A SMC will make recommendations on dosing during the dose escalation and after the parallel backfill cohort has completed the DLT period (see Section 4.4). Exploratory expansion cohorts may be added by protocol amendment in order to investigate M6223 in monotherapy or in combination regimens.

1.2 Schema

Figure 1 **Schematic of Dose Escalation with M6223 Alone (Part 1A) and Dose Escalation with M6223 in Combination with Bintrafusp alfa (also designated as M7824, Part 1B)**



BA = Bintrafusp alfa, DL = Dose level, DLX = Dose level to be defined, Q2W = Every 2 weeks, Q3W = Every 3 weeks, RDE = Recommended dose for expansion.

The study will comprise 2 parts: Part 1A, dose escalation with M6223 monotherapy and Part 1B, dose escalation of M6223 combined with bintrafusp alfa (formerly M7824). The starting dose of M6223 and other details of the overall study design (including backfill of cohorts) are further detailed in Section 4.1.

1.3 Schedule of Activities

1.3.1 M6223 Monotherapy Dose Escalation (Part 1A)

For schedule related to electrocardiogram (ECG) assessment and blood sampling for pharmacokinetics (PK), anti-drug antibody (ADA), pharmacodynamics (Pd), biomarker and pharmacogenomics (PGx), see Table 4 and Table 5. Note that there are additional visits at Cycles 10, 13, and every 6 cycles after Cycle 13 for blood sampling and ECG assessment (Table 4 and Table 5).

Table 1 Schedule of Activities for M6223 Monotherapy Part 1 Dose Escalation (every 2 weeks)

Assessments and Procedures	Screening	Intervention Period (2-week cycles)				EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5		Cycles 2, 4, 6	Cycles ≥ 7					
Day	**-28 to -1**	**1**	**8 (C1 only)**	**1**	**1**	**EoT**	**FU1 Last dose + 30 Days**	**FU2 Last dose + 90 Days**	**Every 3 months**	**Additional visits are conducted for blood sampling only. See Table 4**
Visit window (days)		**(± 1)**	**(± 1)**	**(± 1)**	**(± 3)**	**(+ 7)**	**(± 5)**	**(± 14)**	**(± 7)**	**EoT within 7 days of decision to discontinue but before start of subsequent anticancer treatment**
M6223 Administration		X		X	X					
Informed consent	X									
Inclusion and Exclusion criteria	X									In- and exclusion criteria will be reviewed during Screening and need to be still met prior to initial dosing on Cycle 1 Day 1.
Demography	X									
Medical and disease history (includes substance usage)	X									Substances: drugs including anticancer medication If available, collection of historical CT/MRI scans up to 100 days prior to enrollment (Section 8.1).
HBV, HCV, HIV testing (if applicable)	X									HIV testing according to country policy.

Assessments and Procedures	Screening	Intervention Period (2-week cycles)				EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5		Cycles 2, 4, 6	Cycles ≥ 7					
Day	**-28 to -1**	**1**	**8 (C1 only)**	**1**	**1**	**EoT**	**FU1 Last dose + 30 Days**	**FU2 Last dose + 90 Days**	**Every 3 months**	**Additional visits are conducted for blood sampling only. See** Table 4
Physical examination with height & weight	X	X	X	X	X	X	X			Collect height at Screening only. Full examination at Screening and EoT. Symptom-oriented examination at other visits. If Screening physical examination is done within 3 days of Cycle 1 Day 1, it does not have to be repeated at Cycle 1 Day 1. **Also, Day 2 and Day 5 of Cycle 1**.
ECOG PS	X	X		X	X	X	X			If the Day 1 ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Day 1 (unless the Investigator notices a decline that would exclude the participants from study participation).

Assessments and Procedures	Screening	Intervention Period (2-week cycles)				EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5		Cycles 2, 4, 6	Cycles ≥ 7					
Day	**-28 to -1**	**1**	**8 (C1 only)**	**1**	**1**	**EoT**	**FU1 Last dose + 30 Days**	**FU2 Last dose + 90 Days**	**Every 3 months**	**Additional visits are conducted for blood sampling only. See Table 4**
Serum/urine pregnancy test (WOCBP only)	X	X		X	X		X			Serum β-HCG at Screening and Day 1 of each Cycle (1 to 7) and every even cycle thereafter; urine β-HCG thereafter for WOCBP. Results of most recent pregnancy test should be available at every cycle prior to administration of study intervention.
Core chemistry			X	X	Every even cycle					Day 8 on Cycle 1 only. See Table 18 for individual tests in each laboratory panel. Blood samples must be drawn and results to be reviewed within 48 hours prior to dose administration.
Full serum chemistry Panel A	X	X			Every uneven cycle	X	X			See Notes for Core Chemistry.
Full serum chemistry Panel B	X									See Notes for Core Chemistry.
Hematology and Hemostaseology	X	X	X	X	X	X	X			
T4 and TSH	X			X*	Every 4 cycles	X				*Start at Cycle 4 and every 4 cycles after.
Urinalysis	X			X*	Every 4 cycles	X				*And every fourth cycle after Cycle 6.

Assessments and Procedures	Screening	Intervention Period (2-week cycles)				EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5		Cycles 2, 4, 6	Cycles ≥ 7					
Day	**-28 to -1**	**1**	**8 (C1 only)**	**1**	**1**	**EoT**	**FU1 Last dose + 30 Days**	**FU2 Last dose + 90 Days**	**Every 3 months**	**Additional visits are conducted for blood sampling only. See** Table 4
Vital signs	X	X	X	X	X	X	X			See Section 8.2.2. **Also, Day 2 and Day 5 of Cycle 1.**
AE & SAE Review	X	X	X	X	X	X	X	X		**Also, Day 2 and Day 5 of Cycle 1.**
Concomitant Medication Review	X	X	X	X	X	X	X	X		**Also, Day 2 and Day 5 of Cycle 1.**
Tumor biopsy or archived surgical specimen	X			X*						See Biomarker Section 8.8. * An on-treatment biopsy at Cycle 2 Day 1 (predose) is not mandatory, but highly recommended. **For participants in the backfill cohort, however, biopsies at Screening and at Cycle 2 Day 1 (predose) are mandatory.**

Assessments and Procedures	Screening	Intervention Period (2-week cycles)				EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5		Cycles 2, 4, 6	Cycles ≥ 7					
Day	**-28 to -1**	**1**	**8 (C1 only)**	**1**	**1**	**EoT**	**FU1 Last dose + 30 Days**	**FU2 Last dose + 90 Days**	**Every 3 months**	**Additional visits are conducted for blood sampling only. See** Table 4
Tumor assessment	X			X*	Every 8 weeks*		Every 8 weeks	Every 8 weeks	Every 8 weeks	* Start at Cycle 4 and every 8 weeks after (± 3 days). Tumor assessment schedule is independent of treatment delays. If available, collection of historical CT/MRI scans up to 100 days prior to enrollment. See Section 8.1.
Subsequent anticancer treatment							X	X	X	

AE=adverse event, β-HCG=beta-human chorionic gonadotropin, C1=Cycle 1, CT=computed tomography, ECOG PS= Eastern Cooperative Oncology Group Performance status, EoT=End of Treatment Visit, FU=Follow-up Visit; HBV=Hepatitis B virus, HCV=Hepatitis C virus, HIV=Human immunodeficiency virus, MRI=magnetic resonance imaging, SAE=serious adverse event, T4=free thyroxine, TSH=thyroid-stimulating hormone, WOCBP=women of childbearing potential.

Table 2 Schedule of Activities for M6223 Monotherapy Part 1 Dose Escalation (every 3 weeks)

Assessments and Procedures	Screening	Intervention (3-week cycles)							EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5			Cycles 2, 4, 6			Cycles ≥ 7					
Day	-28 to -1	1	8 (C1 only)	15 (C1 only)	1	8 (C2 only)	15 (C2 only)	1	EoT	FU1 Last dose + 30 Days	FU2 Last dose + 90 Days	Every 3 months	Additional visits are conducted for blood sampling only. See Table 5.
Visit window (days)		(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 3)	(+ 7)	(± 5)	(± 14)	(±7)	EoT within 7 days of decision to discontinue but before start of subsequent anticancer treatment.
M6223 Administration		X			X			X					
Informed consent	X												
Inclusion and Exclusion Criteria	X												In- and exclusion criteria will be reviewed during Screening and need to be still met prior to initial dosing on Cycle 1 Day 1.
Demography	X												

Assessments and Procedures	Screening	Intervention (3-week cycles)							EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5			Cycles 2, 4, 6			Cycles ≥ 7					
Day	**-28 to -1**	**1**	**8 (C1 only)**	**15 (C1 only)**	**1**	**8 (C2 only)**	**15 (C2 only)**	**1**	**EoT**	**FU1 Last dose + 30 Days**	**FU2 Last dose + 90 Days**	**Every 3 months**	**Additional visits are conducted for blood sampling only. See Table 5.**
Medical and disease history (includes substance usage)	X												Substances: drugs including anticancer medication. If available, collection of historical CT/MRI scans up to 100 days prior to enrollment (see Section 8.1)
HBV, HCV, HIV testing (if applicable)	X												HIV testing according to country policy.

Assessments and Procedures	Screening	Intervention (3-week cycles)							EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5			Cycles 2, 4, 6			Cycles ≥ 7					
Day	**-28 to -1**	**1**	**8 (C1 only)**	**15 (C1 only)**	**1**	**8 (C2 only)**	**15 (C2 only)**	**1**	**EoT**	**FU1 Last dose + 30 Days**	**FU2 Last dose + 90 Days**	**Every 3 months**	**Additional visits are conducted for blood sampling only. See Table 5.**
Physical examination with height & weight	X	X	X	X	X	X	X	X	X	X			Collect height at Screening only. Full examination at Screening and EoT. Symptom-oriented examination at other visits. If screening physical examination is done within 3 days of Cycle 1 Day 1, it does not have to be repeated at Cycle 1 Day 1. **Also, Day 2 and Day 5 of Cycle 1**

Assessments and Procedures	Screening	Intervention (3-week cycles)							EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5			Cycles 2, 4, 6			Cycles ≥ 7					
Day	**-28 to -1**	**1**	**8 (C1 only)**	**15 (C1 only)**	**1**	**8 (C2 only)**	**15 (C2 only)**	**1**	**EoT**	**FU1 Last dose + 30 Days**	**FU2 Last dose + 90 Days**	**Every 3 months**	**Additional visits are conducted for blood sampling only. See Table 5.**
ECOG PS	X	X			X	X		X	X				If the Day 1 ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Day 1 (unless the Investigator notices a decline that would exclude the participants from study participation).

Assessments and Procedures	Screening	Intervention (3-week cycles)							EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5			Cycles 2, 4, 6			Cycles ≥ 7					
Day	**-28 to -1**	**1**	**8 (C1 only)**	**15 (C1 only)**	**1**	**8 (C2 only)**	**15 (C2 only)**	**1**	**EoT**	**FU1 Last dose + 30 Days**	**FU2 Last dose + 90 Days**	**Every 3 months**	**Additional visits are conducted for blood sampling only. See Table 5.**
Serum/urine pregnancy test (WOCBP only)	X	X			X			X		X			Serum β-HCG at Screening and Day 1 of each Cycle (1 to 7) and every even cycle thereafter; urine β-HCG thereafter for WOCBP. Results of most recent pregnancy test should be available at every cycle prior to administration of study intervention.

Assessments and Procedures	Screening	Intervention (3-week cycles)							EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5			Cycles 2, 4, 6			Cycles ≥ 7					
Day	**-28 to -1**	**1**	**8 (C1 only)**	**15 (C1 only)**	**1**	**8 (C2 only)**	**15 (C2 only)**	**1**	**EoT**	**FU1 Last dose + 30 Days**	**FU2 Last dose + 90 Days**	**Every 3 months**	**Additional visits are conducted for blood sampling only. See Table 5.**
Core chemistry			X	X	X			Every even cycle					Day 8 on Cycle 1 only. See Table 18 for individual tests in each laboratory panel. Blood samples must be drawn and results to be reviewed within 48 hours prior to dose administration.
Full serum chemistry Panel A	X	X				X		Every uneven cycle	X	X			See Notes for Core Chemistry.
Full serum chemistry Panel B	X												See Notes for Core Chemistry.
Hematology and Hemostaseology	X	X	X	X	X	X	X	X	X	X			
T4 and TSH	X	X*						Every 3 cycles	X				*Start at Cycle 3 and every 3 cycles after.

Assessments and Procedures	Screening	Intervention (3-week cycles)							EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5			Cycles 2, 4, 6			Cycles ≥ 7					
Day	**-28 to -1**	**1**	**8 (C1 only)**	**15 (C1 only)**	**1**	**8 (C2 only)**	**15 (C2 only)**	**1**	**EoT**	**FU1 Last dose + 30 Days**	**FU2 Last dose + 90 Days**	**Every 3 months**	**Additional visits are conducted for blood sampling only. See Table 5.**
Urinalysis	X	X*						Every 3 cycles	X				*Start at Cycle 3 and every 3 cycles after.
Vital signs	X	X	X	X	X	X	X	X	X	X			See Section 8.2.2. **Also, Day 2 and Day 5 of Cycle 1.**
AE & SAE Review	X	X	X	X	X	X	X	X	X	X	X		**Also, Day 2 and Day 5 of Cycle 1.**
Concomitant Medication Review	X	X	X		X			X	X	X	X		**Also, Day 2 and Day 5 of Cycle 1.**
Tumor biopsy or archived surgical specimen	X*				X*								See Biomarker Section 8.8. * A fresh biopsy at Screening and an on-treatment biopsy at Cycle 2 Day 1 (predose) are mandatory.

Assessments and Procedures	Screening	Intervention (3-week cycles)							EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5			Cycles 2, 4, 6			Cycles ≥ 7					
Day	**-28 to -1**	**1**	**8 (C1 only)**	**15 (C1 only)**	**1**	**8 (C2 only)**	**15 (C2 only)**	**1**	**EoT**	**FU1 Last dose + 30 Days**	**FU2 Last dose + 90 Days**	**Every 3 months**	**Additional visits are conducted for blood sampling only. See Table 5.**
Tumor assessment	X	X*						Every 8 weeks*		Every 8 weeks	Every 8 weeks	Every 8 weeks	* Every 8 weeks from Cycle 1. Tumor assessment schedule is independent of treatment delays. If available, collection of historical CT/MRI scans up to 100 days prior to enrollment. See Section 8.1.
Subsequent anticancer treatment										X	X	X	

AE=adverse event, β-HCG=beta-human chorionic gonadotropin, C1=Cycle 1, C2=Cycle 2, CT=computed tomography, ECOG PS= Eastern Cooperative Oncology Group Performance status, EoT=End of Treatment Visit, FU=Follow-up Visit; HBV=Hepatitis B virus, HCV=Hepatitis C virus, HIV=Human immunodeficiency virus, MRI=magnetic resonance imaging, SAE=serious adverse event, T4=free thyroxine, TSH= thyroid-stimulating hormone, WOCBP=women of childbearing potential.

1.3.2 M6223 Dose Escalation in Combination with Bintrafusp alfa (Part 1B)

For schedule related to ECG assessment and blood sampling for PK, ADA, Pd, biomarker and PGx, see Table 4 and Table 5. Note that there are additional visits at Cycles 10, 13 and every 6 cycles after Cycle 13 for blood sampling and ECG assessment.

Table 3 Schedule of Additional Activities for M6223 Dose Escalation in Combination with Bintrafusp alfa (2-week cycles)

Assessments and Procedures	Screening	Intervention (2-week cycles)				EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5		Cycles 2, 4, 6	Cycles ≥ 7					
Day	-28 to -1	1	8 (C1 only)	1	1	EoT	FU1 Last dose + 30 Days	FU2 Last dose + 90 Days	Every 3 months	Additional visits are conducted for blood sampling only. See Table 4.
Visit window (days)		(± 1)	(± 1)	(± 1)	(± 3)	(+ 7)	(± 5)	(± 14)	(±7)	EoT within 7 days of decision to discontinue but before start of subsequent anticancer treatment.
M6223 Administration		X		X	X					
Bintrafusp alfa Administration		X		X	X					Administration will be before M6223.
Informed consent	X									
Inclusion and Exclusion Criteria	X									In- and exclusion criteria will be reviewed during Screening and need to be still met prior to initial dosing on Cycle 1 Day 1.
Demography	X									
Medical and disease history (includes substance usage)	X									Substances: drugs including anticancer medication. If available, collection of historical CT/MRI scans up to 100 days prior to enrollment (See Section 8.1)

Assessments and Procedures	Screening	Intervention (2-week cycles)				EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5		Cycles 2, 4, 6	Cycles ≥ 7					
Day	**-28 to -1**	**1**	**8 (C1 only)**	**1**	**1**	**EoT**	**FU1 Last dose + 30 Days**	**FU2 Last dose + 90 Days**	**Every 3 months**	**Additional visits are conducted for blood sampling only. See Table 4.**
HBV, HCV, HIV testing (if applicable)	X									HIV testing according to country policy.
Physical examination with height & weight	X	X	X	X	X	X	X			Collect height at Screening only. Full examination at Screening and EoT. Symptom-oriented examination at other visits. If screening physical examination is done within 3 days of Cycle 1 Day 1, it does not have to be repeated at Cycle 1 Day 1. **Also, Day 2 and Day 5 of Cycle 1.**
ECOG PS	X	X		X	X	X				If the Day 1 ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Day 1 (unless the Investigator notices a decline that would exclude the participants from study participation).
Serum/urine pregnancy test (WOCBP only)	X	X		X	X		X			Serum β-HCG at Screening and Day 1 of each Cycle (1 to 7) and every even cycle thereafter; urine β-HCG thereafter for WOCBP. Results of most recent pregnancy test should be available at every cycle prior to administration of study intervention.
Core chemistry			X	X	Every even cycle					Day 8 on Cycle 1 only. See Table 18 for individual tests in each laboratory panel. Blood samples must be drawn and results to be reviewed within 48 hours prior to dose administration.

Assessments and Procedures	Screening	Intervention (2-week cycles)				EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5		Cycles 2, 4, 6	Cycles ≥ 7					
Day	**-28 to -1**	**1**	**8 (C1 only)**	**1**	**1**	**EoT**	**FU1 Last dose + 30 Days**	**FU2 Last dose + 90 Days**	**Every 3 months**	**Additional visits are conducted for blood sampling only. See Table 4.**
Full serum chemistry Panel A	X	X			Every uneven cycle	X	X			See Notes for Core Chemistry.
Full serum chemistry Panel B	X									See Notes for Core Chemistry.
Hematology and Hemostaseology	X	X	X	X	X	X	X			
T4 and TSH	X			X*	Every 4 cycles	X				*Start at Cycle 4 and every 4 cycles after.
Urinalysis	X			X*	Every 4 cycles	X				*And every fourth cycle after Cycle 6.
Vital signs	X	X	X	X	X	X	X			See Section 8.2.2. **Also, Day 2 and Day 5 of Cycle 1.**
AE & SAE Review	X	X	X	X	X	X	X	X		**Also, Day 2 and Day 5 of Cycle 1.**
Concomitant Medication Review	X	X	X	X	X	X	X	X		**Also, Day 2 and Day 5 of Cycle 1.**
Tumor biopsy or archived surgical specimen	X			X*						See Biomarker Section 8.8. * An on-treatment biopsy at Cycle 2 Day 1 (predose) is not mandatory, but highly recommended.

Assessments and Procedures	Screening	Intervention (2-week cycles)				EoT	Safety FU		Long-term FU	Notes
		Cycles 1, 3, 5		Cycles 2, 4, 6	Cycles ≥ 7					
Day	**-28 to -1**	**1**	**8 (C1 only)**	**1**	**1**	**EoT**	**FU1 Last dose + 30 Days**	**FU2 Last dose + 90 Days**	**Every 3 months**	**Additional visits are conducted for blood sampling only. See Table 4.**
Tumor assessment	X			X*	Every 8 weeks*		Every 8 weeks	Every 8 weeks	Every 8 weeks	* Start at Cycle 4 and every 8 weeks after (± 3 days). Tumor assessment schedule is independent of treatment delays. If available, collection of historical CT/MRI scans up to 100 days prior to enrollment. See Section 8.1.
Subsequent anticancer treatment							X	X	X	
Skin assessment	X			X*	Every 3 cycles		X**	X**		*Skin assessment at Screening, on Cycle 4 Day 1 only and then every 3 cycles thereafter. **Before start of subsequent anticancer therapy.

AE=adverse event, β-HCG=beta-human chorionic gonadotropin, C1=Cycle 1, CT=computed tomography, ECOG PS= Eastern Cooperative Oncology Group Performance status, EoT=End of Treatment Visit, FU=Follow-up Visit; HBV=Hepatitis B virus, HCV=Hepatitis C virus, HIV=Human immunodeficiency virus, MRI=magnetic resonance imaging, SAE=serious adverse event, T4=free thyroxine, TSH= thyroid-stimulating hormone, WOCBP=women of childbearing potential.

1.3.3 ECG Assessment, Pharmacokinetic, Anti-Drug Antibody, and Biomarker Sampling

Table 4 ECG Assessment and Blood Sampling Schedule (2-week cycles)

Cycle (Day) 2-week cycles	Time	Bintrafusp alfa (for Part 1B only)				M6223						Note
Visit windows correspond to those in Table 1		PK*	ADA	ctDNA ctRNA	CCI	PK*	ADA	TIGIT TO	Soluble factors	Immune phenotyping	12-lead ECG (See Section 8.2.3)	*The exact time of start and stop of M6223 and bintrafusp alfa administration and of each draw must be recorded. A protocol deviation is defined as a sample not drawn.
Screening				X							X	
Cycle 1 (Day 1)	-2 h to predose	X	X			X	X	X	X	X	X	Monotherapy: before the start of the infusion of M6223. Combination therapy: before the start of infusion of bintrafusp alfa. *Optional. At baseline or any visit after.
	EOI	X				X					X	Immediately after completion of the respective infusion.
	4-6 h					X						After the start of infusion of M6223.
Cycle 1 (Day 2)	25-31 h					X		X	X	X	X	After the start of infusion of M6223.
Cycle 1 (Day 5)	**± 1 day***					X						* Visits on Days 5 and 8 should be at least 48 hours apart.
Cycle 1 (Day 8)	**± 1 day***					X					X	* Visits on Days 5 and 8 should be at least 48 hours apart.
Cycle 2 (Day 1)	-2 h to predose	X	X			X	X	X	X	X	X	Monotherapy: before the start of the infusion of M6223. Combination therapy: before the start of infusion of bintrafusp alfa.
	EOI					X					X	Immediately after completion of infusion of M6223.
	4-6 h					X						After the start of infusion of M6223

Cycle (Day) 2-week cycles	Time	Bintrafusp alfa (for Part 1B only)		M6223							Note
Visit windows correspond to those in Table 1		PK*	ADA	ctDNA ctRNA	CCI [redacted]	PK*	ADA	TIGIT TO	Soluble factors	Immune phenotyping	12-lead ECG (See Section 8.2.3)	*The exact time of start and stop of M6223 and bintrafusp alfa administration and of each draw must be recorded. A protocol deviation is defined as a sample not drawn.
Cycle 3 (Day 1)	-2 h to predose	X	X	X		X	X				X	Monotherapy: before the start of the infusion of M6223. Combination therapy: before the start of infusion of bintrafusp alfa.
Cycle 4 (Day 1)	-2 h to predose	X	X			X	X	X	X	X	X	Monotherapy: before the start of the infusion of M6223 Combination therapy: before the start of infusion of bintrafusp alfa.)
	EOI	X				X					X	Immediately after completion of the respective infusion
	4-6 h					X						After the start of infusion of M6223
Cycle 5 (Day 1)	-2 h to predose	X				X						See note for Cycle 1 (Day 1)
Cycle 6 (Day 1)	-2 h to predose	X				X						See note for Cycle 1 (Day 1)
Cycle 7 (Day 1)	-2 h to predose	X	X	X		X	X				X	See note for Cycle 1 (Day 1)
Cycle 10 (Day 1)	-2 h to predose	X	X			X	X					See note for Cycle 1 (Day 1)
Cycle 13 (Day 1)	-2 h to predose	X	X	X		X	X				X	See note for Cycle 1 (Day 1)
Cycle 19 (Day 1) and every 6 cycles thereafter	-2 h to predose	X	X	X		X	X				X	See note for Cycle 1 (Day 1)
End of Treatment		X	X	X		X	X				X	

Cycle (Day) 2-week cycles	Time	Bintrafusp alfa (for Part 1B only)			CCI	M6223						Note
Visit windows correspond to those in Table 1		PK*	ADA	ctDNA/ ctRNA		PK*	ADA	TIGIT TO	Soluble factors	Immune phenotyping	12-lead ECG (See Section 8.2.3)	*The exact time of start and stop of M6223 and bintrafusp alfa administration and of each draw must be recorded. A protocol deviation is defined as a sample not drawn.
30-day Safety follow-up		X	X			X	X				X	
Blood Samples (number)		14	10	6		21	10	4	4	4		
Blood volume per sample (mL)		3.5	5	10		3.5	5	4	5	5		
Total blood (mL)		49	50	60		73.5	50	16	20	20		

ADA=Anti-drug antibody; ctDNA= Circulating tum[redacted]A; ctRNA= Circulating tumor RNA; d=day; ECG=electrocardiogram; EOI=end of intervention; CCI [redacted] PK=pharmacokinetic; TO=target occupancy.

Table 5 ECG Assessment and Blood Sampling Schedule (3-week cycles)

Cycle (Day) 3-week cycles	Time	M6223							Note
Visit windows correspond to those in Table 2		ctDNA/ ctRNA	CCI [redacted]	PK*	ADA	TIGIT TO	Soluble factors	Immune phenotyping	12-lead ECG (See Section 8.2.3)	*The exact time of start and stop of M6223 and of each draw must be recorded. A protocol deviation is defined as a sample not drawn.
Screening		X							X	
Cycle 1 (Day 1)	-2 h to predose			X	X	X	X	X	X	Monotherapy: before the start of the infusion of M6223. *Optional. At baseline or any visit after
	EOI			X					X	Immediately after completion of the infusion of M6223
	4-6 h			X						After the start of infusion of M6223
Cycle 1 (Day 2)	25-31 h			X		X	X	X	X	After the start of infusion of M6223
Cycle 1 (Day 5)	± 1 day*			X						* Visits on Days 5 and 8 should be at least 48 hours apart.
Cycle 1 (Day 8)	± 1 day*			X					X	* Visits on Days 5 and 8 should be at least 48 hours apart.
Cycle 1 (Day 15)	± 1 day			X					X	
Cycle 2 (Day 1)	-2 h to predose	X		X	X	X	X	X	X	Monotherapy: before the start of the infusion of M6223.
	EOI			X					X	Immediately after completion of infusion of M6223
	4-6 h			X						After the start of infusion of M6223
Cycle 2 (Day 8)	± 1 day			X					X	
Cycle 3 (Day 1)	-2 h to predose			X	X				X	Monotherapy: before the start of the infusion of M6223.

Cycle (Day) 3-week cycles	Time	M6223								Note
Visit windows correspond to those in Table 2		ctDNA/ ctRNA	CCI	PK*	ADA	TIGIT TO	Soluble factors	Immune phenotyping	12-lead ECG (See Section 8.2.3)	*The exact time of start and stop of M6223 and of each draw must be recorded. A protocol deviation is defined as a sample not drawn.
Cycle 4 (Day 1)	-2 h to predose			X	X	X	X	X	X	Monotherapy: before the start of the infusion of M6223
	EOI			X					X	Immediately after completion of M6223
	4-6 h			X						After the start of infusion of M6223
Cycle 5 (Day 1)	-2 h to predose			X						See note for Cycle 1 (Day 1)
Cycle 6 (Day 1)	-2 h to predose			X						See note for Cycle 1 (Day 1)
Cycle 7 (Day 1)	-2 h to predose	X		X	X				X	See note for Cycle 1 (Day 1)
Cycle 10 (Day 1)	-2 h to predose			X	X					See note for Cycle 1 (Day 1)
Cycle 13 (Day 1)	-2 h to predose	X		X	X				X	See note for Cycle 1 (Day 1)
Cycle 19 (Day 1) and every 4 cycles thereafter	-2 h to predose	X		X	X				X	See note for Cycle 1 (Day 1)
End of Treatment		X		X	X				X	
30-day Safety follow-up				X	X				X	
Blood Samples (number)		6		23	10	4	4	4		
Blood volume per sample (mL)		10		3.5	5	4	5	5		

Cycle (Day) 3-week cycles	Time	M6223							Note
Visit windows correspond to those in Table 2		ctDNA/ ctRNA	CCI	PK*	ADA	TIGIT TO	Soluble factors	Immune phenotyping	12-lead ECG (See Section 8.2.3)	*The exact time of start and stop of M6223 and of each draw must be recorded. A protocol deviation is defined as a sample not drawn.
Total blood (mL)		60		80.5	50	16	20	20		

ADA=Anti-drug antibody; ctDNA= Circulating tumor DNA; ctRNA= Circulating tumor RNA; d=day; ECG=electrocardiogram; EOI=end of intervention; CCI PK=pharmacokinetic; TO=target occupancy.

2 Introduction

This study investigates M6223 as a single agent, and in combination with bintrafusp alfa (also designated as M7824), as a potential treatment for participants who have histologically or cytologically proven locally advanced or advanced solid malignancies and who are refractory to or have progressed under standard treatment and have no other treatment options known to confer clinical benefit.

M6223 (also known as MSB0011570C and anti-TIGIT) is a fully human antagonistic anti-TIGIT antibody under investigation for immunotherapy in patients with advanced-stage cancer. M6223 is an immunomodulatory agent that binds specifically to TIGIT and inhibits the interaction of TIGIT with its ligands, CD155 and CD112, thereby inhibiting an immunosuppressive pathway. M6223 can also interrupt the interaction of TIGIT with the co-stimulatory receptor CD226, leading to increased CD226 dimerization and co-stimulatory signaling. By blocking these interactions, M6223 has the potential to stimulate antitumor immunity. M6223 has shown antitumor activity as a single agent in preclinical studies suggesting the investigation of M6223 monotherapy in clinical studies. M6223 has not been previously investigated in humans, although other anti-TIGIT agents have entered Phase 1 studies.

Bintrafusp alfa is an investigational bifunctional fusion protein that combines an anti-programmed death ligand 1 (PD-L1) antibody and the extracellular domain of TGFβRII as a TGFβ neutralizing 'trap', into a single molecule. Bintrafusp alfa has demonstrated promising antitumor activities in Phase I studies which included several cohorts in defined solid tumors. Bintrafusp alfa has also demonstrated an acceptable safety profile to date in more than 600 patients with solid tumors.

M6223 in combination treatment with bintrafusp alfa significantly enhanced antitumor activity and extended survival compared with monotherapies in syngeneic tumor models in mice. This finding is supported by the study of Blessin (Blessin 2019), in which TIGIT expression was associated with Programmed Death 1 (PD-1) expression on T cells, suggesting that combined blockade of both immune checkpoints simultaneously should be explored. Blessin et al. also described the expression level of TIGIT on various tumor entities, which may support patient selection for anti-TIGIT treatment. M6223 showed slightly greater antitumor activity when combined with bintrafusp alfa in comparison to M6223 combined with only PD-L1 blockade. This suggests that TGFβ inhibition may add to the antitumor activity of blockade of TIGIT and PD-L1.

Complete information on the chemistry, pharmacology, efficacy, and safety of M6223 and bintrafusp alfa is in the Investigator's Brochure (IB) of the corresponding agent.

CCI [redacted]

[redacted]

2.2 Background

M6223 is a fully human IgG1 antibody that inhibits the interaction of TIGIT with its ligands.

Cancer immunotherapy targeting immune checkpoint pathways has achieved impressive clinical results across many different cancer types. However, a significant unmet need is still present in most advanced cancers, especially after failure of current standard treatment options which include immunotherapies in several tumor entities. TIGIT (T cell Ig and ITIM domain), a member of the poliovirus receptor /nectin family, also known as WUCAM, Vstm3 or Vsig9, is emerging as a new target for cancer immunotherapy. TIGIT is expressed in lymphocytes, with the highest expression being on regulatory T cells (Tregs), effector $CD8^+$ and $CD4^+$ T cells, follicular helper $CD4^+$ T cells, and NK cells.

Treatment with TIGIT blocking antibodies including M6223 has exhibited antitumor immune responses in multiple murine models, and $TIGIT^{-/-}$ mice display significantly reduced tumor growth. Further details are provided in the M6223 IB.

Blockade of TIGIT in combination with blockade of other immune checkpoints has also shown potent antitumor activity in multiple syngeneic mouse tumor models. The combination of TIGIT blockade with PD-1/PD-L1 pathway blockade effectively induced superior antitumor responses relative to PD-1/PD-L1 blockade alone, supporting the combined targeting of TIGIT and other checkpoint receptors as a promising anticancer therapeutic strategy. Indeed, blockade of both

[redacted] CCI [redacted]

M6223 has not been previously investigated in humans.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

Bintrafusp alfa (anti-PD-L1 and TGFβ Trap also designated as M7824) is an investigational bifunctional fusion protein that combines an anti-PD-L1 antibody and the extracellular domain of TGFβRII as a TGFβ neutralizing 'trap', into a single molecule. TGFβ has growth inhibitory effects on normal epithelial cells and acts as a tumor suppressor during early carcinogenesis. The TGFβ cytokine is overexpressed in various cancer types. Many types of cells in the TME produce TGFβ, including the tumor cells themselves, immature myeloid cells, regulatory T cells, and stromal fibroblasts; these cells collectively generate a large reservoir of TGFβ in the extracellular matrix. TGFβ signaling contributes to tumor progression by promoting metastasis, stimulating angiogenesis, and suppressing innate and adaptive antitumor immunity.

CCI [redacted]

CCI [redacted]

As of October 2021, 3 randomized clinical trials in the bintrafusp alfa development program in 2 indications (NSCLC and BTC) have been discontinued.

CCI [redacted]

In preclinical studies, M6223 in combination treatment with bintrafusp alfa, significantly enhanced antitumor activity and extended survival were observed compared with monotherapies. This finding is supported by the study of Blessin (Blessin 2019), in which TIGIT expression was associated with PD-1 expression on T cells.

In summary, M6223 is an anti-TIGIT that has promise as a cancer immunotherapy, particularly in combination with PD-L1 inhibition or in combination with bintrafusp alfa, which is an anti-PD-L1 antibody with TGFβ growth inhibitory effects.

2.3 Benefit/Risk Assessment

2.3.1 Benefit/Risk Assessment of M6223

Based on preclinical studies, M6223 administration in patients with malignancies is expected to block interaction of TIGIT with its ligands and thereby restore the antitumor immune response pathways resulting in immune-mediated rejection of the tumor. This was demonstrated in syngeneic mouse models. M6223 mediates Fc-mediated effector function activity, and it was demonstrated that antitumor activity in these models is critically dependent on the Fc-mediated effector function properties of M6223. Competitor compounds targeting TIGIT have been shown in exploratory clinical studies to exert antitumor activity in participants with advanced, heavily pretreated tumors. Treatment in these studies included anti-TIGIT monotherapy or combination treatment with PD-1 targeting antibodies. The safety profile of these antibodies was acceptable (Sharma 2018, Golan 2018).

No important risks of M6223 have been identified prior to initial human exposure.

The following are important potential risks of M6223 administration based on preclinical data, theoretical considerations and/or information from other TIGIT-targeting antibodies developed by competitors.

Infusion-related Reactions/Hypersensitivity

The incidence and severity of potential IRRs/hypersensitivity are unknown for M6223 prior to initial investigations in humans. However, IRRs/hypersensitivity have been identified as a class-risk of mAB. If they occur, they can be managed by careful observation following dosing and adequate treatment. As a precaution, administration has to occur in a setting providing emergency equipment for resuscitation and treatment of shock.

In vitro, in a cytokine release assay with human peripheral blood mononuclear cells (PBMCs), M6223 as single agent or combined with bintrafusp alfa caused a release of several important cytokines, involved in acute phase reactions and other immune responses. Bintrafusp alfa caused increases mainly in IL-6, GM-CSF and TNF-α and weaker increases in IL-1β, IL-10 and sporadic release of IL-8 were observed. M6223 alone, at concentrations in the expected therapeutic concentration range, induced release of several cytokines, mainly IL6, IL-8, and TNF-α, from whole blood and isolated prestimulated PBMCs derived from healthy human donors. The combination of M6223 with bintrafusp alfa had an additive effect on the release of IL6, IL-8, and TNF-α when tested in whole blood. This additive effect was minor when tested in PBMCs and was neither time nor concentration dependent in whole blood.

To limit any potential IRRs by M6223 in monotherapy or combined with bintrafusp alfa, premedication with acetaminophen and an antihistamine for the first 2 infusions has been implemented into this protocol as a risk mitigation measure.

Immune-related Adverse Events

The exact pattern of potential irAEs with M6223 is unknown prior to initial human exposure. CCI [redacted] M6223 exposure in humans may result in irAEs similar to those observed for bintrafusp alfa (see below) or other immune checkpoint inhibitors. Management guidelines for irAEs related to M6223 or M6223 and bintrafusp alfa treatments have been implemented as risk mitigation measure into this protocol (see Appendix 9).

Thromboembolic Events

CCI [redacted]

Grade 3 AEs of pulmonary embolism and embolism related to etigilimab were observed in 11.1% of participants each (Sharma 2018). No thromboembolic events were reported in a Phase I clinical study of TIGIT antibody MK-7684 in monotherapy or in combination with PD-1 antibody pembrolizumab in participants with advanced cancers (Golan 2018).

Thromboembolic events are therefore considered important potential risks of M6223.

2.3.2 Benefit/Risk Assessment of Bintrafusp alfa

Bintrafusp alfa is a protein molecule comprised of a PD-L1 targeting antibody and a TGFβ-trapping component. Risks and mitigation strategies for bintrafusp alfa are summarized in Table 6.

Table 6 Bintrafusp alfa Risk Classification - Identified and Potential Risks with Mitigation Strategies

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Bintrafusp alfa		
Important Identified Risks:		
Immune-related adverse events[a]: • Immune-related pneumonitis • Immune-related hepatitis • Immune-related colitis • Immune-related nephritis and renal dysfunction • Immune-related endocrinopathies: thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorders • Immune-related rash • Other immune-related events (myositis, myocarditis, encephalitis)	In general, immune-related adverse events (irAEs) are known class effects of anti-PD 1/anti-PD-L1 anticancer immunotherapies (Postow 2018) and have been carefully monitored in the bintrafusp alfa clinical studies. irAEs of different nature have occurred in patients receiving bintrafusp alfa in the pooled monotherapy studies and these irAEs have been classified as important identified risks.	Management of irAEs and instructions for study treatment discontinuation or interruption in case of irAEs is described in Section 6.8.3. Regular laboratory tests on parameters indicative for autoimmune disorders, such as thyroid-stimulating hormone (TSH), will be performed as detailed in the Schedule of Activities (see Section 1.3).
TGFβ inhibition mediated skin reactions	TGFβ inhibition mediated skin adverse eventss are important identified risks because neutralization of TGFβ by bintrafusp alfa may induce the development of skin lesions such as hyperkeratosis, keratoacanthoma, cutaneous squamous cell carcinoma (Lacouture 2015). Such skin lesions have indeed been observed in the clinical studies with bintrafusp alfa, but not in patients treated with the anti-PD L1 antibody avelumab. Thus, it is plausible that skin tumors observed in patients treated with bintrafusp alfa may be related to the TGFβ signal pathway inhibition.	Monitoring will include skin assessments as defined in the Schedule of Activities (see Section 1.3). Management of TGFβ inhibition mediated skin reactions is described in Section 6.9.1.4.1.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Bintrafusp alfa		
Anemia	Anemia is considered an important identified risk. Toxicological findings with bintrafusp alfa in cynomolgus monkey indicated a decrease in hemoglobin, red blood cell count, and hematocrit. This decrease was fully reversible or showed trend towards recovery after treatment discontinuation). These nonclinical findings were also observed in clinical studies. The mechanism for the effect remains to be fully elucidated, however, the occurrence of hemorrhages may contribute to the observed effect.	Management of anemia is described in Section 6.9.1.4.2. Regular laboratory tests on parameters indicative for anemia, such as hemoglobin, hematocrit, erythrocyte), will be performed as detailed in the Schedule of Activities (Section 1.3).
Bleeding adverse events	Bleeding adverse events are considered important identified risk. Participants treated with bintrafusp alfa were commonly reported with mild to moderate mucosal adverse events such as epistaxis, hemoptysis, gingival bleeding and hematuria, and in lower frequencies, with Grade ≥3 hemorrhages including tumor bleeding. Other TGFβ inhibitors like fresolimumab are also known to be associated with bleeding (refer to Morris 2014; Vincenti 2017). No bleeding events were observed during the nonclinical studies with bintrafusp alfa.	Management of bleeding adverse events is described in Section 6.9.1.4.3. Regular laboratory tests on coagulation parameters, such as aPTT, PTT and INR, will be performed as detailed in the Schedule of Activities (Section 1.3).
Identified Risks		
Infusion-related reactions	IRRs are known class effects of monoclonal antibodies including anti-PD-L1 antibodies and have been observed in the clinical studies with bintrafusp alfa. However, the frequency and severity of IRRs was relatively low, and no premedication is required to prevent the occurrence of IRRs. Therefore, IRRs are classified as identified (non-important) risk.	Special precautions and management of IRRs and immediate hypersensitivity reactions are described in Section 6.8.1.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Bintrafusp alfa		
Important Potential Risks		
Immune-related adverse events (irAEs) • Guillain-Barré syndrome • Uveitis • Pancreatitis • Myasthenia gravis/ myasthenic syndrome	irAEs like Guillain-Barré syndrome, uveitis, pancreatitis and myasthenia gravis/myasthenic syndrome have not been observed for bintrafusp alfa in the pooled monotherapy studies and are therefore considered as important potential risks, as these are known risks of the therapeutic drug class of anti-PD-1/anti-PD-L1 antibodies including avelumab.	Management of irAEs and instructions for study treatment discontinuation or interruption in case of irAEs is described in Section 6.8.3.
Impaired wound healing	Impaired wound healing is considered as an important potential risk (a theoretical risk based on literature findings) for bintrafusp alfa, given the role of TGFβ in wound healing, repair of skin, and other tissue injuries (Pakyari 2013).	Management should be discussed with the Medical Monitor for participants requiring surgery on study. It is recommended to hold study intervention for approximately 4 weeks post major surgery for observation. Postoperative wound healing will be closely monitored.
Embryo-fetal toxicity	Embryo-fetal toxicity is a known risk of anti-PD-1/anti-PD-L1 antibodies, and therefore considered as important potential risk for bintrafusp alfa. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue.	An appropriate contraception warning is provided as part of the inclusion criteria. Participants with pregnancy or in lactation are prohibited from enrolling in bintrafusp alfa clinical trials and adequate contraceptive measures are recommended during the study to minimize or eliminate the potential risk to the developing fetus.

[a] For non-serious AESIs, an AESI Report Form has to be completed; for any serious events, an SAE Report Form has to be used (see Section 8.3.4).

2.3.3 Potential Benefits and Risks of Combining M6223 with Bintrafusp alfa

The potential benefits of the combination of M6223 with bintrafusp alfa are anticipated to be enhanced activation of T-effector and NK cells and thereby enhancement of antitumor effects in patients where each single agent may not confer clinical benefit.

The potential risks of such combination are based on theoretical considerations as no dedicated preclinical combination toxicity studies have been conducted. No overt gross toxicity was observed in CCI pharmacology studies of M6223 CCI in monotherapy or in combination with bintrafusp alfa. Based on the risk profiles of each of the compounds as detailed above, and theoretical considerations, the risks of combination treatment are:

- Increased frequency of AEs associated with each single compound
- Increased severity of AEs associated with each single compound

Specifically, for irAEs/autoimmune disorders, there is the potential for enhanced AEs in the combination cohorts compared to generally observed irAEs in the PD-1/PD-L1 class as both PD- L1, TGFβ and TIGIT are negative immune regulators. Immune-related adverse events (irAEs)/autoimmune disorders will be carefully monitored during Phase I for M6223 as single agent and combined with bintrafusp alfa. Guidance to Investigators include treatment algorithms to track severity and progression and give guidance for medical management (e.g., steroid use), drug interruption or discontinuation. Autoimmune parameters such as TSH and liver function tests will be monitored (see Table 11). Furthermore, aggravated IRRs of M6223 with bintrafusp alfa may occur when administered sequentially on the same day.

Risk management measures for M6223 and bintrafusp alfa are summarized in protocol in Sections 6.8 and 6.9 and Appendix 9.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of M6223 and bintrafusp alfa may be found in Section 4.2 and the respective IBs.

Based on the available nonclinical data for M6223 and the nonclinical and clinical data with bintrafusp alfa data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

3 Objectives and Endpoints

The study objectives and their corresponding endpoints are presented in Table 7. For the statistical aspects of the endpoints, see Section 9.4.

Table 7 Objectives and Endpoints

Objectives	Endpoints
PRIMARY	
To determine safety and tolerability and (if observed) the maximum tolerated doses (MTD) of M6223 as a single agent (Part 1A) for both the Q2W and Q3W regimens and of M6223 combined with bintrafusp alfa (Part 1B) for the Q2W regimen in participants with advanced solid tumors who are refractory to or have progressed under standard treatment and have no other treatment options known to confer clinical benefit.	Occurrence of DLTs during the first 4 weeks (Day 1 to Day 28) of study intervention. Occurrence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events. Incidence, nature, and severity of TEAEs and deaths, including cause of death, from Screening up to the 30 days Safety Follow-up Visit. Changes (from start of treatment until 30 days after End of Treatment) in clinical laboratory measures from baseline, safety ECGs measures, vital signs, ECOG performance status.
To determine the recommended doses of M6223 monotherapy (Part 1A) for both the Q2W and Q3W regimens and of M6223 combined with bintrafusp alfa (Part 1B) for the Q2W regimen for further exploratory clinical development.	Primary endpoints (see above) and available data for secondary and exploratory endpoints (see below).
SECONDARY	
To characterize the PK profile of M6223 when given alone (Part 1A) or when combined with bintrafusp alfa (Part 1B).	PK parameters of M6223 in terms of AUC_{0-t}, $AUC_{0-\infty}$, AUC_T, C_{max}, C_{trough}, t_{max}, $t_{1/2}$ and λ_z (Part 1A and Part 1B) on Day 1 of Treatment of Cycle 1, 2 and 4 from time zero to 14 (Q2W) or 21 (Q3W) days postdose.

To characterize the PK of bintrafusp alfa in combination with M6223 (Part 1B) by sparse sampling.	PK parameters of bintrafusp alfa in terms of C_{max} and C_{trough} on Day 1 of Treatment of Cycle 1 and 4 from time zero to 14 days postdose.
To characterize immunogenicity of M6223 when given alone and immunogenicity of M6223 and bintrafusp alfa when given in combination and its relationship to drug exposure.	Immunogenicity of M6223 (Part 1A and Part 1B) and bintrafusp alfa (Part 1B), as measured by anti-drug antibody (ADA) assays, from predose of Cycle 1 Day 1 through 30 days safety follow-up Visit.
To characterize the relationship between exposure and QT interval of M6223 alone and in combination with bintrafusp alfa.	QT interval from Cycle 1 to Cycle 7.
To characterize preliminary clinical activity parameters of M6223 in monotherapy (Part 1A) and in combination with bintrafusp alfa (Part 1B) using RECIST v1.1.	OR, DOR, time to response, disease control (DC), progression-free survival (PFS) using RECIST v1.1, per Investigator, and overall survival (OS).
EXPLORATORY	
To assess the peripheral TIGIT target occupancy with M6223 alone (Part 1A) and combined with bintrafusp alfa (Part 1B) and exposure/ target occupancy relationship.	Target occupancy at Cycle 1, 2 and 4.

CCI [redacted]

4 Study Design

4.1 Overall Design

This is a First-in-Human open-label, multicenter, Phase I study designed to determine the safety, tolerability, PK, Pd, and preliminary antitumor activity of M6223 as monotherapy (Part 1A) and in combination with bintrafusp alfa (Part 1B). The protocol may be amended at a later point in time to add exploratory expansion cohorts (potential Part 2). The target population is participants with advanced solid malignancies who are refractory to or have progressed under standard treatment and have no other treatment options known to confer clinical benefit. In each part of the study, study intervention will be administered in sequential cohorts investigating M6223 or M6223 combined with bintrafusp alfa at dose levels as guided by the Safety Monitoring Committee (SMC) (see Section 6.6.1 on dose selection and Section 6.6.1.4 on the SMC). The SMC will receive results from a Bayesian linear regression model (see Appendix 8). Except for the first 2 cohorts (at 10 mg and 30 mg with a single participant each), each cohort will typically enroll 3 participants. However, the SMC may recommend to change the size of the dose escalation cohorts in a range from 3 to 6. In case of unacceptable toxicities seen in the first or second participants in a cohort, the SMC may decide to stop enrollment into a cohort before the enrollment has reached 3 participants. Participants will be observed for DLT during the first 28 days starting from the first administration of study intervention.

For cohorts enrolling more than one participant, the first participant of each dose level will be observed for at least 3 days before the second participant can be treated. Subsequent participants may receive first dosing at no less than 48 h intervals between participants for the first 4 dose escalation cohorts of monotherapy (Part 1A) and combination therapy (Part 1B). If the safety

profile is acceptable as recommended by the SMC, the 48 h observation after participant 2 may be removed beyond Cohort 4 in each study part (for details on SMC, see Section 6.6.1.4).

The study will include a screening period of up to 28 days, a treatment period consisting administrations of M6223 either as single agent (Part 1A) or combined with bintrafusp alfa (Part 1B), End of Treatment (EoT) Visit up to 7 days after the decision to stop study intervention, and a Safety Follow-up period including a visit at 30 ± 5 days and at 90 ± 2 weeks (as a phone call) after the last M6223 or bintrafusp alfa administration as applicable. The EoT Visit should take place within 7 days after last study intervention (M6223 or bintrafusp alfa) but before the start of subsequent anticancer treatment. During long-term follow-up, participants will be followed every 3 months for documentation of subsequent anticancer therapy until end of study (Section 4.4).

Participants who tolerate M6223 or M6223 combined with bintrafusp alfa without significant clinically relevant toxicities may continue to receive their assigned treatment as long as there is no evidence of confirmed disease progression. Participants who discontinue treatment for any reason will complete the EoT and Safety Follow-up Visits. Participants who discontinue treatment in the absence of disease progression will continue all tumor assessments as scheduled until confirmed disease progression or stop of study intervention, whichever occurs later. An end of study page will be completed upon discontinuation of a participant from the study.

The study will commence with Part 1A. Part 1B may be started once the conditions defined in Section 6.6.1.2.2 have been met. Part 1A may still be ongoing when Part 1B is started.

Backfill Cohort

In addition to the M6223 monotherapy Q2W dose escalation cohorts, up to 8 evaluable participants with mandatory paired (at Screening and on treatment) biopsies will be enrolled in the relevant M6223 monotherapy Q2W dose levels to evaluate the functional Pd effect of M6223 in the TME and PK/Pd relationship to inform the selection of the potential RDE(s).

M6223 monotherapy dose levels 900 mg and 1600 mg Q2W in Part 1A will be expanded after the SMC decision to escalate to the next dose level or decision that a dose is safe enough for enrolment of backfill participants. For evaluating tumor Pd, up to 3 participants will be enrolled in 900 mg M6223 monotherapy Q2W and up to 5 participants in 1600 mg M6223 monotherapy Q2W in a single cohort, starting in parallel to dose escalation. Participants in the backfill cohort could still be enrolled after all dose escalation cohorts have been filled.

At study initiation, participant enrollment will be prioritized to fill the dose levels currently open for DLT assessment (first Part 1A, then Part 1B) over enrollment to the backfill cohort.

Up to 8 patients in the Q2W backfill cohort and 6 patients in the Q3W regimen with mandatory paired biopsies are included to collect sufficient number tumor samples for a meaningful Pd characterization of M6223 effect on TME. For participants in the backfill cohort, tumor biopsies are mandatory both at Screening and on treatment as indicated in the Schedule of Activities (SoA; Section 1.3), inclusion Criterion 8, and in Section 8.8.

The data available from participants in the backfill cohort, including any DLTs, will be considered in the Bayesian model and reviewed by the Sponsor during the regular SMC meetings (Section 6.6.1.4). In addition, an SMC meeting will be held after all participants in the backfill cohort have completed the study DLT period.

The maximum of 8 participants in the M6223 monotherapy Q2W backfill cohort with mandatory biopsies does not restrict the number of cohorts or participants per dose level considered necessary for the determination of safety and MTD (if reached) and RDE by the SMC.

4.2 CCI [redacted] for Study Design

Monoclonal antibodies targeting TIGIT have been investigated in humans previously and have demonstrated an acceptable safety profile. Furthermore, M6223 has demonstrated antitumor activity both as monotherapy and enhanced antitumor activity when combined with bintrafusp alfa in preclinical studies (see the M6223 IB). As safety, tolerability, and anticancer activity of M6223 have never been investigated in humans, the target population for initial investigation is restricted to adult participants who have histologically or cytologically proven locally advanced or advanced solid malignancies and who are refractory to or have progressed under standard treatment and have no other treatment options known to confer clinical benefit.

Escalating doses of M6223 are considered an acceptable approach to establish safety, PK, Pd and early signs of antitumor activity without putting participants at high risk of experiencing undue toxicity. Supervision of participants and data by an SMC is necessary in order to frequently review safety and re-assess benefit and risk.

The investigation of M6223 combined with bintrafusp alfa (Part 1B) in the Q2W regimen will start after investigation of M6223 monotherapy (Part 1A Q2W) in a staggered fashion to establish initial safety of M6223 before exposing participants to combination treatment.

A Bayesian logistic regression model will be used in both Part 1A and Part 1B to support SMC recommendations. Application of such a model for dose escalation will enable implementation of alternative dose levels not defined a priori to ensure participant safety and optimized definition of the RDE and MTD as compared to a classical 3 + 3 dose escalation approach.

The backfill cohort in Part 1A is justified to increase datapoints for confirmation of the RDE specially to get paired biopsies and to provide additional information on M6223 action in the tumor microenvironment.

4.3 Justification for Dose

4.3.1 Monotherapy Dose Escalation M6223

The starting dose of M6223 administered during dose escalation, 10 mg, IV, for Q2W in the first dose cohort of cancer participants, has been determined based on CCI [redacted] pharmacology and CCI [redacted] safety data.

The PK translation from CCI to human was done using allometric scaling to estimate clearance and volume of distribution. A target mediated drug disposition (TMDD) model developed in the CCI was scaled to predict the PK behavior in humans. The predicted $t_{1/2}$ of M6223 was approximately 16 days in human when estimated at the linear dose range.

Drug efficacy was determined in ex-vivo human whole blood by measuring target occupancy of anti-TIGIT antibody M6223. An EC_{50} of 240 ng/mL, with a calculated EC_{99} of 23.8 µg/mL was estimated using the standard E_{max} equation of the form $E = E_{max}*C/(EC_{50} + C)$. In order to maintain minimum concentration of EC_{99} across various dosing intervals, the corresponding doses are 1.02 mg/kg for Q2W dosing schedule.

In addition, M6223 was dosed in a human TIGIT knock-in mouse model implanted with MC38 tumor. The PK values obtained at 0.25 mg/kg, 2.5 mg/kg and 25 mg/kg were used to parametrize a TMDD mouse-specific mathematical model. Tumor growth curves, obtained at 0.2, 1, 5 and 25 mg/kg, were fit to the Simeoni tumor growth model, with corresponding PK calculated from the developed mouse TMDD model (Simeoni 2004, Rochetti 2007).

Concentration to achieve 50 percent tumor growth inhibition (IC_{50}) was estimated as 210 µg/mL. The doses needed to achieve trough serum levels of 210 µg/mL in humans were calculated to be 8.6 mg/kg for Q2W dosing schedule.

Additionally, tumor static concentration was estimated to be 550 µg/mL (tumor static concentration is not EC_{99} but describes concentration needed to prevent additional tumor growth). The doses needed to achieve trough serum levels of 550 µg/mL in humans were calculated to be 21.8 mg/kg for Q2W dosing schedule or 39 mg/kg if administered Q3W.

Taken together, the analysis predicts the efficacious human dose range to be 1.0 to 22 mg/kg for Q2W dosing schedule or 1.8 mg/kg to 39 mg/kg for Q3W dosing schedule.

The human starting dose of 10 mg Q2W is fully supported by nonclinical safety data. In monkeys, the NOAEL was determined at 300 mg/kg once weekly. This dose translates to a human equivalent dose of 96 mg/kg. Considering a starting dose in human of 10 mg Q2W and assuming 60 kg body weight, this provides a safety factor of 570. The lowest predicted efficacious dose of 1 mg/kg is based on 99% target occupancy in blood at trough level. The 10 mg proposed starting dose, which is below the predicted efficacious dose range of 1-22 mg/kg, is expected to achieve target occupancy level of 86% in blood at trough level. Thus, 10 mg Q2W is likely to be pharmacologically active to some extent.

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(Sharma 2018) and MK-7684 (Golan 2018) were generally well tolerated and had a manageable safety profile up to highest dose level tested at 20 mg/kg and 700 mg, respectively. Therefore, in view of the high NOAEL observed in CCI and its human equivalent dose of 96 mg/kg and predicted human efficacious dose range up to 21.8 mg/kg Q2W or 39 mg/kg Q3W, the highest dose initially planned for the dose escalation in Part 1A is 1600 mg which is expected to provide adequate exposure and safety assessments in a range that is potentially therapeutic. Although target occupancy as measured in peripheral blood will be considered by the SMC evaluating dose escalation, the stopping dose for the dose escalation of M6223 will be determined by the SMC

(Section 6.6.1) primarily based on safety consideration, as experience with other checkpoint inhibitors indicates that target occupancy may not be well correlated to efficacy and require doses higher than those saturating target occupancy in peripheral blood (Sheng 2017).

The starting dose of M6223 in the Q3W regimen will be proposed by the SMC based on the totality (available) of safety, PK and Pd data gathered from the Q2W regimen (see Section 6.6 for further details). The starting dose of M6223 for the Q3W regimen will not be more than 50% higher than the highest M6223 Q2W tested and considered acceptable by the SMC at this time.

4.3.2 Combination with Bintrafusp alfa

In this combination dose finding part (Part 1B), a single agent dose escalation approach will be utilized, escalating the dose of M6223 while keeping the bintrafusp alfa dose stable at the previously established recommended doses for Q2W infusions. Dose reductions and dose interruptions for bintrafusp alfa are allowed only for management of specific toxicities (Section 6.6). The rationale for the bintrafusp alfa dose of 1200 mg Q2W intravenously is provided in the bintrafusp alfa IB. These doses have been established as a clinically active and tolerable dose which traps serum TGF-beta and reaches maximum target occupancy of PD-L1 in peripheral blood.

Based on known clearance mechanisms for the 2 investigational agents, PK interactions are not considered likely at the proposed dosing regimens.

IRRs are important potential risks for M6223 and important identified risks for bintrafusp alfa. irAEs are potential risks for M6223 and important identified risks for bintrafusp alfa. The co-administration of both study interventions may be associated with more frequent or more severe AEs in this category. Premedication to prevent IRRs are in place to mitigate the risk in Part 1A and Part 1B. Management guidelines for irAEs are in place for both parts 1A and 1B to mitigate this risk. Importantly, no MTD has been reached for bintrafusp alfa nor for other TIGIT mAB etigilimab and MK-7684 (Golan 2018, Sharma 2018). Furthermore, co-administration of MK7684 with PD-1 antibody pembrolizumab did not result in aggravated toxicity. Therefore, co-administration of M6223 with bintrafusp alfa is regarded as justified and risk mitigation measures have been implemented.

4.4 End of Study Definition

The end of the study is defined as the date of the last participant having finished at least 12 months of treatment or 90-day Safety Follow-Up or having dropped out.

A participant has completed the study if he/she has completed all study parts, including the 90-day Safety Follow-Up Visit after EoT. Long-term Follow-up visits will continue until the end of the study.

The Sponsor may terminate the study at any time once access to study intervention for participants still benefitting is provided via 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 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.

Type of Participant and Disease Characteristics

2. Participants have histologically or cytologically proven locally advanced or advanced solid malignancies who are refractory to or have progressed under standard treatment and have no other treatment options known to confer clinical benefit.

3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1 at Screening.

4. Adequate hematological function as defined below:
   a. Absolute neutrophil count ≥ 1,500/mm^3 or ≥ 1.5 × 10^9/L
   b. Platelet count ≥ 100,000/mm^3 or ≥ 100 × 10^9/L
   c. Hemoglobin ≥ 9 g/dL.

5. Adequate hepatic function defined: by a total bilirubin level ≤ 1.5 × upper limit of normal (ULN), an aspartate aminotransferase (AST) level ≤ 2.5 × ULN, and an alanine aminotransferase (ALT) level ≤ 2.5 × ULN
   a. Participants with documented Gilbert disease are allowed if total bilirubin > 1.5 × ULN but < 3 × ULN
   b. Participants with tumor involvement in their liver: AST < 5.0 × ULN, ALT < 5.0 × ULN, with total bilirubin ≤ 1.5 × ULN

6. Adequate renal function defined by an estimated glomerular filtration rate > 30 mL/min according to the Cockcroft-Gault formula or normal creatinine laboratory values (Glomerular

filtration rate [mL/min/1.73 m^2] = 175 × serum creatinine (Scr)-1.154 × age - 0.203 × 1.212 [if African American] × 0.742 [if female]).

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

8. Availability of formalin-fixed paraffin-embedded block containing tumor tissue or a minimum of 15 (preferably 25) unstained tumor slides suitable for immunohistochemistry-based staining of protein expression. Tissue should be from a recently obtained biopsy or a fresh baseline tumor biopsy collected from a non-irradiated area ideally at or after progression on the most recent line of anticancer treatment.

Note: For participants in the M6223 Q3W and backfill cohort, a fresh biopsy taken during the screening period and an on-treatment biopsy on Cycle 2, Day 1 are mandatory (Section 1.3).

9. Life expectancy of at least 12 weeks according to Investigator judgment.

10. Measurable disease according to RECIST1.1.

Sex

11. Are male or female.

12. Male participants:

Agree to the following during the study intervention period and for at least 30 days before first dose of study intervention (as appropriate), during the treatment period and for at least 175 days after the last dose of study treatment of M6223 as single agent or for at least 120 days after the last dose of bintrafusp alfa (Part 1B) whichever is later, and must refrain from donating sperm during this period

PLUS, either:

a. Abstain from intercourse with a woman of childbearing potential (WOCBP)

OR

b. Use a male condom: When having sexual intercourse with a WOCBP, who is not currently pregnant, and advise her to use a highly effective contraceptive method with a failure rate of <1% per year, as described in Appendix 3, since a condom may break or leak.

13. Female participants: Are not pregnant or breastfeeding, and at least one of the following conditions applies:

a. Not a WOCBP.

OR

b. If a WOCBP, use a highly effective contraceptive method (i.e., with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 3 for the following time periods:

   i. Before the first dose of the study intervention(s), if using hormonal contraception.

   ii. Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses.

OR

   i. 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.

   ii. After the study intervention period (i.e., after the last dose of study intervention is administered) for at least 115 days for M6223 when administered as single agent or 120 days when combined with bintrafusp alfa after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period.

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

   iv. Have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test on day 1 before dosing, as required by local regulations, within 24 hours before the first dose of study intervention.

   v. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.

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

Informed Consent

14. Capable of giving signed informed consent, as indicated in Appendix 2 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

15. Signed written ICF before any study-related procedure is undertaken that is not part of the standard participant management.

5.2 Exclusion Criteria

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

Medical Conditions

1. Persisting toxicity related to prior therapy Grade > 1 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 5.0; however, alopecia, sensory neuropathy Grade ≤ 2, or other non-immune-related Grade ≤ 2 not constituting a safety risk based on Investigator's judgment are acceptable.

2. Prior organ transplantation including allogeneic stem cell transplantation.

3. Prior toxicity related to an immune checkpoint inhibitor Grade ≥ 3 NCI-CTCAE v 5.0 unless resolved to Grade ≤ 1 prior to study inclusion.

4. All participants with known brain metastases, except those meeting the following criteria:
   a. Brain metastases that have been treated locally and are clinically stable for at least 4 weeks prior to the start of treatment.
   b. 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).
   c. Participants must be either off steroids or on a stable or decreasing dose of < 10 mg daily prednisone (or equivalent).

5. Current significant cardiac conduction abnormalities, including corrected QT interval (QTcF, corrected with Fridericia formula) prolongation of > 450 ms on triplicate 12-lead ECG or impaired cardiovascular function, ventricular tachycardia, hypokalemia or a history of paroxysmal atrial fibrillation, serious cardiac arrhythmia and family history of sudden death or long QT syndrome.

6. A history of vascular, cardiovascular or cerebrovascular disease as follows: 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), deep vein thrombosis (< 3 months prior to enrollment) or pulmonary thrombosis/embolism (< 3 months prior to enrollment).

7. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent including but not limited to inflammatory bowel diseases, autoimmune hepatitis, interstitial lung disease of immunologic origin, systemic lupus erythematosus, etc, with the following exceptions:
   a. Participants with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

8. Pneumonitis and history of pneumonitis.

9. Significant acute or chronic infections requiring systemic therapy including, but not limited to:
   a. History of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome.
   b. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (defined as, HBV surface antigen positive and HBV core antibody positive with reflex to positive HBV DNA or HBV core antibody positive alone with reflex to positive HBV DNA or positive HCV antibody with reflex to positive HCV RNA). Participants with a history of infection must have polymerase chain reaction documentation that infection has cleared.
   c. Active tuberculosis (history of exposure or history of positive TB test with presence of clinical symptoms, physical, or radiographic findings).

10. Known hypersensitivity to one or more of the excipients of M6223 or bintrafusp alfa or known severe hypersensitivity reactions to mAB (Grade ≥ 3 NCI-CTCAE 5).

11. Uncontrolled asthma (i.e., 3 or more features of partially controlled asthma).

Prior/Concomitant Therapy

12. Prior treatment with a TIGIT-targeting drug.

13. Concurrent treatment with a nonpermitted drug/intervention:
    a. Anticancer treatment (eg, cytoreductive therapy, radiotherapy, immune therapy, cytokine therapy, monoclonal antibody, targeted small molecule therapy) or any investigational drug within 4 weeks prior to start of study treatment, or not recovered from AE related to such therapies, with the following exceptions:
       i. Palliative bone-directed radiotherapy is permitted (concurrently or within pretreatment period, see further details under prohibited medicines, Section 6.5.3).
       ii. Hormonal therapies acting on the hypothalamic pituitary gonadal axis are permitted (i.e., luteinizing hormone releasing hormone agonist/antagonists). No other hormonal anticancer therapy is permitted.
    b. Major surgery (as deemed by the Investigator) for any reason, except diagnostic biopsy, within 4 weeks of the study treatment and/or if the participant has not fully recovered from the surgery within 4 weeks of the study treatment.
    c. Participants receiving immunosuppressive agents (such as steroids), for any reason, should be tapered off these drugs before start of study treatment, with the following exceptions:
       i. Participants with adrenal insufficiency may continue corticosteroids at physiologic replacement dose, equivalent to < 10 mg prednisone daily.
       ii. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation).
       iii. Previous or ongoing administration of systemic steroids for the prophylaxis or treatment of an acute allergic phenomenon is acceptable as long as it is anticipated

that the administration of steroids will be completed in 14 days, or that the dose after 14 days will be equivalent to ≤ 10 mg prednisone daily.

14. Known current alcohol and drug abuse as determined by the Investigator.

15. Administration of a live vaccine within 28 days prior to study entry.

Prior/Concurrent Clinical Study Experience

16. Participation in any clinical study within 4 weeks or 5 half-lives of the investigational treatment (whichever is shorter) prior to first dose or during participation in this study.

17. Participation in a randomized trial with bintrafusp alfa (applies to Part 1B only).

Other Exclusions

18. Pregnancy or lactation (also see inclusion criteria and Appendix 3).

19. Legal incapacity or limited legal capacity if no consent by legal representative.

20. Any psychiatric condition that would prohibit the understanding or rendering of Informed Consent, or interfere with compliance to study requirements and procedures in the opinion of Investigator and/or Sponsor.

5.3 Lifestyle Considerations

The study does not have any lifestyle restrictions.

5.3.1 Meals and Dietary Restrictions

The study does not have any meals and dietary restrictions.

5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoid

The study does not have any caffeine, alcohol, tobacco and/or cannabinoid restrictions.

5.3.3 Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities (e.g., watching television or reading).

5.4 Screen Failures

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

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

Study Intervention Name (Part 1A and 1B):	M6223
Dose Formulation:	Concentrate for solution for infusion
Unit Dose Strength(s)/Dosage Level(s):	240 mg per vial at 20 mg/mL
Route of Administration:	Intravenous
Dosing Instructions:	Flat doses of M6223 as applicable for the allocated cohort, See Section 6.6 for dose selection and modification.
Supplier/Manufacturer:	Sponsor will supply M6223.
Packaging and Labeling	The investigational medicinal product is supplied in glass vials. Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

Study Intervention Name (Part 1B):	Bintrafusp alfa
Dose Formulation:	Concentrate for solution for infusion
Unit Dose Strength(s)/Dosage Level(s):	600 mg per vial at 10 mg/mL
Route of Administration:	Intravenous
Dosing Instructions:	Flat dose of 1200 mg every 2 weeks unless recommended otherwise by the Safety Monitoring Committee. See Section 6.6 for dose selection and modification.
Supplier/Manufacturer:	Sponsor will supply bintrafusp alfa.
Packaging and Labeling	The investigational medicinal product is supplied in glass vials. Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

6.1.1 Medical Device(s) Use

Not applicable.

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

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

- Upon receipt of the study intervention(s), the Investigator or designee 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 Manual of Preparation.

- 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 documents that participants were provided the doses specified in this protocol, and 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 site according to local requirements.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Manual of Preparation.
- M6223 and bintrafusp alfa drug product should be stored in a refrigerator (2°C to 8°C) until use. M6223 and bintrafusp alfa must not be frozen and should be stored in the original packaging.
- Additional instructions for the preparation, handling and storage of M6223 and bintrafusp alfa will be provided in the Manual of Preparation.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Study using IVRS/IWRS	The IVRS/IWRS will be used to assign unique participant numbers and allocate study intervention to participants at each study intervention visit. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site. The site will contact the IVRS/IWRS prior to starting study intervention administration for each participant.

6.3.2 Blinding

Not applicable. This is an open-label dose escalation study.

6.3.3 Emergency Unblinding

Not applicable.

6.4 Study Intervention Compliance

In this study, participants will receive study interventions at the investigational site. Well-trained medical staff will monitor and perform the administration of study interventions. The information of each study intervention administration including the date, time, and dose of study intervention will be recorded on the electronic case report form (eCRF). The Investigator will ensure 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 consecutive cycle of study intervention for nonmedical reasons and barring any extenuating circumstances in the opinion of the Investigator. If 1 cycle is missed and the interval between the subsequent treatment cycle and the last administered treatment cycle is longer than 30 days for nonmedical reasons, the criteria of insufficient compliance are met as well. Continuation of treatment should be discussed with the Medical Monitor under consideration of scientific integrity of the data, potential benefits and risks of study interventions and any alternative options (see Sections 7.1 and 7.2).

6.5 Concomitant Therapy

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

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

6.5.1 Rescue Medicine

For prevention or management of adverse reactions to the study interventions (M6223, bintrafusp alfa), see Section 6.8 and Section 6.9.

6.5.2 Permitted Medicines

- Hematopoietic growth factors or blood transfusions can be used if medically indicated according to standard of care only after the DLT period of 28 days. In case administration of growth factors during the DLT period is deemed necessary by the Investigator to prevent serious conditions, administration will be regarded as "dose limiting" if considered to be related to study intervention. In such case a DLT needs to be documented.
- Rescue medications may be administered due to anticipated adverse reactions or anticipated emergency situations (see Section 6.5.1).
- Administration of corticosteroids through a route known to result in a minimal systemic exposure (topical, intranasal, intra-ocular, or inhalation) and anti-infectious drugs are permitted.
- Short-term administration of corticosteroids to treat or prevent recurrence of IRRs is permitted in case they cannot be replaced with nonsteroidal premedication as judged by the Investigator.

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

6.5.3 Prohibited Medicines

Prohibited medicines at study entry are indicated in the exclusion criteria (see Section 5.2).

During administration of study intervention and before the EoT Visit, any other investigational drug, chemotherapy, extensive radiotherapy (involving $\geq 30\%$ of bone marrow) or any other anticancer therapy (cytotoxics, biologics or other targeted therapy) are prohibited.

The following treatments must not be administered during the study:

- Immunotherapy including interferons, immunosuppressive drugs (e.g., chemotherapy or systemic corticosteroids or other experimental pharmaceutical products).
  - Exception: Endocrine replacement therapy at low-dose prednisone (≤ 10 mg daily) or equivalent, short-term treatment of allergic reactions, or treatment of irAEs or other appropriate short-term steroid use). Short-term administration of systemic steroid (e.g., for treatment or prophylaxis of recurring IRRs or prevention of hypersensitivity to concomitant medication including contrast media) or other immunosuppressant such as infliximab or mycophenolate (i.e., for allergic reactions or the management of irAEs) is allowed. Steroids with no or minimal systemic effect (topical, inhalation) are allowed. For participants with glioblastoma, steroid use is allowed.

Prophylactic use of corticosteroids for infusion-related reactions is prohibited unless for prevention of recurrence after prior reactions or unless recommended by the SMC.

- Any live vaccine therapies for the prevention of infectious disease within 28 days prior to study entry and during study. Administration of inactivated vaccines is allowed (e.g., inactivated influenza vaccines) and should ideally be administered in the window between 2 administrations of study intervention.
- Blood transfusions and growth factors are not allowed during the 28-day DLT observation period in Part 1A and Part 1B except to avoid damage to the participant. In case a blood transfusion or use of growth factors during the DLT observation period is necessary, participants are considered to have had a DLT if the underlying reason is assessed as related to the study intervention.
- Radiotherapy, with the exception of palliative short course, limited field (i.e., ≤ 10 fractions and ≤ 30% bone marrow involvement or per institutional standard) radiotherapy, which may be administered during the study.

Note: The assessment of progressive disease (PD) will be made according to RECIST v1.1 (Eisenhauer 2009) and not based on the necessity for palliative radiotherapy.

If the administration of a nonpermitted concomitant drug becomes necessary during the study, the Medical Monitor must be contacted to discuss whether the study intervention must be discontinued.

No formal drug interaction studies and trials have been conducted with M6223 in humans. Currently, there is no knowledge about potential drug interaction with M6223. Since the metabolism, distribution and elimination of antibody are not mediated by CYP450 or drug transporters, from mechanistic perspective, the likelihood of direct antibody-antibody interaction occurring during co-administration of M6223 and bintrafusp alfa is unlikely to be high. During the Phase 1 study, cytokines will be monitored to evaluate potential cytokine-mediated PK interactions. Other potential PK interactions will be evaluated for specific agent(s) used in combination trials.

6.5.4 Other Interventions

Premedication for M6223 and for Bintrafusp alfa

In order to mitigate potential IRRs, premedication with an antihistamine (diphenhydramine 25 mg to 50 mg IV or PO) and with acetaminophen (500 mg to 650 mg PO) approximately 30 to 60 min prior to each dose of M6223 or bintrafusp alfa is mandatory for the first 2 infusions. It is optional and at the discretion of the Investigator after the second infusion. If Grade ≥ 2 infusion reactions are seen during the first 2 infusions, premedication should not be stopped. This regimen may be modified based on local treatment standards and guidelines as appropriate. Steroids as premedication are not permitted.

When bintrafusp alfa and M6223 are administered on the same day, premedication only needs to be administered before the first of the 2 infusions if the time from administration of the premedication for the first infusion until the end of the second infusion will not exceed 4 hours. On days of co-administration of M6223 and bintrafusp alfa, bintrafusp alfa will be administered before M6223. Initially, there should be a gap of at least 1 hour between the end of the bintrafusp

alfa and start of the M6223 administration in order to facilitate attribution of potential adverse effects. The SMC may recommend to modify this gap based on safety data during the study.

6.6 Dose Selection and Modification

6.6.1 Dose Selection

Justification of the starting dose of M6223 is detailed in Section 4.3. The recommendation to proceed to the next dose level, an intermediate dose level, to decrease the dose in the next cohort or to expand the current dose level to include additional participants will be made by the SMC based on safety, tolerability, and available PK and available Pd data. For the backfill cohort, see Section 4.1. The SMC receives outputs of a Bayesian 2-parameter logistic regression model (Neuenschwander 2008) containing estimated DLT probabilities for potential next dose levels. The Bayesian model will be based on prior, observed number of participants evaluable for dose escalation and on the number of participants with DLT (for evaluability definition see DLT analysis set in Section 9.3). Based on the observed toxicity profile, available PK and available Pd data, a different doses or dose level(s) that are higher or lower than the prespecified doses may be recommended by the SMC. The SMC might also recommend a different dosing regimen.

Further details on the Bayesian model are provided in Section 9.4.2.1 and Appendix 8. Dose recommendations from the model for exemplary scenarios are also shown in Appendix 8. Further details on the SMC are provided in Section 6.6.1.4 and in the SMC charter.

6.6.1.1 DLT Definition

A DLT is defined as any Grade ≥ 3 non-hematologic AE or any Grade ≥ 4 hematologic AE according to the NCI-CTCAE v 5.0, occurring during the DLT observation period (28 days from first administration of study intervention) that is not clearly related to the underlying disease or any previous or concomitant medication, concomitant disease or unrelated illness. A DLT must be confirmed by the SMC. AEs that fulfill the DLT definition but occur outside of the DLT window will also be considered by the SMC.

In addition, a DLT is considered if the following related AEs occur:

- Grade ≥ 3 neutropenia with clinical signs/symptoms (e.g., febrile neutropenia).
- Grade ≥ 3 thrombocytopenia with medically concerning bleeding.
- A study intervention-related treatment-emergent AE that in the opinion of the SMC is of potential clinical significance such that further dose escalation would expose participants to unacceptable risk.
- Grade ≥ 3 hematological AE with symptoms that require growth factor support or transfusion to prevent further damage to the participant.

The following treatment-related AEs are exceptions to the above mentioned DLT definition and are **not** considered to be DLTs:

- Isolated Grade 4 lymphopenia without clinical correlate.

- Any Grade 4 neutropenia of < 7 days duration not associated with any clinical symptoms.
- Single laboratory values out of normal range that have no clinical correlate, and resolve to Grade ≤ 1 or to baseline within 7 days with adequate medical management.
- Any Grade 3 autoimmune thyroid-related toxicity that clinically resolves to Grade ≤ 1 within 7 days of initiating therapy.
- Grade 3 diarrhea persisting < 72 hours after initiation of medical management.
- Grade 3 non-recurrent skin toxicity that resolves to Grade ≤ 1 in less than 7 days after initiation of medical management.
- Transient Grade 3 local reactions, flu-like symptoms, fever, headache, nausea, and emesis, that resolves to Grade ≤ 1 in < 48 hours after initiation of medical management.
- Transient Grade 3 fatigue that resolves to Grade ≤ 1 in < 72 hours after initiation of medical management.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor that resolve to Grade ≤ 1 within 6 days.
- Grade 3 infusion-related reaction resolving to Grade ≤ 1 within 6 hours from the end of infusion and controlled with medical management.
- Any death clearly due to the underlying disease or extraneous causes.

6.6.1.2 M6223

M6223 administration: All participants will receive an IV infusion of M6223 over 1 hour (-10 min/+20 min, i.e., over 50 to 80 min) Q2W (on Day 1 of each 2-week Cycle) or Q3W (on Day 1 of each 3-week Cycle) if not recommended otherwise by the SMC (supported by the results from the Bayesian 2-parameter logistic regression model). For Part 1B, during administration visits, M6223 will be administered after bintrafusp alfa.

6.6.1.2.1 Part 1A (M6223 Monotherapy Dose Escalation)

M6223 monotherapy dose escalation will start at a dose of 10 mg M6223 IV Q2W. The SMC will review safety and available PK, available Pd and other clinical data to recommend the dose and the dosing regimen for subsequent cohorts.

In principle, dose escalation of M6223 (Part 1A) will proceed according to the recommendation of the SMC to at least the upper end of the above given dose range (1600 mg), unless the MTD has been reached or there is excess of PK nonlinearity, or the SMC recommends to stop further dose escalation following review of safety, tolerability, PK and Pd results. Depending on the observed toxicity profile and available PK and Pd, a dose regimen different to or dose(s) higher/lower than the prespecified doses may be tested.

Separate Bayesian logistic regression models will be used for guidance of dose escalation for each study part and regimen. Available data from Part 1A will be considered when defining the prior of Part 1B Q2W regimen and all available data from Part 1A Q2W will be considered when defining

the prior for the Q3W regimen. If different prior distribution values to those specified in Appendix 8 are used, this will be specified in the SMC charter before dosing of the first participant in the different part or regimen.

The MTD will be defined by the SMC as defined in Section 9.4.2.1. The estimated median DLT rate from the model for the selected MTD is not allowed to exceed 30%.

The following criteria will be applied to define the RDE of M6223 as monotherapy:

- The dose has been judged by the SMC as safe for M6223 monotherapy. The estimated median DLT rate for the RDE is not allowed to exceed 30%. In case MTD is reached, RDE is lower or equal to the MTD.
- The target occupancy for M6223 monotherapy at that dose level is approximating a plateau.

In case several dose levels fulfill these criteria, additional data from the study will be considered by the SMC for recommendation of the RDE.

The cohort at the suggested RDE will be expanded to at least 6 participants evaluable for RDE determination at that dose level. The SMC may also recommend to expand other dose levels to collect sufficient number tumor samples for a meaningful Pd characterization of M6223 effect on tumor microenvironment. Participants are evaluable for RDE determination if they are in the DLT analysis set and samples for PK and Pd are available from baseline and at least 1 on-study Visit.

Table 8 presents suggested dose levels of M6223 monotherapy for consecutive investigation in cohorts of usually 1 participant (DL 1 and DL 2) or 3 participants (DL 3 and above). The SMC may recommend modification of dose levels or change of dosing intervals from 2-week cycles to 3-week cycles. The SMC may recommend a modification of the number of participants in a dose escalation cohort between 3 to 6 with guidance by the Bayesian model (e.g., if the data of 3 participants would not be sufficient that the model would recommend the next higher anticipated dose) and available PK data. The final decision will be taken by the Sponsor based on the SMC recommendation.

Additionally, a Q3W regimen of M6223 will be tested after the RDE declared by the SMC of M6223 Q2W has been reached. The SMC will then decide on the corresponding (starting) dose of M6223 in the Q3W regimen considering all safety, PK and Pd data gathered from the Q2W regimen of M6223 available at that time. This starting Q3W dose will not exceed 50% higher than the RDE for Q2W and considered acceptable by the SMC at this time. Additionally, the median estimated probability for a DLT at the selected starting dose (estimated in the Q2W model) will not exceed 30%. Although it is anticipated that only one dose needs to be tested in the Q3W, the SMC may decide to test additional cohorts at the same or other (lower or higher) doses in the Q3W regimen depending on the safety, PK, and Pd observed.

A fresh biopsy at Screening and during treatment (C2D1 predose) are mandatory for participants in the M6223 Q3W cohort.

Table 8 Suggested Dose Levels of M6223 Monotherapy Dose Escalation for Consecutive Investigation

Dose level	M6223 dose and dosing interval
Dose level 1 (DL 1=Starting dose level):	10 mg Q2W
DL 2	30 mg Q2W
DL 3	100 mg Q2W
DL 4	300 mg Q2W
DL 5	900 mg Q2W
DL 6	1600 mg Q2W
DL7	2400 mg Q3W

DL= dose level; Q2W= every 2 weeks; Q3W= every 3 weeks

6.6.1.2.2 Part 1B (Dose Escalation of M6223 Combined with Bintrafusp alfa)

The SMC will recommend the starting dose of M6223 Q2W for Part 1B, which cannot be higher than the highest tolerable dose of M6223 in Part 1A of the study at the time Part 1B is started. Part 1B can only start after safety data of at least 2 different dose levels of Part 1A are available. Part 1A may still be ongoing when Part 1B is started.

The starting dose of M6223 combined with bintrafusp alfa will be chosen as follows:

- In case no DLTs of M6223 have been observed in Part 1A at the time Part 1B is started, the starting dose of M6223 in Part 1B will be the highest dose declared safe by the SMC at that time.
- In case DLTs have been observed in Part 1A at the time Part 1B is started, the starting dose level of M6223 in Part 1B will be at least one dose level lower than the highest tolerable dose of M6223 at that time.

In Part 1B, for the Q2W regimen M6223 is to be escalated up to the RDE of M6223 in Part 1A unless the MTD in Part 1B is reached earlier or the SMC recommends to stop the dose escalation following review of safety, tolerability, PK and Pd results, whatever occurs first. The maximum dose of M6223 combined with bintrafusp alfa will not exceed any potential MTD of M6223 in monotherapy determined in Part 1A of the study.

The DLT observation period, SMC decision process, decision criteria (eg, for escalation, MTD and RDE), dose modifications, and overall treatment duration, as well as expansion to 6 participants evaluable for RDE selection at the suggested RDE, will be handled as in Part 1A (see Section 6.6.1.2.1).

Table 9 and Table 10 present potential dose levels of M6223 combined with bintrafusp alfa for consecutive/parallel investigation in cohorts of usually 3 participants. These are examples for 2 different scenarios regarding whether or not DLTs are observed in Part 1A assuming start of Part 1B after DL4 300 mg. Additional details on the starting dose of M6223 in combination with bintrafusp alfa are provided in Section 6.6.1.2. Dose levels and dosing intervals and cohort size may be modified by SMC recommendation as guided by the Bayesian model.

Table 9 Example 1 of Potential Dose Levels of Dose Escalation of M6223 Combined with Bintrafusp alfa for Consecutive Investigation

Highest Dose level of M6223 declared safe in Part 1A at the time of start of Part 1B: DL4=300 mg Q2W. No DLTs observed in Part 1A at the time of start of Part 1B	M6223 dose and dosing interval	Bintrafusp alfa dose and dosing interval
DL4 (DL4=Starting dose level)	300 mg Q2W	1200 mg Q2W
DL5	900 mg Q2W	1200 mg Q2W
DL6	1600 mg Q2W	1200 mg Q2W

DL= dose level; Q2W= every 2 weeks.

Table 10 Example 2 of Potential Dose Levels of M6223 Combined with Bintrafusp alfa for Consecutive Investigation

Highest Dose level of M6223 declared safe in Part 1A at the time of start of Part 1B: DL4=300 mg Q2W. One or more DLTs observed in Part 1A at the time of start of Part 1B	M6223 dose and dosing interval	Bintrafusp alfa dose and dosing interval
DL2 (de-escalation step, if needed)	30 mg Q2W	1200 mg Q2W
DL3 (DL3=Starting dose level)	100 mg Q2W	1200 mg Q2W
DL4	300 mg Q2W	1200 mg Q2W
DL5	900 mg Q2W	1200 mg Q2W
DL6	1600 mg Q2W	1200 mg Q2W

DL= dose level; Q2W= every 2 weeks.

6.6.1.3 Bintrafusp alfa (Combined with M6223)

All participants will receive IV infusion of bintrafusp alfa 1200 mg (Q2W) flat dose over 1 hour (-10 min/+20 min, i.e., over 50 to 80 min). Bintrafusp alfa will be administered before administration of M6223. A waiting time of 30 to 60 minutes is recommended to allow assessment of potential infusion-related reactions to bintrafusp alfa. See guidance on premedication in Section 6.5.4.

6.6.1.4 Safety Monitoring Committee

The SMC consists of core (voting) members from the Sponsor (Global Patient Safety Product Lead (Chair), Medical Responsible, Clinical Pharmacologist and Biostatistician), the Coordinating Investigator, and the Medical Monitor of the Clinical Research Organization. Ad hoc members may be invited as needed. During the dose escalation part of the study, the SMC will evaluate the safety (including DLTs) and available PK, as well as available Pd and other study data. The SMC will decide on dose escalation, de-escalation, additional enrollment on same dose level, MTD, and suspension of enrollment. The SMC may recommend to change the size of the dose escalation cohorts in a range from 3 to 6. In case of unacceptable toxicities seen in the first or second

participant in a cohort, the SMC may decide to stop enrollment into a cohort before the enrollment has reached 3 participants.

In cases where enrollment of the last participant in a dosing cohort with more than one participant was delayed, the SMC may decide (based on available data) upon enrollment and dose for the next dosing cohort before all participants in a cohort have completed the DLT period (except for the first cohort). For this participant, the SMC will consider all available data and any subsequent emerging data at a subsequent meeting. An ad hoc meeting will be convened if this participant experiences a DLT.

A SMC meeting with selection of dose for next cohort will also be held if not all participants of a cohort are evaluable. If no evaluable participant from a cohort is left, the SMC will still convene to decide upon the continuation of the study and the number of participants for the next cohort. An additional SMC meeting will be held after all participants in the backfill cohort have completed the DLT period.

The specific working procedures will be described in an SMC charter, which will be established prior to the start of dosing.

6.6.2 Dose Modification

Dose reductions for individual participants are not allowed for M6223. However, suspension or permanent discontinuation of dosing due to AEs has been defined in the management guidelines for IRR and irAE. In Part 1B, in case of AEs clearly related to only one of the 2 study interventions (M6223, bintrafusp alfa) suspension or discontinuation of only this study intervention may be acceptable. The Medical Monitor should be consulted. Dose modification of bintrafusp alfa due to bleeding events and severe anemia is described in Section 6.9.2.

6.7 Study Intervention After the End of the Study

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

6.8 Special Precautions

As a part of precautionary safety measures, the following risk management guidance is defined for both study interventions (M6223 and bintrafusp alfa) for IRRs and irAEs, which may arise due to the nature of the study interventions (mABs) and due to the common mechanism, i.e., the inhibition of immune checkpoints leading to activation of the immune system.

6.8.1 Infusion-related Reactions Including Immediate Hypersensitivity

Infusion-related reactions including immediate hypersensitivity are identified risks for bintrafusp alfa and important potential risks for M6223.

Infusion reactions may vary in manifestation and timing, and signs and symptoms usually develop during or shortly after drug infusion which generally resolves completely within 24 hours of completion of infusion. Infusion reactions like cytokine release syndrome may manifest similar signs and symptoms of an immediate hypersensitivity/allergic reaction.

All study interventions will be administered on an outpatient basis. As a routine precaution, for the first 2 infusions, all participants enrolled in this study must be observed for 2 hours post end of infusion, in an area with resuscitation equipment and emergency agents. At all times during bintrafusp alfa or M6223 treatment, immediate emergency treatment of an IRR or a severe hypersensitivity reaction according to institutional standards must be assured. In order to treat possible hypersensitivity reactions like anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation. If no IRRs are observed during the first 2 infusions, the mandated 2-hour post infusion observation time is no longer required.

Premedication with an antihistamine (diphenhydramine 25 to 50 mg IV or PO) and with acetaminophen (500 to 650 mg PO) approximately 30 to 60 min prior to each dose of M6223 or bintrafusp alfa is mandatory for the first 2 infusions. It is optional and at the discretion of the Investigator after the second infusion. If Grade ≥ 2 infusion reactions are seen during the first 2 infusions, premedication should not be stopped. This regimen may be modified based on local treatment standards and guidelines as appropriate. Steroids as premedication are not permitted. If both M6223 and bintrafusp alfa are administered on the same day, premedication before the second infusion is only necessary if the time between administration of the premedication for the first infusion and the end of the second infusion is longer than 4 hours.

6.8.2 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) 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 is described in Section 6.9.1.1.

6.8.3 Immune-Related Adverse Events

Immune-related AEs are specific to immunotherapies and vary by organ system. Immune-related AEs are important identified risks for bintrafusp alfa and important potential risks for M6223. In general, the potential spectrum of irAEs are expected to be similar for both bintrafusp alfa and M6223.

Immune-related AEs should be documented as an 'Adverse Event of Special Interest,' (see Section 6.9) and it is recommended to involve the Medical Monitor at first incidence and as needed for follow-up. Details of the diagnostic work-up will be requested by the study team.

The recommendations for irAE management, in accordance with the joint American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines (Brahmer 2018) and National Comprehensive Cancer Network (NCCN) (NCCN Guidelines®) are included in Appendix 9.

6.8.4 TGFβ-Inhibition Mediated Skin Reactions

Skin AEs possibly due to TGFβ inhibition by bintrafusp alfa, including hyperkeratosis, actinic keratosis, keratoacanthoma (KA), basal cell carcinoma (BCC), lip squamous cell carcinoma (SCC), cutaneous squamous cell carcinomas (cSCC), and Bowen's disease, are important identified risks for bintrafusp alfa and are described in Section 6.9.1.4. Cases of KA and cSCC have also been reported for patients under treatment with other checkpoint inhibitors as well (Freites-Martinez 2017, Bednarek 2018).

Skin assessments are performed at Screening, on Cycle 4 Day 1 only and then every 3 cycles thereafter for participants on the monotherapy and Q2W combination regimens and every 2 weeks for participants on the Q3W regimen (see Section 1.3). A detailed medical history of genetic or iatrogenic skin conditions, skin type, geographical location, occupational or environmental exposure to radiation or chemicals will be queried. For participants experiencing a dermatologic-related AE (hyperkeratosis, KA, or cSCC), initial biopsy with pathology report of initial AE is expected.

Additional excisional biopsies of suspicious lesions should occur, and management discussed with the Medical Monitor as indicated. Dermatology consultation is encouraged for diagnosis, outcome and follow-up.

6.8.5 Anemia

Anemia is an important identified risk and AESI of bintrafusp alfa (refer to the bintrafusp alfa IB and Section 6.9.1.4.2). Notably, there are many reasons for anemia in patients with advanced cancer, which is why a thorough investigation of new anemia cases of unspecified etiology is requested.

For new anemia events assessed as treatment-related, 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 (see Section 6.9.1.4.2 for management of anemia).

Table 11 Evaluation Guidance of Suspected Anemia Adverse Events

Baseline anemia evaluation (prior to transfusion, if feasible)	
Hb and CBC with differential (e.g., MCV, RDW, ANC, hematocrit, reticulocytes counts) Peripheral blood smear for cell morphological assessment Complete metabolic panel including liver panel-LFTs, bilirubin, LDH, renal function, and serum folate, B12 values and other chemistries Coagulation factors (PT, PTT, INR) Urinalysis including culture Iron panel (TIBC, ferritin, iron) TSH/hormonal panel Fecal-occult blood testing Erythropoietin Haptoglobin	
Further recommendation based on suspected etiology (in addition to Baseline anemia testing)	
Unknown etiology, suspect possible hemolysis	Coombs test, fibrinogen, 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; Hb = 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; RDW = red cell distribution width; TIBC = total iron-binding capacity; TSH = thyroid-stimulating hormone.

6.8.6 Thromboembolic Events

Thromboembolic events are important potential risks and are considered an AESI for M6223. Monitoring for thromboembolic events will include monitoring of coagulation at baseline and on study, as well as clinical monitoring by physical examination and adverse event reporting.

6.9 Management of Adverse Events of Special Interest, Identified and Potential Risks, and Adverse Drug Reactions

6.9.1 Adverse Events of Special Interest

Adverse events of special interest are serious or non-serious AEs specific to the known mechanism of action of the treatment drug. These events are of clinical interest, which require close monitoring and rapid communication for optimal management. The method of AESI recording and reporting of serious AEs will follow the guideline for AE recording and reporting (see Appendix 5). Safety

measures to mitigate risks of AESIs include decisions for inclusion/exclusion criteria prior to study enrollment and guidance for prevention, monitoring, diagnostic work-up and management of potential risks, as well as guidance on study intervention interruption or discontinuation for study participants.

6.9.1.1 Infusion-Related Reactions, Including Immediate Hypersensitivity

Any signs or symptoms experienced by participants during the infusion or any event occurring during or within 1 day of drug administration should be evaluated as a potential IRR. Infusion-related reactions are common adverse drug reactions (ADRs) with mAbs that occur temporally related to drug administration. Reported signs/symptoms have included anaphylaxis, anaphylactoid reactions, and cytokine release syndrome, among others. Infusion-related reactions and hypersensitivity are AESIs for bintrafusp alfa, and important identified risks for bintrafusp alfa and important potential risk for M6223.

An assessment for possible IRR should be triggered based upon the development of specific symptoms within 24 hours of an infusion. These possible IRRs are identified based on a list of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and divided into reactions versus signs and symptoms.

- An IRR should be considered when onset is on the day of infusion (during or after the infusion) or the day after the infusion (irrespective of resolution date) for any infusion-related reaction, drug hypersensitivity, anaphylactic reaction, hypersensitivity and/or Type 1 hypersensitivity.

Signs and symptoms of IRRs and hypersensitivity/allergic reactions should be considered when onset is on the day of infusion (during or after the infusion) and resolved completely with the end date within 2 days after onset. Signs and symptoms may include, but are not limited to, rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, fever, dyspnea, back pain, abdominal pain, and urticaria.

Table 12 Treatment Modification for Symptoms of Infusion-related Reactions

NCI-CTCAE v5.0 Grade	Treatment Modification
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Increased monitoring of vital signs as medically indicated, presuming these participants are deemed medically stable.

NCI-CTCAE v5.0 Grade	Treatment Modification
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 M6223/ bintrafusp alfa infusion. Increased monitoring of vital signs as medically indicated as participants are deemed medically stable by 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 schedule. 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 M6223/bintrafusp alfa infusion immediately and disconnect infusion tubing from the participant with additional appropriate medical measures and close monitoring until deemed medically stable by attending Investigator. Hospitalization may be indicated. • Participants will be permanently withdrawn immediately from M6223/ bintrafusp alfa treatment and must not receive any further M6223/ bintrafusp alfa treatment.

IV = intravenous; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

For Grade 3 or 4 infusion-related reactions, M6223/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 dose modifications indicated in Table 12 (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 (for example, famotidine or ranitidine), in addition to premedication, for select participants. However, prophylactic steroids are NOT permitted. At 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 participant removed from treatment.

Precautions are discussed in Section 6.8.1.

6.9.1.2 Immune-related Adverse Events

Immune-related AEs are defined as off target immune-mediated side effect associated with exposure to an immunogenic drug. In the evaluation of irAEs, a full differential diagnosis should be considered in the diagnostic work-up, including possible etiologies such as neoplastic, infectious, metabolic, toxin, etc. Serologic, histologic (biopsy), and/or immunologic work-up should be performed as indicated to evaluate the differential diagnosis and/or support an immune-mediated cause. Immune-related AEs are AESIs and important identified risks for bintrafusp alfa and important potential risk for M6223.

General management by NCI-CTCAE v5.0 grading, as per ASCO, is listed below:

- Grade 1: study treatment should be continued with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities.
- Grade 2: study treatment 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/d of prednisone or equivalent).
- Grade 3: study treatment is generally suspended and the high-dose corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisolone 1 to 2 mg/kg/d) 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 treatment is recommended, with the exception of endocrinopathies that have been controlled by hormone replacement at the Investigator's discretion.

For organ/system specific management guidelines, review ASCO guideline tables in Appendix 9.

Precautions are discussed in Section 6.8.3.

6.9.1.3 Thromboembolic Events

Thromboembolic events are an important potential risk and are considered an AESI for M6223. This is due to 1 animal with multifocal thrombosis in a M6223 DRF toxicity study, pathology findings of multifocal thrombi and mixed vascular/perivascular infiltrates in a M6223 GLP toxicity study, and pulmonary embolism and embolism, 11% each, in a Phase I study of anti-TIGIT antibody etigilimab (Sharma 2018). Risk mitigation includes implementation of related exclusion criteria and screening on coagulation function and medical monitoring on clinical signs and coagulation function during the treatment. This event should be reported to the Sponsor within 24 hours of learning of its occurrence. The need for discontinuation of treatment with M6223 in case of major thromboembolic events should be discussed with the Medical Monitor. Management of any potential thromboembolic events will be according to local practice.

6.9.1.4 Adverse Events of Special Interest for Bintrafusp Alfa

6.9.1.4.1 TGFβ Inhibition Mediated Skin Reactions

Skin AEs, possibly due to TGFβ inhibition, including hyperkeratosis, actinic keratosis, KA, BCC, lip SCC, cSCC, and Bowen's disease, are AESIs and important identified risks for bintrafusp alfa. The distribution of lesions tends to be in sun-exposed areas.

Skin assessments will be performed for all participants per the SoA (see Section 1.3). For participants who are reinitiating treatment with bintrafusp alfa after treatment discontinuation within the rollover study, a thorough skin assessment as defined at the baseline should also be performed.

Management guidelines for potential TGFβ inhibition mediated skin reactions are:

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

2. Emollients may continue to be used.

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

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

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

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

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

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

6.9.1.4.2 Anemia

Anemia is considered an important identified risk based on data from 765 participants included in bintrafusp alfa clinical studies (refer to the bintrafusp alfa IB v.7.0). Anemia AEs are AESIs for bintrafusp alfa. For more information, refer to the bintrafusp alfa IB.

General guidance for anemia management and evaluation includes the following:

1. Routine blood test parameters are required per SoA (Section 1.3).

2. Transfusion should be performed at the discretion of the Investigator based on clinical assessment and considered when the participant experiences severe anemia. An attempt should be made to initiate work-up (as specified below) for the cause of anemia prior to transfusion,

if clinically feasible, to not confound this work-up. In general, blood transfusions and erythroid growth factors are permitted as clinically indicated.

Guidance for evaluation of suspected treatment-related anemias is provided in Table 11. Discuss further management with the Medical Monitor for clinically significant anemias.

In case of rapid decrease of Hgb, see Section 6.9.1.4.3.

6.9.1.4.3 Bleeding Adverse Events

Bleeding events are AESIs and an important identified risk for bintrafusp alfa.

Mucosal/Nontumor Bleeding

Mucosal bleeding events of mild to moderate severity were observed in participants treated with bintrafusp alfa in ongoing studies. Events may include epistaxis, hemoptysis, gingival bleeding or hematuria amongst others. In general, these reactions resolve without discontinuation of treatment.

For Grade 2 nontumor bleeding, see Section 6.9.3 for general management of Grade 2 ADRs.

For Grade ≥3 nontumor bleeding, study treatment must be permanently discontinued unless an alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic event, etc.). In case of alternative explanations for the Grade 3 bleeding event, study treatment should be held until the event recovers to Grade ≤ 1. If Grade ≥3 bleeding event is observed, regardless of causality with the study intervention, upon resumption of study intervention, bintrafusp alfa dose should be reduced to 600 mg Q2W. Once there is stable resolution and no recurrence of bleeding on the reduced dose, the Investigator is encouraged to communicate with the Medical Monitor on potential dose re-escalation after careful benefit-risk assessment.

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

In case of rapid decrease of hemoglobin (Hgb), such as a decrease ≥ 2.0 g/dL across a 2-week period, withhold the subsequent cycles of study intervention until Hgb is stabilized and do a thorough assessment of bleeding (for example, upper and lower GI endoscopy, enhancement CT, etc.) (see Section 6.9.1.4.2). If Grade 1 or greater bleeding is observed or suspected, withhold the bintrafusp alfa until the bleeding is resolved/controlled and resume the dose of bintrafusp alfa reduced to 600 mg Q2W. Once Hgb decrease is recovered to ≤ Grade 1 or baseline and stably controlled, the Investigator is encouraged to communicate with Medical Monitor to re-escalate the dose. The dose of bintrafusp alfa may be re-escalated to full dose (1200 mg) once Hgb is stabilized without further need for blood transfusion in the subsequent cycles. The timing of re-escalation may need a case-by-case decision.

Tumor Bleeding

For Grade ≥ 2 tumor bleeding, study treatment must be held until the event recovers to Grade ≤ 1.

If Grade ≥ 3 bleeding event has been observed, regardless of causality with the study intervention upon resumption of bintrafusp alfa, bintrafusp alfa dose should be reduced to 600 mg Q2W. Once there is stable resolution and no recurrence of bleeding on reduced dose, the Investigator is encouraged to communicate with the Medical Monitor potential dose re-escalation after careful benefit-risk assessment.

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

In case of rapid decrease of Hgb, see Mucosal/Nontumor Bleeding section above.

6.9.2 Additional Identified and Potential Risks

6.9.2.1 Impaired Wound Healing

Due to the involvement of TGFβ in tissue and skin repair, impaired wound healing is an important potential risk. No relevant event is reported in the ongoing bintrafusp alfa clinical studies. Monitoring of any surgical wounds while on study is recommended. In general, a 2-week delay from treatment is recommend following minor surgery and 4-week delay for major surgery, but cases should be discussed with the Medical Monitor.

6.9.2.2 Embryo-fetal Toxicities

Embryo-fetal toxicities are a known risk of the PD-1/PD-L1 targeting class. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue (see bintrafusp alfa IB). Embryo-fetal and reproductive toxicities have also been investigated in animal models for a humanized monoclonal antibody targeting TGFβ1. At doses as high as 30 mg/kg, no maternal reproductive toxicity or embryo-fetal lethality were observed in rabbits (Hilbish, 2016). To mitigate these potential risks, pregnant participants are excluded from the study, and all participants of childbearing/conceiving potential must use highly effective contraception.

6.9.3 Adverse Drug Reactions Requiring Treatment Discontinuation

Adverse drug reactions are defined in this study as any AEs related to study intervention assessed by the Investigator and/or Sponsor. Serious adverse reactions are ADRs which are assessed as serious. Any questions or concerns with regards to management and/or follow-up of ADRs should be discussed with the Medical Monitor.

Immune-related AEs, IRRs, anemia, and potentially TGFβ-mediated skin AEs are managed and followed up in their respective sections. Permanent treatment discontinuation may be recommended, so the relevant section must be reviewed:

- For infusion-related reactions and hypersensitivity reactions guidance, see Section 6.8.1.
- For management and guidance of suspected irAEs, see Section 6.8.3.
- For guidance and management for potentially TGFβ mediated skin AEs, see Section 6.8.4.
- For anemia guidance, see Section 6.8.5.

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.

Grade 3 ADRs:

1. Participants with any severe or Grade 3 treatment-related adverse reactions that recur should be permanently discontinued. Exceptions may be considered as follows after discussion with Medical Monitor:
    a. Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management.
    b. Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to ≤ Grade 1 or baseline.
    c. Tumor flare phenomenon, defined as local pain, irritation, or rash localized at sites of known or suspected tumor, that resolves to Grade ≤ 1 within 6 days.
    d. Grade 3 hemoglobin decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor.
    e. 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).
    f. Keratoacanthomas and/or cSCC (see Section 6.8.4 for management).
    g. Grade 3 non-tumor bleeding requiring intervention or hospitalization if alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic events, etc.).
2. For suspected Grade 3 irAEs, see Section 6.8.3 as many require permanent treatment discontinuation, including pneumonitis and nephritis.
    a. 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 last dose of treatment.

Grade 2 ADRs should be managed as follows:

a. If a Grade 2 ADR resolves to Grade ≤ 1 by the day before the next infusion, treatment may continue.

b. If a Grade 2 ADR 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 clinically reasonable to administer the following infusion.

Grade 4 ADRs:

Participants with any Grade 4 ADRs require permanent treatment discontinuation except:

a. 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.

b. Endocrinopathies controlled with hormone replacement therapy at the Investigator's discretion.

See Section 7.1 for other suspected Grade 4 irAEs, as most require permanent treatment discontinuation.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Participants must be withdrawn from study interventions if any of the following occurs:

- Participants meeting the definition of confirmed PD while on treatment based on RECIST v1.1. Participants who experience PD may continue treatment with study interventions under conditions described in Section 7.1.1 if the Investigator believes the participant will experience clinical benefit from the treatment and there is no unacceptable toxicity resulting from the treatment. Such participants will be withdrawn from the treatment if any other criteria for withdrawal are met or if alternative treatment options are available and indicated.
- Note: In case of premature withdrawal from the study interventions for reasons other than PD, participants will be asked to continue tumor assessments until confirmed PD, end of study, or death.
- Significant clinical deterioration (clinical progression), defined as new symptoms that are deemed by the Investigator to be clinically significant or significant worsening of existing symptoms.

- Unacceptable toxicity, including occurrence of a DLT. When the resumption of treatment following the resolution of a DLT is deemed in the best interest for the participant, the Medical Monitor and the Sponsor Medical Responsible should be consulted to discuss.
- Withdrawal of consent from further treatment or from further study participation. In case of selective withdrawal from study intervention, other study-related procedures and assessments should be continued as planned.
- Occurrence of an exclusion criterion, which is clinically relevant and affects the participant's safety, if study intervention discontinuation is considered necessary by the Investigator and/or Sponsor.
- Therapeutic failure requiring urgent alternative anticancer treatment (if available).
- Occurrence of AEs resulting in the discontinuation of the study interventions being desired or considered necessary by the Investigator and/or the participant.
- Occurrence of AEs (including irAEs) requiring discontinuation of study interventions as described in Section 6.9.3.
- Use of a prohibited concomitant drug, as defined in Section 6.5.3, where the predefined consequence is withdrawal from the study intervention if considered necessary by the Investigator or the Sponsor.
- Noncompliance if the benefit-risk assessment for continuation of treatment is negative according to Investigator assessment.
- Pregnancy.

The SoA specifies the data to collect at study intervention discontinuation (EoT Visit) and follow-up, and any additional evaluations that need to be completed (See Section 1.3).

7.1.1 Study Intervention Beyond Progression

A: Treatment beyond initial progression

Participants will receive M6223 with or without bintrafusp alfa as study interventions as outlined in the SoA until confirmed disease progression. Study interventions may continue past the initial determination of disease progression according to RECIST v1.1 as long as the following criteria are met:

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

A radiographic assessment should be performed within 4 to 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical

benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with study intervention.

B: Treatment beyond confirmed progression

After confirmed PD, if the Investigator feels that the participant continues to achieve clinical benefit by continuing administration of study intervention, the participant should remain on the intervention and continue to receive monitoring according to the SoA. The decision to continue administration of study intervention beyond confirmed PD should be discussed with the Medical Monitor and documented in the study records.

Participants who continue beyond confirmed progression will be followed as per the protocol schedule. Study interventions 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. Treatment will also be discontinued once any other criteria for withdrawal are met.

7.1.1.1 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 (Section 7.1.1) are met in addition to the following:

- Tumor assessment showing disease progression of brain lesion has been performed and was documented according to RECIST v1.1. prior to the procedure.
- Brain metastases have been treated locally and are clinically stable for at least 2 weeks prior to re-initiation 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 v1.1. prior to the procedure.
- It has been at least 2 weeks and the participant has fully recovered from the surgery.
- Benefit-risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator.

7.1.2 Temporary Discontinuation

Study intervention (M6223 or M6223 combined with bintrafusp alfa) may be temporarily discontinued in case local treatment of disease progression is necessary as described in Section 7.1.1.1.

7.1.3 Rechallenge

Not applicable.

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.
- 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 he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must 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 must make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner for information. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/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 (Section 1.3).
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns should be 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 must 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.

8.1 Efficacy Assessments and Procedures

8.1.1 Tumor Assessment

CT or MRI scans will be performed and collected until confirmed PD is assessed by the Investigator according to RECIST v1.1 (Eisenhauer 2009) or until start of new anticancer therapy in case of continuation of study intervention beyond PD, according to the SoA (Section 1.3).

Whenever available, historical CT/MRI scans over a period of up to 100 days prior to enrollment should be collected in order to assess tumor growth dynamics prior to study enrollment. For comparability, target lesions in both historical and on-treatment scans should match, if possible.

All Images should be available for collection and potential retrospective central analysis.

For participants with initial determination of PD, if clinically feasible, a subsequent scan 4 to 6 weeks after initial assessment should be collected to confirm PD.

Radiographic images and physical findings (physical assessments) will be used by the Investigator for the local determination of PD and participant's treatment decisions.

For each participant, tumor response assessment will be performed by CT scan or MRI (if MRI is used, chest CT is mandatory) imaging of the chest/abdomen/pelvis (plus other regions as specifically required) and other established assessments of tumor burden if CT/MRI imaging is insufficient for the individual participant. All scans performed at Screening and other imaging performed as clinically required (other supportive imaging) need to be repeated at subsequent

visits. In general, lesions detected at Screening need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

For each participant, the Investigator will designate 1 or more of the following measures of tumor status to follow for determining response: CT or MRI images of primary and/or metastatic tumor masses, physical examination findings, and the results of other assessments. All available images collected during the study period will be considered. The most appropriate measures to evaluate the tumor status of a participant should be used. The measure(s) to be chosen for sequential evaluation during the study must correspond to the measures used to document the progressive tumor status that qualifies the participant for enrollment. The tumor response assessment will be assessed and listed according to the SoA (Section 1.3).

Treatment decisions will be made by the Investigator based on the Investigator's assessment of disease status. Investigator's assessment of objective tumor response to treatment will be performed according to RECIST v1.1 (all measurements should be recorded in metric notation, as described in RECIST v1.1).

- At Baseline, tumor lesions will be categorized in target and non-target lesions as described in RECIST v1.1.
- Results for these evaluations will be recorded with as much specificity as possible so that pretreatment and post treatment results will provide the best opportunity for evaluating tumor response.
- Any complete response (CR) or partial response (PR) should be confirmed, preferably at the next subsequent scheduled imaging interval, but no sooner than 6 weeks after the initial documentation of CR or PR.
- The Investigator may perform scans in addition to a scheduled study scan for medical reasons or if the Investigator suspects PD. Participants who withdraw from the investigational treatment for clinical or symptomatic deterioration before objective documentation of PD or who discontinue from investigational treatment for reasons other than objective PD will be requested to continue appropriate imaging according to the study schedule until determination of confirmed PD or discontinuation of the study, whichever occurs earlier. Every effort should be made to confirm a clinical diagnosis of PD by imaging.

The clinical endpoints to be assessed for efficacy evaluation according to RECIST v1.1 include:

- Clinical endpoints: best overall response (BOR), disease control rate, duration of response (DOR), and progression-free survival per Investigator according to RECIST v1.1.
- Progression-Free Survival (PFS) time is defined as the time from start date of treatment to the date of the first documentation of objective progression of disease or death due to any cause, whichever occurs first. Progression-Free Survival 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 a new anticancer therapy 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 postbaseline tumor assessments will be censored on the

treatment start date unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

- Best overall response will be determined according to RECIST v1.1. It is defined as the best response obtained among all tumor assessment visits after the date of first study drug administration until documented disease progression. The BOR rate is defined as the number of participants whose BOR was either confirmed CR or PR, relative to the number of participants belonging to the study of interest.
- Only tumor assessments performed before the start of any further anticancer treatment will be considered in the assessment of BOR. Clinical deterioration will not be considered as documented disease progression.
- Disease control at each assessment date is defined as having CR, PR or SD at or after that timepoint and not having had a PD assessment before that. Disease control (CR, PR, or SD) must be confirmed at the next scheduled assessment (no less than 6 to 8 weeks in case of an unscheduled assessment). Disease control rate is the proportion of participants with disease control.
- DOR is defined, for participants with an objective response, as the time from first documentation of objective response (CR or PR) to the date of first documentation of objective progression of disease or death due to any cause whichever occurs first. If a participant has not had an event (progressive disease or death), DOR is censored at the date of last adequate tumor assessment.
- Tumor assessment during follow-up: See SoA (Section 1.3). Participants without progressive disease according to RECIST v1.1 at the EoT Visit will be followed for disease progression according to the SoA until PD was confirmed or the maximum duration of study intervention has been reached or the study ended, whatever is reached first.

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.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of general appearance and dermatological, pulmonary, cardiovascular, gastrointestinal, genitourinary, lymphatic, neurologic and musculoskeletal systems, head/neck, extremities, eyes, ears, nose, throat, and cognitive status. Height (at Screening) and weight will also be measured and recorded according to the SoA (Section 1.3).

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen) and should be a focused physical examination with attention paid to irAEs.
- Investigators should pay special attention to clinical signs related to previous serious illnesses. All newly diagnosed or worsening conditions, signs, and symptoms observed from Screening, whether related to study intervention or not, are to be reported as AEs.

8.2.2 Vital Signs

- Height at Screening and weight (Screening every cycle, and at Safety FU1) will be measured and recorded.
- Oral or tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed pre and postinfusion (see Table 1). For Part 1B, vital signs should be taken prior to administration of bintrafusp alfa, prior to M6223 and after M6223 administration.
- 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. The 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).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

8.2.3 Electrocardiograms

Triplicate 12-lead ECG in digital format will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals until Cycle 7. Subsequent ECGs will be obtained as single recordings (normal non-triplicate safety ECGs). For immediate safety assessments, ECG will be locally analyzed at each time point.

- All digital ECGs obtained in triplicate will be uploaded to a central site for storage of the digital files for potential future usage. All digital triplicate ECGs may be centrally read later if necessary. All ECGs obtained in triplicate will be analyzed using concentration effect modeling for QTcF (QT corrected with Fridericia formula) (see Section 9.4.2.2).
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes and should occur in a resting state (participants will rest in a recumbent position for at least 5 to 10 minutes. Start and end of resting time will be documented in the eCRF) without prior procedure such as blood draw.

8.2.4 Clinical Safety Laboratory Assessments

- Appendix 6 (Clinical Laboratory Tests) lists the laboratory tests that will be analyzed for the study for each panel (e.g., hematology, chemistry, urinalysis).

- Hematology includes complete blood count with differential and platelet counts. Blood samples for hematology will be obtained prior to administration of study intervention.
- A full urinalysis is required at Screening and the EoT Visit and includes pH, ketones, specific gravity, bilirubin, protein, blood, urobilinogen, nitrite, leukocyte esterase and glucose. A basic urinalysis (protein content only) is required at Day 1 of Cycles 2, 4, and 6 and every fourth cycle thereafter for monotherapy and the Q2W regimen, and at Day 1 of Cycle 3 and every third cycle thereafter for the Q3W regimen. If urinalysis is positive for protein, sediment will be evaluated.
- β-human chorionic gonadotropin must be determined from serum at Screening and from urine thereafter in WOCBP (see SoA Table 1). A negative urine pregnancy test on Day 1 of each Cycle (1 to 7) and every even cycle thereafter prior to administration of study intervention needs to be available.
- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 6 at the time points listed in the SoA prior to administration of study intervention (see SoA Table 1, Table 4 and Table 5). 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 this 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.

8.2.5 Suicidal Ideation and Behavior Risk Monitoring

Not applicable.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and an 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 through the first safety follow-up, after the last dose, 30 days, until the second Safety Follow-up, after the last dose, 90 days.

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 and all non-serious AEs of special interest must be additionally documented and reported using the appropriate Report Form as specified in Appendix 4.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

AEs are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 and are assessed for their outcome at the End of Study Visit. All SAEs (related and unrelated to study intervention), non-serious AEs classified as related to interventions by the Investigator and AESIs that are ongoing at the End of Study 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.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE (particularly life threatening and deaths) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met. The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

Individual Case Safety Reports will be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators within 15 days.

An Investigator or sub-investigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g., Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will review the safety reports and confirm completion of this review. This information will be filed it in the Investigator's Site File, and the IRB/IEC will be notified, if appropriate, according to applicable local laws/regulations and site SOPs.

In this global clinical multicenter study, the Sponsor is in the best position to determine an unanticipated problem (as defined in US Regulations 21 CFR 312.66). The Sponsor will immediately notify all Investigators of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IRB's approval/favorable opinion to continue the study. An unanticipated problem is a serious adverse event that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report, specified in Section 2.

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 must be recorded in the AE page/section of the eCRF for both pregnancies in female participants and pregnancies in female partners of male 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 SAEs, AEs of Special Interest, and DLTs.

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 Adverse Event 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 M6223 greater than the maximum dose in the study or in the program that is considered safe and well tolerated within a 24-hour time period will be considered an overdose. The Sponsor does not recommend specific treatment for an overdose. There are no known symptoms of M6223 overdose to date.

The participant will be monitored for any overdose reaction. Even if it not associated with an AE or a SAE, any overdose is recorded in the eCRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 4. Overdoses are reported on a SAE Report Form (see Section 8.3.4).

8.5 Pharmacokinetics

Non-compartmental analysis will be performed to estimate PK parameters using actual sampling time (nominal time will be used for SMC purpose only). In addition, population PK analysis will be conducted, be reported separately and not be included in the clinical study report (CSR).

M6223

The following PK parameters will be calculated, when appropriate:

Symbol	Definition
AUC_{0-t}	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last}, as estimated using the linear regression from λz determination. $AUC_{0-\infty}=AUC_{0-t}+C_{last}$ pred/ λ_z
AUC_τ	The area under the concentration-time curve (AUC) over the dosing interval from T_1=0 h to T_2=τ h. Calculated using the mixed log-linear trapezoidal rule (linear up, log down). For single dose, AUCτ is calculated as a partial area with the defined time range. In multiple dose profiles AUCτ is calculated at steady state from one predose time point to the dosing interval time. In cases where the actual observation time is not equal to the scheduled observation time AUCτ will be calculated based on the estimated concentration at τ hours, and not the concentration at the actual observation time.
λ_z	Terminal first order (elimination) rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve.
C_{max}	Maximum observed concentration.
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values).
C_{trough}	The concentration observed immediately before next dosing (corresponding to predose or trough concentration for multiple dosing).
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$

- Whole blood samples of approximately 3.5 mL will be collected for measurement of serum concentrations of M6223, as specified in the SoA (see Table 4 and Table 5). 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 M6223 in serum will be performed using a validated method. Concentrations will be used to evaluate the PK of M6223.
- Remaining samples collected for analyses of M6223 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 Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

Bintrafusp alfa

Pharmacokinetics of bintrafusp alfa for all the participants will be recorded using a sparse sampling approach. Plasma concentrations from sparse PK sampling for avelumab will allow population PK analyses. The population PK report will be a separate document and not be included in the CSR. In addition, the following PK parameters will be calculated using non-compartmental analysis, when appropriate:

Symbol	Definition
C_{max}	Maximum observed concentration
C_{trough}	The concentration observed immediately before next dosing (corresponding to predose or trough concentration for multiple dosing)

- Whole blood samples of approximately 3.5 mL will be collected for measurement of serum concentrations of bintrafusp alfa, as specified in the SoA (see Table 4 and Table 5). 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 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 Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

8.6 Pharmacodynamics

- Blood samples will be collected for measurement of Pd at times specified in Section 1.3 (SoA). Details on pharmacodynamic biomarkers are described in Section 8.8 (Biomarkers).
- Details on processes for collection and shipment of these samples are in Laboratory Manuals. The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

CCI [redacted]

CCI [redacted]

8.8 Biomarkers

- Collection of participant samples for biomarker research is also part of this study and is governed by the appropriate ICF.
- The following participant samples for biomarker research are required and will be collected from all participants in this study, as specified in the SoA:
- Blood samples for TIGIT target occupancy will be collected at baseline and on-treatment time points specified in Section 1.3. The blood volume is approximately 4 ml per visit as described in the Laboratory Manual. Blood samples will be tested using flow cytometry to evaluate TIGIT target occupancy and exposure relationship.

CCI [redacted]

- Archival formalin-fixed paraffin-embedded tumor tissues (ideally< 6 months old and after last progression of underlining disease) or fresh baseline tumor samples (collected within 28 days before first dose) will be collected at Screening. CCI [redacted]

Note: A fresh tumor biopsy during the screening period and on treatment (Cycle 2 Day 1 predose) is mandatory for participants in the backfill and M6223 monotherapy Q3W cohorts. Up to 8 patients in the Q2W backfill cohort and 6 patients in the Q3W regimen with mandatory paired biopsies are included to collect sufficient number tumor samples for a meaningful Pd

characterization of M6223 effect on TME. Biopsies are only to be obtained from safely accessible tumor tissue/sites.

CCI [redacted]

Analyses of all proposed biomarkers detailed in this section may depend on the quality of materials obtained and the availability of technology. Details on processes for collection and shipment of these samples are in Laboratory Manual. The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

8.9 Immunogenicity Assessments

- Whole blood samples of approximately 5 mL will be collected for detection of antibodies against M6223 in serum, as specified in the SoA (see Table 4 and Table 5). Samples will be collected prior to any M6223 administration on the same study day.
- The detection of antibodies to M6223 will be performed using a validated assay method with tiered testing of screening, confirmatory and titration. Confirmed positive antibodies may be further characterized.
- Whole blood samples of approximately 5 mL will be collected for detection of antibodies against bintrafusp alfa in serum, as specified in the SoA (see Table 4 and Table 5). Samples will be collected prior to any bintrafusp alfa administration on the same study day.
- The detection of antibodies to bintrafusp alfa will be performed using a validated assay method with tiered testing of screening, confirmatory and titration. Confirmed positive antibodies may be further characterized.
- Remaining samples collected for analysis of anti-M6223 or anti-bintrafusp alfa antibodies may also be used to evaluate drug concentration or exploratory biomarkers during or after the study.
- Details on processes for collection and shipment of these samples are in 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

This is an exploratory study. There is no formal significance level for this study and all analyses are considered descriptive.

9.2 Sample Size Determination

The planned cohort size for the first 2 dose levels (10 mg and 30 mg) is 1 participant, and is 3 participants for the higher dose levels. However, the SMC may recommend modification of the size of an individual dose escalation cohort from 3 to 6 participants. The final decision will be taken by the Sponsor under consideration of the SMC recommendation.

This is a dose escalation study and the total sample size will depend on the number of cohorts to be evaluated and cannot be predefined. Data observed during the dose escalation (e.g., number of DLTs) have an impact on the number of cohorts. The sample size for the RDE dose level needs to be at least 6.

For Part 1A, the monotherapy escalation it is estimated that 17 to 26 participants (2 projected dose levels with 1 participant each and 4 projected dose levels with 3 to 9 participants each) may be needed. The "minimal" scenario testing all 6 dose levels as planned would be: 1 participant each on the first 2 dose levels, 3 participants on 3 dose levels each and 6 participants at the suggested RDE, i.e., in total 17 participants. A "many DLT" scenario considering that DLTs occur and dose levels are extended and maybe an intermittent dose level tested could be: 1 participant on dose level 1, 4 participants on dose level 2, 3 participants on dose level 3, 6 participants on dose level 4, 6 participants on intermittent dose level 4 to 5, 6 participants on dose level 5, i.e., 26 participants in total. The same total number would be reached in a scenario not adding an intermittent dose but having 2 doses with 1 participant, 1 dose with 3 participants, 2 doses with 6 participants and one with 9 participants.

In the Q3W regimen, it is expected that 1 dose level will be tested in 2 cohorts (approximately 6 participants).

Considering the backfill option, the sample size for monotherapy escalation will be increased by up to 8 additional participants.

For Part 1B, the combination escalation, it is expected that about 3 dose levels will need to be tested in the Q2W regimen and the estimated sample size for this including the RDE confirmation will be 12 to 15 participants.

9.3 Populations for Analyses

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock (except for DLT analysis set). For DLT analysis set the decision is taken by the SMC.

Table 13 Analysis Sets

Analysis Set	Description
Screening (SCR)	All participants, who provided informed consent.
Safety (SAF)	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.
Dose-Limiting Toxicity (DLT)	The DLT analysis set will include all participants who received at least one dose of study intervention and meet at least one of the following criteria: • Experienced at least one DLT during the DLT period, regardless of the administered number of doses of study treatment/completion of the DLT period. • Received at least 80% of the planned cumulative dose of each treatment during the DLT period and completed the DLT period. • Additionally, participants that did not receive 80% of the planned total dose of study treatment during the DLT period, but at least 80% dosing of a different (lower) dose cohort during the completed DLT period are eligible for the DLT analysis set to be analyzed in the highest dose cohort for which they received 80% of dosing.
Pharmacokinetics (PK)	All participants, who receive at least one dose of study intervention, have no clinically important protocol deviations or important events affecting PK, and provide at least one measurable postdose concentration. Participants will be analyzed per the actual study intervention they received. The PK population will include all participants: • Who have completed all study periods without any relevant protocol deviations and factors likely to affect the comparability of PK results. • With adequate study intervention compliance. • With evaluable PK data, i.e., non-missing values for primary endpoints in each study period. If participants received prohibited concomitant therapy or medicines, as specified in Section 6.5, they will be excluded from the PK population. Relevant decisions will be made before database lock. All PK analyses will be based on this analysis set.
Pharmacodynamic (Pd)	All participants, who receive at least one dose of study intervention, have no clinically important protocol deviations or important events affecting Pd, and provide at least one measurable Pd endpoint postdose. Participants will be analyzed per the actual study intervention they received. All Pd analyses will be based on this analysis population.
Immunogenicity	All participants who receive at least one dose of study intervention and have at least one valid anti-drug antibody (ADA) result. All ADA analyses will be based on this analysis set.
Electrocardiogram (ECG)	All participants, who receive at least one dose of study intervention, have no clinically important protocol deviations or important events affecting ECG, and provide at least one measurable postdose ECG endpoint.

9.4 Statistical Analyses

General Considerations

All analyses will be prepared by study part, regimen and dose level and will be described in detail in the Integrated Analysis Plan.

There is no formal significance level for this study and all analyses are considered descriptive.

9.4.1 Efficacy Analyses

Table 14 Statistical Methods for Efficacy Endpoints

Endpoint	Statistical Analysis Methods
Primary	No primary efficacy endpoint is specified.
Secondary	In general, continuous variables will be summarized using number of participants (n); mean, standard deviation; median, 25th Percentile to 75th Percentile (Q1 to Q3), minimum, and maximum. If there are less than 5 observations available, only mean and the observed data will be given. Categorical variables will be summarized using frequency counts and percentages. The calculation of proportions will be based on the number of participants in the analysis set of interest, unless otherwise specified in the study Integrated Analysis Plan. Besides the details outlined below, more details will be specified in the Integrated Analysis Plan finalized before database lock.
OR, BOR	Objective response rate, incl. 95% two-sided Clopper Pearson Confidence interval, Count and percentage per BOR category.
DOR, PFS, OS	Kaplan-Meier estimates (product-limit estimates) will be presented for the analysis of DOR, PFS and OS together with a summary of associated statistics (median survival time, 6 to, 12-month survival rate estimates and estimates for every 6 months thereafter if applicable) including the corresponding 2-sided 95% CIs.
Tertiary/Exploratory	Will be specified in the Integrated Analysis Plan finalized before database lock.

9.4.2 Safety Analyses

Except for the analysis of DLTs (a primary endpoint), all safety analyses will be performed on the Safety Analysis population.

Table 15 Statistical Methods for Safety Endpoints

Endpoint	Statistical Analysis Methods
Primary: DLT	Bayesian logistic regression analysis as described below and in Appendix 8. At interim analysis (after end of dose escalation) and main analysis, the number and proportion of participants experiencing DLTs will be reported by dose level, based on observations during the first 4 weeks (Day 1 to Day 28) of study intervention. Posterior probabilities (2.5%, 25%, 50%, 75%, and 97.5% quantiles) for DLT probabilities at selected doses will be estimated from the Bayesian logistic regression model. A sensitivity analysis will be performed using frequentist modeling (without prior).
Secondary	In general, continuous variables will be summarized using number of participants (n); mean, standard deviation; median, 25th Percentile to 75th Percentile (Q1-Q3), minimum, and maximum. If there are less than 5 observations available only mean and the observed data will be given. Categorical variables will be summarized using frequency counts and percentages. The calculation of proportions will be based on the number of participants in the analysis set of interest, unless otherwise specified in the study Integrated Analysis Plan. Besides the details outlined below, more details will be specified in the Integrated Analysis Plan finalized before database lock.

Endpoint	Statistical Analysis Methods
TEAEs, Treatment-Related Adverse Event	Adverse events will be coded according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded by the Investigator using the NCI-CTCAE (Version 5) toxicity grades. TRAEs will be defined as any AE considered as related to M6223. Incidence of TEAEs and TRAEs summarized by SOC and Preferred term.
Deaths	Counts and percentages.
Changes in laboratory measurements	Summary statistics and boxplots. Laboratory results will also be classified by Grade according to NCI-CTCAE. Worst on-treatment grades as well as shifts to worst on treatment grades will be summarized. For measurements without NCI_CTCAE grading will be summarized by above, within and below normal limits.
CCI [redacted]	

9.4.2.1 Dose Escalation

Analyses to decide on dose escalation will be performed on the DLT set.

To support the decision on dose escalation, the SMC will receive results of a Bayesian dose-DLT model, including the recommendation of next dose level.

For each SMC meeting, the model will be updated with the number of DLTs and participants evaluable for DLT (DLT analysis set) per dose level. Based on the observed data the model will suggest the next dose level. The recommendation for dose escalation, de-escalation or expansion on the same dose level from the Bayes model will be based on a loss function (Neuenschwander 2008). The dose suggested by the model for the next cohort will be the dose with minimal Bayesian Risk (among all considered doses). The following dose levels for monotherapy are foreseen: 10, 30, 100, 300, 900, 1600 mg. However, the SMC may decide to have different or additional dose levels or skip dose levels.

The SMC may choose a different dose than suggested by the Bayesian escalation approach. Also, the SMC may recommend to change the dosing regimen. In such a case, the dose-DLT model will be extended, or a separate model will be set up.

Usually, decisions on dose escalation are taken once all participants of the most recent cohort have completed the DLT period or dropped out. In exceptional cases, however, the SMC may decide on the next cohort earlier, i.e. before the last participant of a cohort has finished the DLT period (considering the model recommendation and risk of overdose). Per definition of the Dose Escalation set, participants who have not completed the DLT period are not included for update of the model, unless they experienced a DLT. However, data of such participants will be included at next SMC (if criteria for the Dose Escalation set are then fulfilled).

The increase in number of evaluable participants by backfill as well as any DLTs that may occur in backfill participants will be considered in the Bayesian model at each SMC.

Separate models will be set up for each regimen in M6223 monotherapy (Part 1A) and for the combination escalation (Part 1B).

Details on analyses for SMCs will be described in the SMC Integrated Analysis Plan (see Section 6.6.1.4 for a description of the SMC).

Before first dosing, the assumed relationship between dose level and toxicity is specified through the prior distribution. The prior distribution chosen for the monotherapy dose escalation of this study corresponds to the following mean/median estimates of DLT probability (Table 16):

CCI [redacted]

Details of the model, including the prior distribution can be found in Appendix 8. The prior of the combination dose escalation in Q2W regimen will be based on the data seen in the monotherapy dose escalation up to start of Q2W combination escalation. Likewise, all available data from the M6223 monotherapy in the Q2W regimen will be considered when defining the prior for the Q3W regimen. The Q2W modeling will be used as a proxy for estimating the probability for a DLT at the selected starting dose for the Q3W regimen. As a Q3W regimen is less intensive, this will give a conservative estimate. For supporting the SMC decision for dose if additional cohorts in Q3W regimen are tested, a separate model for Q3W will be set up. The priors for the Q2W combination and the Q3W, if different prior distribution values to the ones specified in the Appendix 8 are used, each will be defined in the SMC charter before the first participant is treated in the respective regimen.

MTD definition

The MTD (for each part/regimen, if available) will be defined by the SMC. The target DLT rate for the MTD definition is 30%. The MTD suggested by the model (if reached) will be defined as follows:

CCI [redacted]

The SMC will be notified of a potential MTD if a tested dose fulfills the above last 2 criteria. The SMC defines the MTD and can deviate from the suggestion of the model. However, the MTD chosen by the SMC must have an estimated median DLT rate from the model for the selected MTD not exceeding 30%.

9.4.2.2 ECG Endpoints

ECG Endpoints by Triplicate

This applies to the triplicate ECG data only. If triplicate ECG has been centrally read, this applies to centrally read triplicate ECG data only. Average values will be calculated for triplicate ECGs.

The following analysis will be conducted:

- Summary statistics by time point.

The 12-lead ECG data (QTcF, QT, HR, PR and QRS), will be analyzed for change from baseline values by time point in each dose group separate for Part 1A and 1B and tabulated using descriptive statistics such as mean (including maximum mean over the time points by cohort and dose) with an associated 90% confidence interval for QTcF (90% CI is calculated for the dose cohort having no less than 6 participants) and mean (including maximum mean over time points by cohort and dose) with standard deviation for other parameters. This analysis will be reported in clinical study report.

- Categorical analysis will be performed for ECG data.

A categorical analysis will be performed in order to identify the frequency of postbaseline outliers for ECG parameters by cohort (separated for Part 1A and 1B), dose level, and participant identifier in a listing according the categories specified in Table 17 and abnormal values of ECG will be flagged according to the following criteria:

Table 17 Potentially Clinically Significant Abnormalities Criteria for ECG

Parameter	Potentially Clinically Significant Abnormalities (PCSA) Criteria
Heart rate	≤ 50 bpm and decrease from baseline ≥ 20 bpm. ≥ 120 bpm and increase from baseline ≥ 20 bpm.
PR interval	≥ 220 ms and increase from baseline ≥ 20 ms.
QRS	≥ 120 ms.
QTcF absolute	Borderline: 430-450 ms (Male), 451-470 ms (Female) Prolonged: > 450 ms (Male), >470 ms (Female) ≥ 500 ms
QTcF change from baseline	Borderline: Increase from baseline ≥ 30 ms and ≤ 60 ms Prolonged: Increase from baseline > 60 ms

- Concentration-QTcF analysis.

Time-matched, replicate ECGs and PK samples collected will be used to analyze for QTcF responses using slope analysis of exposure/response.

Analysis will be further detailed either in the Integrated Analysis Plan or in a separate analysis plan.

ECG Endpoints by Local Read (Including Single Safety ECGs)

Information on ECGs by local read will be presented by cohort, dose level, and participant identifier in a listing. Abnormal values of ECG will be flagged according to the criteria presented in Table 17.

9.4.3 Other Analyses

Pharmacokinetic, immunogenicity, Pd, and biomarker exploratory analyses will be specified in the Integrated Analysis Plan finalized before database lock. Integrated analyses across studies if any, such as the population PK analysis and pharmacodynamic analyses will be presented separately from the main CSR.

Pharmacokinetic Profile

Estimation of Individual PK Parameters:

- Pharmacokinetic parameters will be calculated using standard non-compartmental methods and the actual administered dose. PK parameters will be calculated using the actual elapsed time since dosing. When the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data.
- Non-compartmental computation of PK parameters will be performed using the computer program Phoenix® WinNonlin® version 6.3, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA).
- The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.1 or higher) may be used to produce tables, listings and figures and in the calculation of PK Parameters if appropriate.

Pharmacokinetic analyses will be specified in the Integrated Analysis Plan finalized before database lock.

Immunogenicity (ADA)

The participants which are preexisting positive, transient treatment-emergent positive, or persistent treatment-emergent positive will be listed. The impact of ADA formation on PK may be evaluated based on the data available. The details will be described in the Integrated Analysis Plan.

TIGIT Target Occupancy Profile

Analysis of TO profile and concentration/target occupancy relationship will be specified in the Integrated Analysis Plan.

9.4.4 Sequence of Analyses

This is an exploratory study.

The SMC will review available data during study conduct. The cut-off for dose escalation assessments by the SMC will usually be triggered by the completion of the DLT period (or dropout) of the last participant in the respective dose escalation cohort. When enrollment of the last participant in a dosing cohort is delayed, the SMC may decide (based on available data) upon enrollment and dose for the next dosing cohort before all participants in a cohort have completed Cycle 1. In these cases, cut-off can be earlier (e.g., after DLT period of the first 2 participants is finished or they experienced a DLT).

The cut-off for an exploratory interim analysis of the safety, available PK, available Pd and preliminary antitumor activity data from each study part will be triggered when all participants enrolled in the respective study part either:

- Have reached the first on-study intervention tumor assessment (including confirmatory scan), or
- Have died, or
- Have been withdrawn from the study intervention or from the study for any reason.

The main analysis will be after the study is completed.

Additional analysis during the study might be conducted, e.g., for publication purposes.

10 References

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11 Appendices

Appendix 1 Abbreviations

2L	Second-Line
ADA	Anti-Drug Antibody
ADL	Activity of Daily Life
ADR	Adverse Drug Reactions
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BOR	Best Overall Response
CR	Complete Response
(e)CRF	(electronic) Case Report Form
cSCC	Cutaneous Squamous Cell Carcinomas
CSR	Clinical Study Report
CT	Computed Tomography
DC	Disease Control
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
DRF	Dose-Range Finding
ECG	Electrocardiogram
ECOG	Eastern Cooperative of Oncology Group

EoT	End of Treatment
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
irAE	Immune-Related Adverse Event
IRB	Institutional Review Board
IRR	Infusion-Related Reactions
IV	Intravenous
KA	Keratoacanthoma
mAB	Monoclonal Antibodies
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NK	Natural Killer Cells
NOAEL	No Observed Adverse Effect Level
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
OR	Objective Response

PBMC	Peripheral Blood Mononuclear Cell
Pd	Pharmacodynamics
PD	Progressive Disease
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PFS	Progression-Free Survival
CCI	[redacted]
PK	Pharmacokinetics
PR	Partial Response
PT	Prothrombin Time
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
QTcF	QT Interval Corrected By Fridericia Formula
RBC	Red Blood Cell
RDE	Recommended Dose for Expansion
SAE	Serious Adverse Event
SCC	Squamous Cell Cancer
SD	Stable Disease
SMC	Safety Monitoring Committee
SoA	Schedule of Activities
TEAE	Study Intervention Treatment-Emergent Adverse Event
TMDD	Target Mediated Drug Disposition
TME	Tumor Microenvironment
ULN	Upper Limit of Normal
WOCBP	Women of Childbearing Potential

Appendix 2 Study Governance

Financial Disclosure

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

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions on the study.
- Participants must be informed that their participation is voluntary.
- Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; the Japanese ministerial ordinance on GCP and local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record must 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 must be re-consented to the most current, approved version.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.

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 must also be explained to the participant.
- 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 clinical study report.

The study will appear in the following clinical studies registries: ClinicalTrial.gov https://clinicaltrials.gov, ISRCTN registry, Canadian Cancer Trials and WHO.

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

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH GCP Guidelines.
  - 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 must review and approve them before the study is initiated.
  - 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.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as

participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).

- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

  When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor (or designee) physician. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor (or designee) physician to assist with the medical emergency.

Clinical Study Insurance and Compensation to Participants

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

Clinical Study Report

After study completion, the Sponsor will write a clinical study report 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 clinical study report 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 drug and therefore may be disclosed as required to other clinical Investigators, to the US 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.
- The Investigator must maintain accurate documentation (source data) that supports the information in the eCRF.
- The Investigator must 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.
- 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 provided to the Investigators at study completion.
- 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, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator 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 must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the following demographic and medical information for the participant, and should be as complete as possible:
  - Participant's full name, date of birth, sex, height, and weight
  - Medical history and concomitant diseases
  - Historical CT/MRI scans up to 100 days prior to enrollment
  - Prior and concomitant therapies (including changes during the study)
  - Study identifier (i.e., the Sponsor's study number) and participant's study number
  - Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
  - Any medical examinations and clinical findings predefined in the protocol
  - All AEs
  - Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable
- All source data must be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document must have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- 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.
- The study monitors will use printouts of electronic files for source data verification. These printouts must be signed and dated by the Investigator and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in eCRF guidelines.

Study and Site Closure

- 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 sufficient 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.

Appendix 3 Contraception

Definitions:

Woman of Childbearing Potential (WOCBP)

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

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

A WOCBP is **not**:

1. Premenarchal
2. A premenopausal female with 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.

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 National Cancer Institute - Common Terminology Criteria for AEs (CTCAE), version 5.0 (publication date: 17 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 M6223 include, but may not be limited to, temporal relationship between the AE and the M6223, known side effects of M6223, 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. 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 IV 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

Adverse events of special interest for combination of M6223 and bintrafusp alfa are:

- Infusion-related reactions including drug hypersensitivity reactions regardless of grade
- Anemia
- TGF-β inhibition mediated skin reactions
- Immune-related AEs
- Thromboembolic events
- Bleeding events

Adverse events of special interest require expedited reporting from the Investigator to the Sponsor within 24 h of learning of its occurrence.

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. If an AE constitutes a DLT this is documented accordingly.

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

Reporting Serious Adverse Events: Adverse Events of Special Interest and Dose-Limiting Toxicities

For paper CRFs:

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 in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a written report must be sent immediately thereafter by fax or e-mail. Names, addresses, and telephone and fax numbers for SAE reporting will be included in the study specific SAE Report Form.

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). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

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.

For electronic CRFs:

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. It is expected that the investigator/sub-investigator signs off this data in the system and any relevant associated data (e.g., additional laboratory tests, medical records, diagnostic reports, histopathological examinations, or consultation with other health care professionals) will be entered as soon as it becomes available.

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.

For paper CRFs:

Adverse Events of Special Interest

In the event of a non-serious AESI, the Investigator will complete the AESI Report Form and send it to the Sponsor/designee within 24 hours. Names, addresses, and telephone and fax numbers for AESI reporting will be included on the Report Form. Serious AESIs must be reported in an expedited manner as SAEs as outlined above.

For eCRFs:

Adverse Events of Special Interest

In the event of a non-serious AESI, the Investigator will notify the Sponsor/designee by completing the electronic AESI Report Form in the EDC system within 24 hours. Serious AESIs must be reported in an expedited manner as SAEs, as outlined above.

Reporting of non-serious AESIs 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 report form. All information from the paper form must be transcribed into the electronic form as soon as the system becomes available.

Dose-Limiting Toxicities

Each event meeting the criteria of a DLT, as specified in Section 6.6.1.1, must be recorded in the eCRF within 24 HOURS after becoming aware of the event. Serious DLTs must be reported in an expedited manner as SAEs, as outlined above.

Appendix 5 Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines

Management of liver toxicities, refer to Table A 2 (Section 2.2 Hepatitis) Appendix 9.

Appendix 6 Clinical Laboratory Tests

Table 18 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments [a]	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: • MCV • MCH • MCHC • RDW SD and CV • %reticulocytes	WBC Count with Differential: • neutrophils (ANC) • lymphocytes (absolute count) • monocytes • eosinophils • basophils	
Hemostaseology	Prothrombin time	INR	aPTT	
Full Clinical Chemistry Panel A	Liver Panel: alkaline phosphatase, ALT, AST, GGT, total and indirect/direct bilirubin, albumin, total protein, and creatine kinase	Serum Electrolytes: sodium potassium, calcium, magnesium, chloride, phosphorus/ phosphates	Renal Panel: BUN or total urea, creatinine, estimated GFR, uric acid	Pancreatic Panel: amylase, lipase
	Glucose			
Full Clinical Chemistry Panel B [b]	Iron Panel: TIBC, iron, ferritin, serum folate/B12	TST (if positive history of tuberculosis exposure) T-SPOT TB test or TST or QuantiFERON or TB Gold Test (QFT-G) are acceptable	Virology: HBV and HCV serology. HIV (according to country policy).	CRP
Core Chemistry	Liver Panel: alkaline phosphatase, ALT, AST, GGT, total and indirect/direct bilirubin, albumin, total protein, and creatine kinase	Serum Electrolytes: sodium, potassium, calcium, chloride.	Renal Panel: BUN or total urea, creatinine, estimated GFR, uric acid	Glucose
Thyroid Panel	• T_4, TSH			
Routine Urinalysis [c]	• Specific gravity, physical appearance, color • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential **only**) • Serum or highly sensitive urine β-hCG pregnancy test (as needed for women of childbearing potential).			

ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CRP = C-reactive protein; GFR = glomerular filtration rate; GGT = gamma-glutamyltransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; RDW = red cell distribution width; T_4 = free thyroxine; TIBC = total iron-binding capacity; TSH = thyroid-stimulating hormone; TST = tuberculin skin test; WBC = white blood cell.

a Performed as indicated in Section 1.3 (Schedule of Activities).

b Performed at Screening only.

c Routine urinalysis performed at Screening and as clinically indicated thereafter.

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Appendix 8 Description of the Bayesian Dose Escalation Model

The Bayesian model is based on the number of DLTs and evaluable participants per dose level. The SMC will receive results of a Bayesian two-parameter logistic regression model updated with the observed DLT data (Neuenschwander, 2008), including a recommendation for the next dose. For a dose level, the relationship between dose and probability of toxicity P (DLT) is defined by:

$$P\left(DLT\middle|d_j,\alpha,\beta\right)=\frac{exp\left(\alpha+exp\left(\beta\right)*log\left(\frac{d_j}{d_{ref}}\right)\right)}{1+exp\left(\alpha+exp\left(\beta\right)*log\left(\frac{d_j}{d_{ref}}\right)\right)},$$

with bivariate normally distributed parameters (α, β) using the following parameterization for the monotherapy escalation:

CCI [redacted]

The target DLT toxicity is 30%. The following toxicity regions for use in dose suggestion will be defined:

Toxicity Intervals	Probability of DLT	Loss term (weight in loss function)
Under-Dosing	[0.0, 0.20]	1
Targeted toxicity	[0.20, 0.35]	0
Excessive toxicity	[0.35, 0.60]	1
Unacceptable toxicity	[0.60, 1.00]	2

Recommendation on the next dose level by the model is determined as follows:

- Select the dose level that minimizes the loss function from the selected doses. The loss function is defined as the sum of products of the probability to lie within each of the toxicity regions, and the associated loss term:

  1 × P (Under-Dosing) + 0 × P (targeted toxicity) + 1 × P (excessive toxicity) +

  2 × P (unacceptable toxicity).

- The recommendation the model can make is restricted to maximally 5-fold increase of previously tested dose.

The model will be provided with the following preselected dose levels: 10 mg, 30 mg, 100 mg, 300 mg, 900 mg, 1600 mg. The set of doses can be changed any time by the SMC.

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In case information arises from other studies that changes current knowledge on the dose toxicity relationship, the prior distribution can be updated prior to the first participant being treated in this study. This change will be documented in the SMC charter.

Decisions of the SMC in different M6223 monotherapy regimens and in the M6223 plus bintrafusp alfa combination escalation will also be supported by a Bayesian two-parameter logistic regression model with the same specifications as for the M6223 monotherapy Q2W dose escalation. If data seen in Q2W monotherapy dose escalation at start of respective part warrant a change in prior for either Q3W regimen or combination therapy, the different prior used will be specified in an appendix of the SMC charter prior to dosing of the first participant in the respective study part.

Posterior distribution and the recommended next dose level suggested by the model will be calculated using EAST version 6.4 or higher/ R version 3.4.2 or higher with library package bcrm (Sweeting 2013) or package CRM pack or SAS version 9.4 (or higher) proc MCMC.

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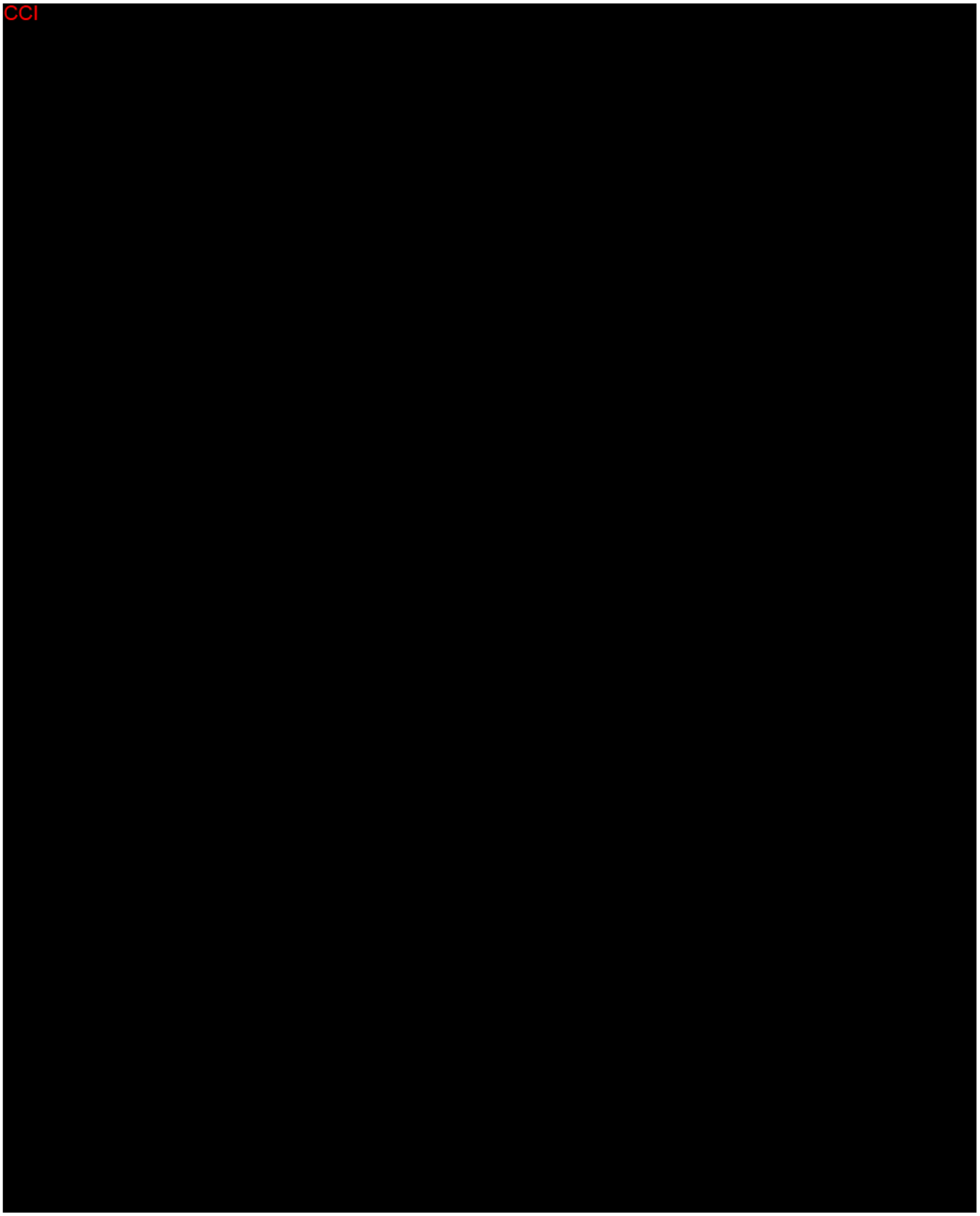

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Appendix 9 The Recommendations for irAE Management, in Accordance with the Joint American Society of Clinical Oncology Clinical Practice Guidelines and National Comprehensive Cancer Network (Brahmer 2018)

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Management of Immunotherapy-Related Toxicities. NCCN April 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Table of Tables for Appendix 9

Table A 1 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 workshop	
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	Immediately hold ICPi and consult dermatology to determine appropriateness of resuming ICPi therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) ≤ 10 mg

1.0 Skin Toxicities	
	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 Consider alternative antineoplastic therapy over resuming ICPis if the skin irAE does not resolve to G1 or less; if ICPi's are the patient's only option, consider restarting once these adverse effects have resolved to a G1 level
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% to 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 above Initiate Class 1 high-potency topical corticosteroid (e.g., clobetasol, betamethasone or equivalent) and re-assess 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

1.0 Skin Toxicities	
	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
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 pusulosis 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	

1.0 Skin Toxicities	
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% to30% 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 (eg, 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 (eg, erythema, purpura, epidermal detachment, mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (e.g., liver function test elevations in the setting of DRESS/DIHS)	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 (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 A 2 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 (eg, 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 4 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 4 to 6 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 to 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 7 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 to 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 to 2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1, and then start taper over 4 to 6 weeks Consider early infliximab 5 to 10 mg/kg if symptoms refractory to corticosteroid within 2 to 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 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	
2.2 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, anti-smooth muscle antibodies, anti-neutrophil cytoplasmic antibodies. If patients with elevated alkaline phosphatase alone, γ-glutamyl transferase should be tested. For isolated elevation of transaminases, consider checking CK for other etiologies	

2.0 GI Toxicities	
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 2 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 to 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 to 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 to 2 days 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-α agents as systemic immune-suppressants 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 to 6 weeks; re-escalate if needed; optimal duration unclear
G4: Decompensated liver function (eg, 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

2.0 GI Toxicities
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations is moderate.

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 A 3 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	Hold ICPi with radiographic evidence of pneumonitis progression May offer one repeat CT in 3 to 4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3 to 4 weeks May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as G2 Monitor patients weekly with history and physical examination and pulse oximetry; may also offer CXR
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 to 2 mg/kg/d and taper by 5 to 10 mg/wk over 4 to 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 to 72 hours of prednisone, treat as G3
Recurrent G2: symptomatic despite drug cessation & adequate treatment 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 to 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 to 6 weeks Pulmonary and infectious disease consults if necessary Bronchoscopy with BAL 6 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 A 4 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 to 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 May admit for IV therapy if signs of myxedema (bradycardia, hypothermia) Thyroid supplementation and reassessment as in G2
Additional considerations	

4.0 Endocrine Toxicity	
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 to 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 to 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 to6 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 to 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 to3 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 (eg, 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 to 2 mg/kg/d or equivalent tapered over 1 to 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.	
4.2 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	

4.0 Endocrine Toxicity	
Grading	Management
G1: Asymptomatic or mild symptoms	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Replacement therapy with prednisone (5 to10 mg daily) or hydrocortisone (10-20 mg orally every morning, 5 to 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 2 to 3 times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20 to 30 mg in the morning, and 10 to20 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 to14 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. 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 6 new severe headaches or complaints of vision changes	

4.0 Endocrine Toxicity	
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 to 2 mg/kg oral daily (or equivalent) tapered over at least 1 to 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. 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

4.0 Endocrine Toxicity	
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 to 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 A 5 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 6 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 to 20 mg/d or equivalent for 4 to 6 weeks If improvement, slow taper according to response during the next 4 to6 weeks; if no improvement after initial 4 to 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	Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to G1 or less Initiate oral prednisone 0.5 to 1 mg/kg If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD Synthetic: Methotrexate, leflunomide Biologic: consider anticytokine therapy such as TNF-α 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

5.0 Musculoskeletal Toxicities	
	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 preexisting 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 3 times or more), initiate prednisone or equivalent at 0.5 to 1 mg/kg 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	Hold ICPi until G1 or less while off immune suppression and permanently discontinue if any evidence of myocardial involvement Consider hospitalization for severe weakness Referral to rheumatologist or neurologist Initiate prednisone 1 mg/kg or equivalent. Consider 1 to 2 mg/kg of methylprednisolone IV or higher dose bolus if severe compromise

5.0 Musculoskeletal Toxicities	
	(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
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 to 4 weeks If no improvement or need for higher dosages after 4 weeks, escalate to G3 Consider referral to rheumatology
G3-4: Severe stiffness and pain, limiting self-care ADL	Hold ICPi and may resume, in consultation with rheumatology, if recover toG1 or less; however, note that cases of toxicity returning upon rechallenge have been reported. 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 A 6 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 of > 0.3 mg/dL; creatinine 1.5 to 2.0 3 mg/dL over baseline	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 2-3 x above baseline	Hold ICPi temporarily Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc); if other etiologies ruled out, administer 0.5 to 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 to6 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 x baseline or > 4.0 mg/dL; hospitalization indicated	Permanently discontinue ICPi
G4: Life-threatening consequences; dialysis indicated	Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc) Administer corticosteroids (initial dose of 1 to 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 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 A 7 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 3 times a day and gradually increase to maximum of 120 mg orally 4 times a day as tolerated and based on symptoms Administer corticosteroids (prednisone, 1 to 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: b-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 to 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	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 to 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 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	

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	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 to 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 to 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	
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 to 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	

7.0 Nervous System Toxicities	
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	
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 to 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 A 8 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 to 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 to 2 mg/kg/d (oral or IV depending on symptoms/speed of development) If worsening or no improvement, 1 to 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 to 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 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	

8.0 Hematologic Toxicities	
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 (eg, 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 to 1 mg/kg/d prednisone
G3: Laboratory findings with clinical consequences (G3 thrombocytopenia, anemia, renal insufficiency > 2) G4: Life-threatening consequences (eg, CNS hemorrhage or thrombosis/embolism or renal failure)	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 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
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	

8.0 Hematologic Toxicities	
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 (eg, renal insufficiency, petechiae) G4: Life-threatening consequences (eg, CNS thrombosis/ embolism or renal failure)	Continue ICPi with close clinical follow-up and laboratory evaluation Supportive care Permanently discontinue ICPi Begin therapy with eculizumab therapy 900 mg weekly for 4 doses, 1200 mg week 5, then 1200 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 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

8.0 Hematologic Toxicities	
G2: Severe, hypocellular marrow < 25% and 2 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%	Hold ICPi and monitor weekly for improvement; if not resolved, discontinue treatment until AE has reverted to G1 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 Continue ICPi, checking CBC weekly for monitoring, initiation of CMV screening Consider holding ICPi 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	

8.0 Hematologic Toxicities	
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	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 thrombocytopenia97; consult for further details)
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 6 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

8.0 Hematologic Toxicities	
	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) 6 rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1 to 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, paroxusmal nocturnal hemoglobinuria; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell count; TTP, thrombotic thrombocytopenic purpura.

Table A 9 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: Hold ICPi and permanently discontinue after G1 High-dose corticosteroids (1 to 2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms) Admit patient, cardiology consultation Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology 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. Holding checkpoint inhibitor therapy is recommended for all grades of 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 (eg, superficial thrombosis)	Continue ICPi Warm compress Clinical surveillance
G2: Venous thrombosis (eg, uncomplicated DVT), medical intervention indicated G3: Thrombosis (eg, uncomplicated PE [venous], nonembolic cardiac mural [arterial] thrombus), medical intervention indicated	Continue ICPi Management according to CHEST, ACC, and/or AHA guidelines and 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 (eg, 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: ACC, American College of Cardiology; AHA, American Heart Association; 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 A 10 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 Systemic corticosteroids (IV prednisone 1 to 2 mg/kg or methylprednisolone 0.8 to 1.6 mg/kg) and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion
Additional considerations: Consider use of infliximab or other TNF-a blockers in cases that are severe and refractory to standard treatment	

10.0 Ocular Toxicities	
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 2/40	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 10 Country-specific Requirements

Not applicable.

Appendix 11 Protocol Amendment History

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

Protocol Version 2.0 (03 February 2021)

Overall Rationale for the Amendment

The key purpose of this amendment is to further assess M6223 treatment with bintrafusp alfa by the addition of a Q3W dosing schedule.

Section # and Name	Description of Change	Brief Rationale
Title page	• Medical Monitor Name was 'to be determined' in the original protocol. The row has now been removed. • Amendment number row was removed. • Medical Responsible contact details updated.	The administrative information is not essential to the protocol. Amendment numbers are not used and can cause confusion with protocol version numbers. To provide the correct contact details.
1.1 Synopsis; 1.2 Schema; 1.3 Schedule of Activities; 3 Objectives; 6.1 Study Intervention(s) Administration; 6.6.1.2 M6223; 6.6.1.2.2 Part 1B (Dose Escalation of M6223 combined with Bintrafusp alfa); 6.6.1.3 Bintrafusp alfa (Combined with M6223); 8.2.4 Clinical Safety Laboratory Assessments	An additional dosing schedule of every 3 weeks (Q3W) and the corresponding recommended dose for expansion (RDE) cohorts have been added to Part 1B. Objectives have been updated to incorporate the Q3W dose regimen addition in Part 1B (PK assessments at 21 days postdose added).	To further assess M6223 treatment with bintrafusp alfa by the addition of a Q3W dosing schedule.
1.2 Schema; 6.6.1.2.2 Part 1B (Dose Escalation of M6223 combined with Bintrafusp alfa)	It has been confirmed that the combination starting dose in Part 1B will be dose level 4 of Part 1A. In the original protocol, dose level 4 **or** 5 was planned. The example tables of potential dose levels have been updated accordingly.	The necessary data to support the starting dose in Part 1B will be generated from the lower dose level.
1.3.1 M6223 Monotherapy Dose Escalation (Part 1A); 1.3.2 M6223 Dose Escalation in Combination with Bintrafusp alfa (Part 1B); 1.3.3 ECG Assessment, Pharmacokinetic, Anti-Drug Antibody, and Biomarker Sampling;	• In Tables 1 and 2, for monotherapy and the every 2 weeks (Q2W) regimen, a window of ± 3 days has been added for the tumor assessment and the on-treatment tumor biopsy on Day 1 of Cycle 2 has been specified as predose. • In Table 4, for the Q2W regimen, the window of ± 1 day has been specified for the Cycle 1 visits on Days 5 and 8 and it has been clarified that the visits should be at least 48 hours apart.	To provide consistency; the same time windows presented in Tables 1, 2, 3 have been added to Table 4.

Section # and Name	Description of Change	Brief Rationale
8.8 Biomarkers	• Further ctDNA/ctRNA samples have been added on Day 1 in Cycles 3, 7, 13, 19 and every 6 cycles thereafter, and at End of Treatment. • In the Schedule of Activities for monotherapy and the Q2W regimen, the requirements for urinalysis were updated to align with Section 8.2.4.	Additional time points added for the purpose of longitudinal disease monitoring. Amended for consistency.
4.1 Overall Design	It has been clarified that Part 1A may still be ongoing when Part 1B starts and the order of priority for backfill has been noted for the 2 regimens in Part 1B.	For clarity and to specify that backfill for the Q2W regimen will be prioritized over the Q3W regimen in Part 1B.
4.2 Scientific Rationale of Study Design; 4.3 Justification for Dose; 9.4 Statistical Analyses; Appendix 8 Description of the Bayesian Dose Escalation Model	Rationale added for the Q3W dosing schedule, and the statistical and pharmacokinetic (PK) methods have been adjusted accordingly.	The rationale and justification for this additional dose level/regimen has been made in the appropriate sections throughout.
1.3 Schedule of Activities; 8.2.2 Vital Signs	• Vital signs assessments added on Days 2 and 5 of Cycle 1 in Parts 1A and 1B. • Clarified that either oral or tympanic temperature will be recorded (and not both). • For Part 1B, it was added that vital signs should be taken prior to bintrafusp alfa, prior to M6223 and after M6223.	• To align vital signs assessments with the other safety assessment time points. • To provide clarity for sites. • To clarify the assessment timing with respect to each dose in Part 1B.
6.6.1.2.1 Part 1A (M6223 Monotherapy Dose Escalation); 9.4.2.1 Dose Escalation	For defining the maximum tolerated dose (MTD) and RDE, the estimated **mean** dose-limiting toxicity (DLT) rate for the MTD/RDE was amended to **median** DLT rate for the MTD/RDE.	Changed to reflect that the posterior samples might show a skewed distribution so median is a more robust measure.
6.6.2 Dose modification	It was clarified that individual dose reductions are not allowed.	For clarity.
6.8.6 Thrombo-embolic Events; 6.9.1.2 Potential Risks	• Thromboembolic events have been noted as an AESI for M6223. • A section on bleeding events was added to note the potential risk for bintrafusp alfa.	To update the protocol in accordance with the current risk profile of each agent.
8.8 Biomarkers	Blood volume for TIGIT target occupancy sample has been reduced to 4 mL.	The necessary blood volume has been reduced.
1.1 Synopsis; 9.2 Sample Size Determination	Sample size description has been adjusted to include the additional dosing schedule in Part 1B.	To adapt the sample size for the inclusion of the additional regimen.
Title page; Appendix 12; Appendix 13; Appendix 14	Title page and signature pages were updated to remove instructional template text and to add the ClinicalTrial.gov identifier for this study.	To correct a minor editorial error and add information made available since finalizing the original protocol.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

Appendix 12 Sponsor Signature Page

Study Title:	Phase I, First-in-Human, Open-Label, Multiple Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M6223 (an Inhibitor of TIGIT) as Single Agent and in Combination with Bintrafusp alfa (anti-PD-L1/TGFβ Trap) in Participants with Metastatic or Locally Advanced Solid Unresectable Tumors
Regulatory Agency Identifying Numbers:	ClinicalTrials.gov Identifier: NCT04457778 IND: CCI
Clinical Study Protocol Version:	Version 3.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	Medical Responsible
Institution:	Merck Healthcare KGaA Global Clinical Development Immuno-Oncology
Address:	Frankfurter Str. 250 64293 Darmstadt Germany
Telephone number:	PPD
Fax number:	
E-mail address:	PPD

Appendix 13 Coordinating Investigator Signature Page

Study Title:	Phase I, First-in-Human, Open-Label, Multiple Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M6223 (an Inhibitor of TIGIT) as Single Agent and in Combination with Bintrafusp alfa (anti-PD-L1/TGFβ Trap) in Participants with Metastatic or Locally Advanced Solid Unresectable Tumors
Regulatory Agency Identifying Numbers:	ClinicalTrials.gov Identifier: NCT04457778 IND: CCI
Clinical Study Protocol Version:	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 on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

07/DEC/2021

Date of Signature

Name, academic degree:	PPD
Function/Title:	PPD
Institution:	PPD
Address:	PPD
Telephone number:	PPD
Fax number:	Not Applicable
E-mail address:	PPD

Appendix 14 Principal Investigator Signature Page

Study Title:	Phase I, First-in-Human, Open-Label, Multiple Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M6223 (an Inhibitor of TIGIT) as Single Agent and in Combination with Bintrafusp alfa (anti-PD-L1/TGFβ Trap) in Participants with Metastatic or Locally Advanced Solid Unresectable Tumors
Regulatory Agency Identifying Numbers:	ClinicalTrials.gov Identifier: NCT04457778 IND: CCI [redacted]
Clinical Study Protocol Version:	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 on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

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

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: