Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase II, Multicenter, Randomized, Open-Label, Parallel-Arm, Umbrella Study of Avelumab (MSB0010718C) in Combination with Other Anti-Tumor Agents as a Maintenance Treatment in Participants with Locally Advanced or Metastatic Urothelial Carcinoma Whose Disease Did Not Progress with First Line Platinum-Containing Chemotherapy
Study Number:	MS100070_0119
Protocol Version:	31 July 2025/Version 5.0
Merck Compound:	avelumab
Merck Registered Compound Name in Japan:	Not Applicable
Study Phase:	II
Short Title:	A Study of the Safety and Efficacy of Various Combinations of Avelumab as Therapy in Locally Advanced or Metastatic Urothelial Carcinoma
Acronym or Abbreviation:	JAVELIN Bladder Medley
Coordinating Investigator:	PPD , MD John Hopkins University, Baltimore, Maryland, US

Sponsor Name and Legal Registered Address:	Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US and Canada: Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 64293, Darmstadt, Germany In the US and Canada: EMD Serono Research & Development Institute, Inc. an affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, 01821, USA
Regulatory Agency Identifying Numbers:	US IND: 156990 EUCT: 2023-510139-12-00
Keywords	• Avelumab • Avelumab in combination • Bladder cancer • M6223 (anti-TIGIT antibody) • PD-L1 • Sacituzumab govitecan (Trop-2 antibody drug conjugate) • NKTR-255 (IL-15 agonist)

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	06 December 2021
2.0	Global amendment to the original protocol	04 February 2022
2.1	Local amendment for France and Germany	20 July 2022
2.2	Local amendment for France and Italy	28 October 2022
3.0	Global amendment to the protocol	20 March 2023
4.0	Global amendment to the protocol	25 September 2024
4.1	Local amendment for study sites within the European Union	10 March 2025
5.0	Global amendment to the protocol	31 July 2025

Protocol Version 5.0 (31 July 2025)

Overall Rationale for the Amendment

This protocol amendment was enacted after primary analysis database lock for the study (05 June 2025); thus, the main data collection was completed at the time of enactment. The main purpose of the amendment is to provide new Schedules of Assessments (SoA) to reduce participant burden and to clarify treatment options for participants who are continuing in the study after the primary analysis database lock. The previous SoAs from Protocol Version 4.0, which are no longer valid, are available in Appendix 11. CCI [redacted] Further sections of the protocol, such as Section 4.4 (End of Study Definition), were updated as applicable.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Replaced Schedule of Activities for all groups	Reduce schedule of assessments to avoid collecting data which will not be analyzed after implementation of this protocol amendment (Protocol Version 5.0), and to reduce participant and site burden

1.3 Schedule of Activities	Deleted Bioanalytical and Biomarkers Schedule of Assessments for all groups	No additional analyses in bioanalytical and biomarkers will be performed after the implementation of this protocol amendment (Protocol Version 5.0). This will reduce site and patient burden
2.3.1 Risk Assessment	Included cytokine release syndrome with avelumab infusion-related reactions in risk assessment table	For consistency with latest information in the Investigator's Brochure update
4.4 End of Study Definition	Updated the end of study definition	To align end of study definition with clarification on post-study supply of study intervention and ensure consistency with Section 6.6
6.5.1 Avelumab	Added cytokine release syndrome (CRS) to possible avelumab infusion-related reactions	For consistency with latest Investigator's Brochure update
6.5.1 Avelumab	Added neutropenia and gastritis as possible avelumab immune-related adverse events and added reference to latest Investigator's Brochure	For consistency with latest Investigator's Brochure update
6.5.2 Sacituzumab Govitecan	Added febrile neutropenia to common adverse reactions to sacituzumab govitecan and recommendation to treat with granulocyte colony-stimulating factor as primary and secondary prophylaxis in patients at increased risk of febrile neutropenia	To reflect latest IB
6.6 Continued Access to Study Intervention After the End of the Study	Updated treatment options and drug supply information for combination treatment and for avelumab monotherapy	To provide updated treatment information for participants still on study treatment after the study has ended
7.1 Discontinuation of Study Intervention	For withdrawal of consent from further treatment, added "with one, or for participants randomized to one of the combination arms, all investigational treatments,"	For clarity
7.1 Discontinuation of Study Intervention	Added permanent unavailability of study intervention due to discontinuation of manufacturing and further drug development as reason for study intervention discontinuation	To reflect current drug development and availability information and for consistency with Section 6.6

8.1 Efficacy Assessments and Procedures	Added text stating with this protocol amendment, tumor assessments will be performed according to local practice guidelines until discontinuation of study treatment.	As the database lock for the primary analysis for this study will have occurred, no additional efficacy/response data (other than OS) will be collected after the implementation of this protocol amendment (Protocol Version 5.0)
8.2.6 Data Monitoring Committee	Added the following statement "After the primary analysis, the Sponsor's routine safety surveillance will continue on a regular basis."	For clarity and assurance that safety surveillance will continue
8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting	Added SUSARs to list of terms defined in Appendix 4	To direct Investigators to SUSAR definition
8.3.3 Regulatory Reporting Requirements for Serious Adverse Events	Added reporting requirements for SUSARs	To be in accordance with Clinical Trial Directive/EU CTR
8.3.4 Pregnancy	Updated time for pregnancy information to be collected from the follow-up visit to 6 months after the last dose of the study intervention for female participants or until 3 months after the last dose of the study intervention for female partners of male participants	For consistency with latest IB
8.3.5.1 Infusion-related Reactions	Added cytokine release syndrome to possible avelumab infusion-related reactions	For consistency with latest Investigator's Brochure update
8.4 Pharmacokinetics	Added statement that as of the implementation of the current protocol Amendment (Version 5.0), no further PK samples will be collected; therefore, the sample collection tables have been deleted.	For clarity and instructions to Investigators
8.6 Biomarkers	Added statement that as of the implementation of the current protocol Amendment (Version 5.0), no further biomarker samples will be collected; therefore, the sample collection tables have been deleted.	For clarity and instructions to Investigators
8.7 Immunogenicity Assessments	Added statement that as of the implementation of the current protocol Amendment (Version 5.0), no further immunogenicity samples will be collected; therefore, the sample collection tables have been deleted.	For clarity and instructions to Investigators
Section 8.9 Patient Reported Outcomes	Added text describing deletion of NCCN FACT, FBISI-18, CCI [redacted]	No further analyses will be performed on patient-reported outcome questionnaires after the Primary Analysis and implementation of this protocol amendment (Protocol Version 5.0)

9.4.4 Sequence of Analyses	Safety and OS update as final analysis added to the sequence of statistical analysis	Final analysis was not specified in the prior version
Appendix 2 Study Governance, Regulatory and Ethical Considerations	Added a clarification that protocol will be conducted in compliance with Regulation [EU] No 536/2014	To be in accordance with Clinical Trial Directive/EU CTR
Appendix 2 Study Governance, Regulatory and Ethical Considerations Clinical Study Report	Clarified that the Clinical Study Report will be written after the primary analysis for the study and that any additional data generated after the primary analysis cut-off date will be summarized in an addendum	To reflect current operational and reporting realities
Appendix 2 Study Governance, Regulatory and Ethical Considerations Study and Site Closure	CCI [redacted]	To reflect current drug development realities
Appendix 4	Added SUSAR definition	To be in accordance with Clinical Trial Directive/EU CTR
Appendix 10 Country-specific Requirements	Added Appendix 10 to describe submission of SUSAR to Eudravigilance database	To be in accordance with Clinical Trial Directive/EU CTR
Appendix 11 Protocol Amendment History	Updated with changes for Version 4.1 and 4.0	Update in history since last amendment

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A Phase II, multicenter, randomized, open-label, parallel-arm, umbrella study of avelumab (MSB0010718C) in combination with other anti-tumor agents as a maintenance treatment in participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with first line platinum-containing chemotherapy

Short Title: A study of the safety and efficacy of various combinations of avelumab as therapy in locally advanced or metastatic urothelial carcinoma

Rationale: The current study explores various post platinum avelumab-based maintenance combination regimens with the objective to further extend the clinical benefit realized with avelumab maintenance monotherapy.

Objectives and Endpoints:

Objectives	Endpoints	Further Estimand Attributes
Primary		
To evaluate PFS of maintenance treatment with avelumab treatment combination regimens compared to maintenance avelumab monotherapy.	PFS as defined from date of randomization to PD according to RECIST v1.1 as assessed by Investigator or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or randomization.	**Population:** Participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with first line platinum-containing chemotherapy. **Treatment:** Maintenance treatment with avelumab treatment combination regimens compared to maintenance avelumab monotherapy. **Strategy for handling intercurrent events:** • Death within 2 scheduled tumor assessments after last evaluable assessment or randomization will be considered as event (composite strategy). • Discontinuation of treatment: The endpoint will be analyzed regardless of whether or not treatment has been discontinued (treatment-policy strategy). • Start of subsequent anticancer treatment: Tumor assessments after start of subsequent anticancer treatment will not be considered for analysis (hypothetical strategy). **Population level summary:** hazard ratio.
To evaluate the safety and tolerability of avelumab combination regimens.	Occurrence of TEAEs, treatment- related AEs, and AESIs as per Qualitative Toxicity Scale (NCI-CTCAE 5.0).	
Secondary		
To evaluate OS of maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy followed by subsequent anticancer treatment.	OS as measured by time from randomization to death.	**Population:** Participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with first line platinum-containing chemotherapy. **Treatment:** Maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy.

Objectives	Endpoints	Further Estimand Attributes
		Strategy for handling intercurrent events: The endpoint will be analyzed regardless of whether or not the following intercurrent events had occurred (treatment-policy strategy): • Treatment discontinuation. • Start of subsequent anticancer therapy. **Population level summary:** hazard ratio.
To evaluate OR of maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy.	OR according to RECIST v1.1 assessed by Investigator.	**Population:** Participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with first line platinum-containing chemotherapy. **Treatment:** Maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy. **Strategy for handling intercurrent events:** • Discontinuation of treatment: The endpoint will be analyzed regardless of whether or not treatment has been discontinued (treatment-policy strategy). • Start of subsequent anticancer treatment: Tumor assessments after start of subsequent anticancer treatment will not be considered for analysis (while not treated with subsequent anticancer therapy strategy). • Progression according to RECIST v1.1 (while not progressed strategy). **Population level summary:** Objective response rate, odds ratio.
To evaluate DoR of maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy.	DoR according to RECIST v1.1 assessed by Investigator defined as time from first documentation of objective response to PD or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or randomization.	**Population:** Participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with first line platinum-containing chemotherapy and confirmed OR according to RECIST v1.1. **Treatment:** Maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy. **Strategy for handling intercurrent events:** Same strategies as defined for PFS.

Objectives	Endpoints	Further Estimand Attributes
		Population level summary: Median DoR.
To collect PK concentration data of avelumab, M6223, SG (derived from total SN-38 and unconjugated SN-38), and NKTR-255 to contribute to respective PopPK analyses and exposure-response analyses.	Concentration will be listed and descriptively summarized as appropriate. Population PK and exposure-response results will be reported separately in a standalone report, as it may also include data from other studies.	
To characterize the immunogenicity of avelumab administered alone or in combination CCI [redacted]	CCI [redacted]	
To evaluate the effect of maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy on disease related physical symptoms during treatment.	Change from baseline score of NCCN FACT FBISI-18 DRS-P at Week 13 visit.	**Population:** Participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with first line platinum-containing chemotherapy. **Treatment:** Maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy. **Strategy for handling intercurrent events:** • Discontinuation of treatment: The endpoint will be analyzed according to the hypothetical strategy, i.e. as if participants were still on randomized treatment at Week 13 visit. • Death: The endpoint will be analyzed according to the hypothetical strategy, i.e. as if participants were still alive and on randomized treatment at Week 13 visit. **Population level summary:** Difference in least-squares means of the change from baseline DRS-P score at Week 13 visit based on a MMRM.

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; DoR = duration of response; DRS-P = disease related symptom-physical subscale; MMRM = mixed model repeated measures; NCCN FACT FBISI-18 = National Comprehensive Cancer Network functional assessment of cancer therapy bladder symptom index; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; OR = objective response; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; RECIST v1.1= Response Evaluation Criteria in Solid Tumors, version 1.1; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event.

Overall Design: This is a Phase II, multicenter, randomized, open-label study of avelumab in combination with sacituzumab govitecan, avelumab in combination with M6223, and avelumab in combination with NKTR-255 compared to avelumab alone as a maintenance treatment after completion of first line platinum-based chemotherapy without evidence of disease progression in participants with unresectable locally advanced or metastatic urothelial carcinoma.

Eligible participants will be randomized 1:2:2:2 to:

- Group A: avelumab 800 mg once every 2 weeks (Q2W).
- Group B: sacituzumab govitecan 10 mg/kg Q1W on Days 1 and 8 of 21-day treatment cycles in combination with avelumab 800 mg Q2W.
- Group C: CCI [redacted]
- Group D: CCI [redacted]

The JAVELIN Bladder Medley Study will have a safety run-in with 21 randomized participants, 3 in Group A and 6 each in Groups B, C, and D.

An internal Data Monitoring Committee (DMC) will start to review the available accumulated safety, clinical, and PK data in an unblinded fashion after the data cutoff, which is defined as 5 weeks after the last of the 21 participants has been randomized into the safety run-in phase. Participant screening and enrollment activities will continue between the enrollment of last participant in the safety run-in to the occurrence of the internal DMC meeting. In addition, the internal DMC will review all available safety, clinical and PK data on a regular basis and decide by consensus on the continuation or suspension of enrollment. The specific working procedures will be described in an internal DMC charter.

In addition, a dedicated team composed of safety and medical representatives will review safety data of participants under treatment in the proposed combinations on a regular basis. Special consideration will be given to any unexpected/unlabeled toxicities Grade ≥ 3, serious adverse events (SAEs) regardless of causality and defined adverse events assessed as related to any of the study interventions. Potential safety signals can be escalated to the internal DMC at any time during the study (Ad hoc internal DMC).

Brief Summary:

The purpose of this study is to assess the safety and efficacy of avelumab in combination with other anti-tumor agents as a maintenance treatment in participants with bladder cancer. Study details include:

- Study Duration: until worsening, growth, or spread of the disease. If study intervention is permanently discontinued due to disease progression or clinical deterioration, the participant will remain in the study to be evaluated for survival long-term follow up.
- Treatment Duration: until unacceptable toxicity, withdraw consent or initiation of a new treatment.

- Visit Frequency: Groups A (avelumab monotherapy) and C (avelumab + M6223) every 2 weeks, Group B every 2 weeks (for avelumab) and Days 1 and 8 every 3 weeks (for sacituzumab govitecan), Group D every 2 weeks (for avelumab) and every 4 weeks (for NKTR-255).

Number of Participants: Approximately a total of 252 participants will be randomly assigned to study intervention with 1:2:2:2 randomization ratio between Group A (control), B, C, and D.

Study Intervention Groups and Duration: Participants will be randomized 1:2:2:2 to Group A, B, C, or D. The planned duration of the study for each participant will be until progressive disease including the following:

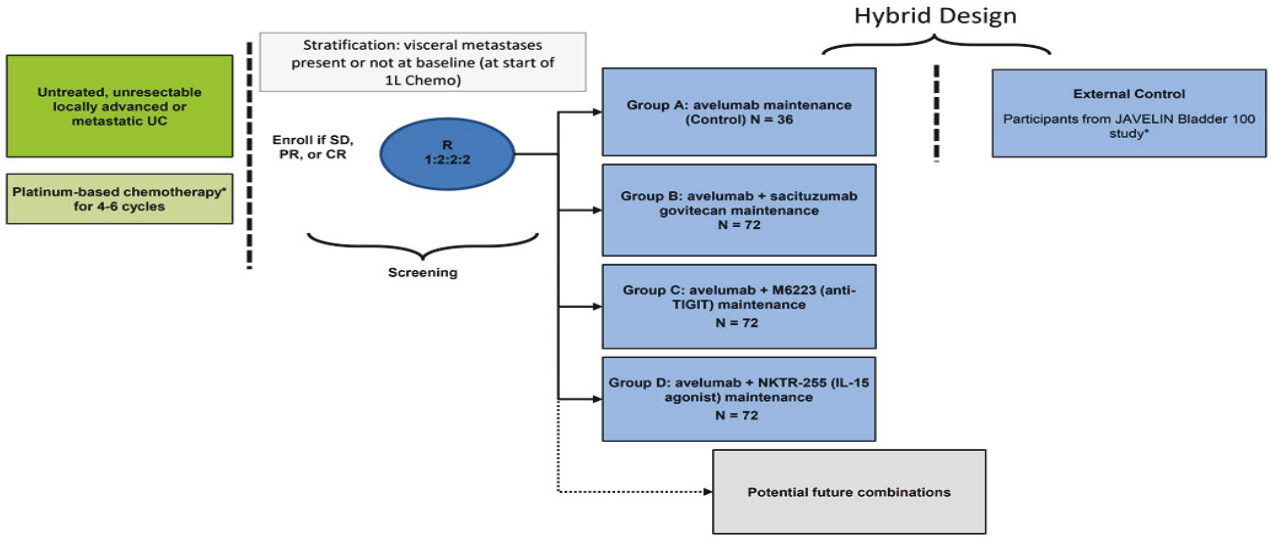
- Up to 4-week Screening Period.
- 30 and 90-day safety follow up period post EOT.
- Long-term follow up period of every 12 weeks thereafter.

Permitted visit windows are detailed in the schedule of activities.

Involvement of Special Committee(s): Yes.

1.2 Schema

Figure 1 MS100070_0119 Study Schema



* The control group of 36 randomized participants will be extended by data from an external control, i.e. the JAVELIN Bladder 100 study. Participants randomized to the investigational arm of the JAVELIN Bladder 100 study (avelumab plus best supportive care) are in line with inclusion/exclusion criteria of the JAVELIN Bladder Medley Study. Comparability between the external and the randomized control groups will be based on baseline information. Platinum-based chemotherapy: gemcitabine + cisplatin, or gemcitabine + carboplatin.

Abbreviations: CR = complete response; N = number of participants; PR = partial response; R = randomization; SD = stable disease; TIGIT = T-cell immune-receptor with Ig and ITM domains; UC = urothelial carcinoma.

1.3 Schedule of Activities

Since the database lock for the primary analysis for this study will have occurred at the time of enactment of this protocol amendment (Version 5.0), the SoAs have been replaced with updated versions containing fewer assessments to avoid collecting data that will not be analyzed after implementation of this protocol amendment and to reduce participant burden. In addition, bioanalytical and biomarker sample collection will no longer be required; therefore, the tables outlining sample collection (Tables 4, 5, and 6 of Protocol Version 4.0) have been deleted. All SoAs as they were applicable prior to implementation of Protocol Version 5.0 are available in Appendix_11.

Table 1 Group B Schedule of Activities(as of enactment of Protocol Version 5.0)

Assessments and Procedures	Intervention Period			End of Treatment/Follow up After Last Dose				Notes
Group B: Avelumab + Sacituzumab Govitecan	**Avelumab + sacituzumab govitecan**			**EOT**	**Safety FU**		**Long-Term FU**	
	Sacituzumab govitecan Days 1 and 8 of each 3-week cycle		**Avelumab Q2W**	**7 days**	**30 days**	**90 days**	**Every 12 weeks**	
	Week 1, 4, 7, 10, 13, 16, 19, 22…	**Week 2, 5, 8, 11, 14, 17, 20, 23…**	**Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…**					
Visit Window	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of avelumab the minimum interval in between doses can be no less than 10 days. In case of sacituzumab govitecan, if treatment delays are greater than 2 days, the next treatment date should be calculated based on the actual treatment day or Day 8 should be skipped. Day 8 administration of sacituzumab govitecan must be no less than 7 days after Day 1. The minimum amount of time between Day 1 and Day 8 of previous cycle must be 14 days.
Physical Examination	X (see Notes)							A physical examination directed to signs and symptoms should be conducted at each visit
Vital Signs	X							Includes respiratory rate, temperature, blood pressure and pulse rate according to SoC and institutional guidelines, but at least every 12 weeks during the treatment phase and at the EOT and 30-day Safety FU. Weight will be measured before each cycle to calculate sacituzumab govitecan dose.
ECOG Performance Status	X			X	X			According to SoC and institutional guidelines, but at least every 4 weeks during the treatment phase.
Serum/Urine Pregnancy Test (WOCBP only)			X (see Notes)	X	X			Every 4 weeks (every other avelumab dosing if sacituzumab govitecan is discontinued before avelumab).

Assessments and Procedures Group B: Avelumab + Sacituzumab Govitecan	Intervention Period			End of Treatment/Follow up After Last Dose				Notes
	Avelumab + sacituzumab govitecan			EOT	Safety FU		Long-Term FU	
	Sacituzumab govitecan Days 1 and 8 of each 3-week cycle		Avelumab Q2W	7 days	30 days	90 days	Every 12 weeks	
	Week 1, 4, 7, 10, 13, 16, 19, 22…	Week 2, 5, 8, 11, 14, 17, 20, 23…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Window	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of avelumab the minimum interval in between doses can be no less than 10 days. In case of sacituzumab govitecan, if treatment delays are greater than 2 days, the next treatment date should be calculated based on the actual treatment day or Day 8 should be skipped. Day 8 administration of sacituzumab govitecan must be no less than 7 days after Day 1. The minimum amount of time between Day 1 and Day 8 of previous cycle must be 14 days.
Clinical Laboratory Tests Hematology[a] and Coagulation	X	X	X (see Notes)	X	X			See Appendix 6. Samples for clinical laboratory tests for all treatment cycles may be drawn up to 72 hours prior of infusion [a]Dosing with sacituzumab govitecan is permitted if absolute neutrophil count is ≥ 1500/mm^3 on Day 1 and ≥ 1000/ mm^3 on Day 8. At Day 1 of every avelumab dosing if sacituzumab govitecan is discontinued before avelumab.
Full Serum Chemistry	X	X	X (see notes)	X	X	X		Full serum chemistry will be performed on Day 1 of every avelumab and/or SG administration
Thyroid Function (TSH and FT4 [or total T4])	Every 6 weeks starting Week 7 or earlier if clinically indicated			X				
Urinalysis	If clinically indicated			X	X			

Assessments and Procedures Group B: Avelumab + Sacituzumab Govitecan	Intervention Period			End of Treatment/Follow up After Last Dose				Notes
	Avelumab + sacituzumab govitecan			EOT	Safety FU		Long-Term FU	
	Sacituzumab govitecan Days 1 and 8 of each 3-week cycle		Avelumab Q2W	7 days	30 days	90 days	Every 12 weeks	
	Week 1, 4, 7, 10, 13, 16, 19, 22…	Week 2, 5, 8, 11, 14, 17, 20, 23…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Window	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of avelumab the minimum interval in between doses can be no less than 10 days. In case of sacituzumab govitecan, if treatment delays are greater than 2 days, the next treatment date should be calculated based on the actual treatment day or Day 8 should be skipped. Day 8 administration of sacituzumab govitecan must be no less than 7 days after Day 1. The minimum amount of time between Day 1 and Day 8 of previous cycle must be 14 days.
12-lead ECG	If clinically indicated			X				Electrocardiograms will be recorded after the participant has been in a supine position, breathing quietly for at least 5 minutes.
Avelumab			X					Avelumab Q2W until unacceptable toxicity. When infusions of sacituzumab govitecan and avelumab occur on the same days, treatment administration will start with avelumab and then the combination agent.

Assessments and Procedures Group B: Avelumab + Sacituzumab Govitecan	Intervention Period			End of Treatment/Follow up After Last Dose				Notes
	Avelumab + sacituzumab govitecan			EOT	Safety FU		Long-Term FU	
	Sacituzumab govitecan Days 1 and 8 of each 3-week cycle		Avelumab Q2W	7 days	30 days	90 days	Every 12 weeks	
	Week 1, 4, 7, 10, 13, 16, 19, 22…	Week 2, 5, 8, 11, 14, 17, 20, 23…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Window	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of avelumab the minimum interval in between doses can be no less than 10 days. In case of sacituzumab govitecan, if treatment delays are greater than 2 days, the next treatment date should be calculated based on the actual treatment day or Day 8 should be skipped. Day 8 administration of sacituzumab govitecan must be no less than 7 days after Day 1. The minimum amount of time between Day 1 and Day 8 of previous cycle must be 14 days.
Sacituzumab govitecan	X	X						Sacituzumab govitecan: Day 1 and 8 of 21-day treatment cycles until unacceptable toxicity or new documented progressive disease after discussing with the medical monitor When infusions of sacituzumab govitecan and avelumab occur on the same days, treatment administration will start with avelumab and then sacituzumab govitecan. The administration of stimulating growth-colony factors as primary and secondary prophylaxis is strongly recommended in participants at increased risk of febrile neutropenia, participants with previous neutropenia, poor performance status, organ dysfunction (including renal, liver, or cardiovascular dysfunction), or multiple comorbid conditions to decrease the effects of neutropenia with sacituzumab govitecan

Assessments and Procedures Group B: Avelumab + Sacituzumab Govitecan	Intervention Period			End of Treatment/Follow up After Last Dose				Notes
	Avelumab + sacituzumab govitecan			EOT	Safety FU		Long-Term FU	
	Sacituzumab govitecan Days 1 and 8 of each 3-week cycle		Avelumab Q2W	7 days	30 days	90 days	Every 12 weeks	
	Week 1, 4, 7, 10, 13, 16, 19, 22…	Week 2, 5, 8, 11, 14, 17, 20, 23…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Window	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of avelumab the minimum interval in between doses can be no less than 10 days. In case of sacituzumab govitecan, if treatment delays are greater than 2 days, the next treatment date should be calculated based on the actual treatment day or Day 8 should be skipped. Day 8 administration of sacituzumab govitecan must be no less than 7 days after Day 1. The minimum amount of time between Day 1 and Day 8 of previous cycle must be 14 days.
AE & SAE Review	⇐==========⇒			X	X	X		Treatment-related non-serious TEAEs and all SAEs will be evaluated and documented at each study visit until the 90-day Safety FU. Ongoing treatment-related AEs and all SAEs at the 30-day and 90-day Safety FU visits must be followed up until resolution, stabilization, or until the outcome is known, unless the participant is documented as “lost to follow-up”.
Concomitant Medication Review	⇐==========⇒			X	X	X		Concomitant medications will be collected at each visit and documented for treatment-related non-serious TEAEs and all SAEs at each study visit until the 90-day Safety FU.
Tumor Assessments	X: (see Notes)							To be performed according to local practice guidelines until discontinuation of study treatment.
Subsequent Anticancer Therapy				X	X	X	X	No further data collection after the date when the last participant is randomized + 2 years (06 June 2026).

Assessments and Procedures	Intervention Period			End of Treatment/Follow up After Last Dose				Notes
Group B: Avelumab + Sacituzumab Govitecan	Avelumab + sacituzumab govitecan			EOT	Safety FU		Long-Term FU	
	Sacituzumab govitecan Days 1 and 8 of each 3-week cycle		Avelumab Q2W	7 days	30 days	90 days	Every 12 weeks	
	Week 1, 4, 7, 10, 13, 16, 19, 22…	Week 2, 5, 8, 11, 14, 17, 20, 23…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Window	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of avelumab the minimum interval in between doses can be no less than 10 days. In case of sacituzumab govitecan, if treatment delays are greater than 2 days, the next treatment date should be calculated based on the actual treatment day or Day 8 should be skipped. Day 8 administration of sacituzumab govitecan must be no less than 7 days after Day 1. The minimum amount of time between Day 1 and Day 8 of previous cycle must be 14 days.
Survival Assessment					X	X	X	90-day and long-term follow up may be telephone visits. No further data collection after the date when the last participant is randomized + 2 years (06 June 2026).

AE = adverse event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT4 = free thyroxine; FU = follow up; PD = progressive disease; PE = physical examination; Q2W = every 2 weeks; SAE = serious adverse event; SoC = standard of care; TEAE = treatment-emergent adverse event; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Table 2 Group A and C Schedule of Activities(as of enactment of Protocol Version 5.0)

Assessments and Procedures Group A: Avelumab Group C: Avelumab + M6223	Intervention Period	End of Treatment / Follow up After Last Dose				Notes
	Q2W	EOT	Safety FU		Long-Term FU	
	Weeks 1, 3, …	7 days	30 days	90 days	Every 12 weeks	
Visit Window	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of treatment delays greater than 2 days, the next treatment date should be calculated based on the actual treatment day. Participants should not be dosed before 10 days from the last dose.
Physical Examination	X	X	X			According to SoC and institutional Guidelines during treatment phase, EOT and Safety FU.
Vital Signs	X	X	X			Includes respiratory rate, weight, temperature, blood pressure, and pulse rate according to SoC and institutional guidelines
ECOG Performance Status	Every 4 weeks	X	X			According to SoC and institutional guidelines, but at least every 4 weeks during the treatment phase.
Serum/Urine Pregnancy Test (WOCBP only)	Every 4 weeks	X	X			Every 4 weeks (every other avelumab dosing).
Clinical Laboratory Tests Full Hematology and Coagulation	X	X	X			Full hematology and coagulation test as detailed in Appendix 6. Coagulation to be continued until M6223 treatment discontinuation and as per local guideline thereafter. Samples for clinical laboratory tests for all treatment cycles may be drawn up to 72 hours prior of infusion.
Full Serum XChemistry	X (See notes)	X	X	X		Full serum chemistry will be performed on Day 1 of every avelumab and/or M6223 administration.
Thyroid Function (TSH and FT4 [or total T4])	Every 6 weeks or earlier if clinically indicated	X				Every 3 avelumab administrations (Week 19, 25, 31…).
Urinalysis	If clinically indicated	X	X			
12-lead ECG	If clinically indicated	X				Electrocardiograms will be recorded after the participant has been in a supine position breathing quietly for at least 5 minutes.
Avelumab	X					Group A: avelumab monotherapy.

Assessments and Procedures Group A: Avelumab Group C: Avelumab + M6223	Intervention Period	End of Treatment / Follow up After Last Dose				Notes
	Q2W	EOT	Safety FU		Long-Term FU	
	Weeks 1, 3, …	7 days	30 days	90 days	Every 12 weeks	
Visit Window	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of treatment delays greater than 2 days, the next treatment date should be calculated based on the actual treatment day. Participants should not be dosed before 10 days from the last dose.
M6223	X					CCI [redacted]
AE & SAE Review	⇐==========⇒	X	X	X		Treatment-related non-serious TEAEs and all SAEs will be documented at each study visit until the 90-day Safety FU. Ongoing treatment-related AEs and all SAEs at the 30-day and 90-day Safety FU visits must be followed up until resolution, stabilization, or until the outcome is known, unless the participant is documented as “lost to follow-up”.
Concomitant Medication Review	⇐==========⇒	X	X	X		Concomitant medications will be documented for treatment-related non-serious TEAEs and all SAEs at each study visit until the 90-day Safety FU
Tumor Assessments	X: see Notes					To be performed according to local practice guidelines until discontinuation of study treatment
Subsequent Anticancer Therapy		X	X	X	X	No further data collection after the date when the last participant is randomized + 2 years (06 June 2026).
Survival Assessment			X	X	X	90-day and long-term follow up may be telephone visits. No further data collection after the date when the last participant is randomized + 2 years (06 June 2026).

AE = adverse event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT4 = free thyroxine; FU = Follow up; PD = progressive disease; PE = physical examination; Q2W = every 2 weeks; SAE = serious adverse event; SoC = standard of care; TEAE = treatment-emergent adverse event; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Table 3 Group D Schedule of Activities(as of enactment of Protocol Version 5.0)

Assessments and Procedures	Intervention Period		End of Treatment/Follow-up After Last Dose				Notes
Group D: Avelumab + NKTR-255	Avelumab + NKTR-255		EOT	Safety FU		Long-Term FU	
	NKTR-255 Q4W	Avelumab Q2W	7 days (± 7 days)	30 days (± 7 days)	90 days (± 7 days)	Every 12 weeks	
	Week 1, 5,9,13,17,21…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Windows	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of treatment delays greater than 2 days, the next treatment date should be calculated based on the actual treatment day. In the case of avelumab, participants should not be dosed before 10 days from the last dose.
Physical Examination	X	X (see Notes)	X	X			According to SoC and institutional guidelines during treatment phase but at least every 12 weeks and at EOT.
Vital Signs	X	X	X	X			Includes height (collect at Screening only), respiratory rate, temperature, weight, blood pressure, and pulse rate according to SoC and institutional guidelines but at least every 12 weeks during treatment phase and at EOT. Weight will be measured before each cycle corresponding to NKTR-255 to calculate appropriate dose
ECOG Performance Status	X	X (see Notes)	X	X			According to SoC and institutional guidelines, but at least every 4 weeks during the treatment phase.
Serum/Urine Pregnancy Test (WOCBP only)	X	X (see Notes)	X	X			Every 4 weeks (every other avelumab dosing if NKTR-255 is discontinued before avelumab).
Clinical Laboratory Tests Full Hematology and Coagulation	X	X	X	X			See Appendix 6. Samples for clinical laboratory tests for all treatment cycles may be drawn up to 72 hours prior of infusion.
Full Serum Chemistry		X (See notes)	X	X	X	-	Full serum chemistry will be performed on Day 1 of every avelumab administration.

Assessments and Procedures	Intervention Period		End of Treatment/Follow-up After Last Dose				Notes
Group D: Avelumab + NKTR-255	Avelumab + NKTR-255		EOT	Safety FU		Long-Term FU	
	NKTR-255 Q4W	Avelumab Q2W	7 days (± 7 days)	30 days (± 7 days)	90 days (± 7 days)	Every 12 weeks	
	Week 1, 5,9,13,17,21…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Windows	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of treatment delays greater than 2 days, the next treatment date should be calculated based on the actual treatment day. In the case of avelumab, participants should not be dosed before 10 days from the last dose.
Thyroid Function (TSH and FT4 [or total T4])	Every 6 weeks starting Week 7 or earlier if clinically indicated		X				
Urinalysis	If clinically indicated		X	X			
12-lead ECG	If clinically indicated		X				Electrocardiograms will be recorded after the participant has been in a supine position breathing quietly for at least 5 minutes.
Avelumab		X					Avelumab Q2W until unacceptable toxicity for all the cohorts.
NKTR-255	CCI						CCI [redacted]
AE & SAE Review	⇐==========⇒		X	X	X		Treatment-related non-serious TEAEs and all SAEs will be documented at each study visit until the 90-day Safety FU. Ongoing treatment-related AEs and all SAEs at the 30-day and 90-day Safety FU visits must be followed up until stabilization or until the outcome is known, unless the participant is documented as “lost to follow-up”.

Assessments and Procedures	Intervention Period		End of Treatment/Follow-up After Last Dose				Notes
Group D: Avelumab + NKTR-255	**Avelumab + NKTR-255**		**EOT**	**Safety FU**		**Long-Term FU**	
	NKTR-255 Q4W	**Avelumab Q2W**	**7 days (± 7 days)**	**30 days (± 7 days)**	**90 days (± 7 days)**	**Every 12 weeks**	
	Week 1, 5,9,13,17,21…	**Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…**					
Visit Windows	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of treatment delays greater than 2 days, the next treatment date should be calculated based on the actual treatment day. In the case of avelumab, participants should not be dosed before 10 days from the last dose.
Concomitant Medication Review	⇐==========⇒		X	X	X		Concomitant medications will be documented for treatment-related non-serious TEAEs and all SAEs at each study visit until the 90-day Safety FU.
Tumor Assessments	X (see Notes)						To be performed according to local practice guidelines until discontinuation of study treatment
Subsequent anticancer therapy			X	X	X	X	No further data collection after the date when the last participant is randomized + 2 years (06 June 2026).
Survival Assessment				X	X	X	90-day and long-term FU may be telephone visits. No further data collection after the date when the last participant is randomized + 2 years (06 June 2026).

AE = adverse event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT4 = free thyroxine; FU = follow-up; PD = progressive disease; PE = physical examination; PK = pharmacokinetics; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; SoC = standard of care; TEAE = treatment-emergent adverse event; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential. .

2 Introduction

MS100070_0119, also known as JAVELIN Bladder Medley, is a Phase II, multicenter, randomized, open-label, parallel-arm, umbrella study of avelumab (MSB0010718C) in combination with other anti-tumor agents as a maintenance treatment in participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with 1L platinum-containing chemotherapy.

The JAVELIN Bladder Medley Study will explore avelumab in combination with other anti-tumor agents such as sacituzumab govitecan, an antibody drug conjugate, M6223, an anti-TIGIT antibody and NKTR-255, an IL-15 receptor agonist. It is hypothesized that avelumab in combination with other agents affecting other pathways will act synergistically to extend the clinical benefit of avelumab.

Avelumab is a programmed cell death-ligand-1 (PD-L1) blocking human antibody indicated for Merkel Cell Carcinoma (MCC), urothelial carcinoma (UC), and renal cell carcinoma (RCC). Detailed information on the chemistry, pharmacology, efficacy, and safety of avelumab is presented in the Investigator's Brochure.

Sacituzumab govitecan is a Trop-2-directed antibody and topoisomerase inhibitor conjugate approved in the US for the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least 2 prior therapies for metastatic disease and with locally advanced and for metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.

M6223 is a fully human IgG1 antibody that binds specifically to T-cell immunoreceptor with Ig and ITIM domains (TIGIT) and inhibits the interaction of TIGIT with its ligands, CD155 and CD112. M6223 can also interrupt the interaction of TIGIT with the costimulatory receptor CD226, leading to increased CD226 homodimerization and costimulatory signaling. M6223 is being developed as a treatment of patient with advanced cancer as a monotherapy or in combination with other immune checkpoint inhibitors such as PD-L1 inhibitors.

NKTR-255 is a novel immunotherapeutic anticancer drug candidate that consists of rhIL-15 covalently bound to a 40 kDa polyethylene glycol (PEG) moiety. NKTR-255 binds to IL-15Rα as well as IL2/IL-15R βγ subunits and has the potential to maintain the full spectrum of IL-15 biology, including sustained PD effects on both CD8+ memory T and NK cells. The PEG moiety of NKTR-255 enlarges the hydrodynamic volume, which serves to extend the effective half-life relative to unconjugated rhIL-15. As a result, NKTR-255 is expected to provide sustained IL-15 biological activity without the need for daily dosing.

2.1 Study Rationale

Urothelial cancer is the 10th most common cancer in the world and the 11th most deadly, estimated to have claimed 212,000 lives in 2020 although there has been a slight decrease in

incidence and death over the past few decades (GLOBOCAN). In the United States, bladder carcinoma is the sixth most common cancer with an estimated 80,470 new cases and 17,600 deaths in 2019 (Saginala 2020). Combination chemotherapy with platinum-based regimens is the standard of care for the first line of locally advanced or metastatic bladder cancer.

The approval of immune checkpoint blockade for patients with metastatic disease as well as platinum-resistant or ineligible metastatic bladder cancer has changed the treatment landscape for patients with advanced UC.

Avelumab as monotherapy for treatment of patients with locally advanced or metastatic UC after progression on 1L platinum-based therapy was approved in the US in May 2017, Israel in January 2018, and Canada in May 2018. Avelumab as a maintenance treatment of patients with locally advanced or metastatic UC that has not progressed with 1L platinum-containing chemotherapy was approved by the Food and Drug Administration (FDA) in June 2020, Canada in December 2020, the European Medicines Agency (EMA) in January 2021, in Japan in February 2021, and also in several other countries, e.g., Australia, Switzerland, Argentina, Brazil, United Kingdom Taiwan, South Korea, Singapore, Russia, Mexico, India, Lebanon, United Arab Emirate, Kuwait, Dominican Republic, and Honduras.

The current study explores various post platinum avelumab-based maintenance combination regimens with the objective to further extend the clinical benefit realized with avelumab maintenance monotherapy.

2.2 Background

2.2.1 Urothelial Cancer

Urothelial cancer includes tumors originating from the urothelial cells lining the bladder, renal pelvis, ureter, and urethra. Bladder cancer alone accounts for 90% of UC, and is the 10th most prevalent cancer worldwide, with approximately 500,000 new cases diagnosed and 200,000 deaths attributed to this disease in 2018. UC occurs more frequently in developed countries: in the EU it is the eighth most common cause of mortality due to cancer and in the United States it also occurs at a very high annual incidence rate of 20.5 per 100,000 persons.

2.2.2 Pharmaceutical and Therapeutic Background

For treatment naive patients, combination chemotherapy with platinum-based regimens is the standard of care for locally advanced or metastatic bladder cancer. Combinations of gemcitabine + cisplatin and gemcitabine + carboplatin regimens are now the preferred regimens for the initial treatment of patients with locally advanced or metastatic UC. However, durable and complete responses following first line chemotherapy in patients with advanced UC are uncommon (von der Maase 2005). In general, long-term survival with combination chemotherapy alone has been reported only in patients with good prognosis.

Complicated treatment regimens and severe side effects limit long-term use of these combination agents and most patients will ultimately experience disease progression within approximately

9 months after initial response and the median overall survival is 14 to 15 months with cisplatin-based regimens and 9 to 10 months with carboplatin-based regimens among patients who are not suitable candidates for cisplatin-based therapy. The 5-year survival rate for patients with bladder cancer in the US is 77.1%. However, the poor prognosis for patients with metastatic bladder cancer is reflected in the survival rate declining to only 4.6% (NCCN 2019).

There was a strong rationale for considering immunotherapy in patients with advanced UC. Urologists led the way in the use of immunotherapy in cancer in 1976, having introduced the tuberculosis vaccine bacille Calmette-Guérin (BCG), which stimulates a robust immune response in most patients and has become the standard of care as locoregional therapy after surgical resection of non-muscle-invasive disease. The programmed cell death-1 /programmed death-ligand 1 pathway has emerged as an important biological pathway in UC. Antibodies blocking PD-1 and PD-L1 have demonstrated significant and durable response in patients with advanced UC.

PD-L1 inhibitors such as avelumab as well as the PD-1 inhibitors nivolumab and pembrolizumab have been approved for the treatment of patients with locally advanced or metastatic UC that has progressed during or after platinum-based chemotherapy or that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Additionally, atezolizumab and pembrolizumab are approved as first line treatment option for patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and whose tumors have a PD-L1 expression.

In addition, pembrolizumab is also approved for the treatment of patients with bacillus Calmette-Guérin–unresponsive, high-risk, non–muscle invasive bladder cancer with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

These new approved therapies have changed the treatment landscape for patients with advanced UC.

2.2.3 Avelumab

Avelumab as monotherapy for the treatment of patients with locally advanced or metastatic UC after progression on first line platinum-based therapy or maintenance treatment of patients that has not progressed with first line platinum-containing chemotherapy was approved in countries as mentioned in Section 2.1. Avelumab is also currently approved in several countries including the United States for metastatic MCC and in combination with axitinib for advanced RCC.

For treatment naive patients, combination chemotherapy with platinum-based regimens followed by avelumab maintenance therapy has become the standard of care for locally advanced or metastatic bladder cancer (Bladder Cancer NCCN Guidelines Version 3.2021). Results from the randomized, Phase 3 JAVELIN Bladder 100 trial showed that avelumab significantly prolonged overall survival in all randomized patients compared to best supportive care alone, with a median OS of 21.4 months versus 14.3 months; HR = 0.69; 95% confidence interval (CI): 0.56-0.86; p = 0.0005, with a favorable safety profile. Avelumab also significantly prolonged overall

survival in the PD-L1 positive population; overall survival at 1 year was 79.1% in the avelumab group and 60.4% in the control group (HR = 0.56; 95% CI: 0.40-0.79; P = 0.0003).

With a median OS of 23.8 months versus 15.0 months in the long-term follow-up from the JAVELIN Bladder 100 trial (median follow-up ≥ 38 months; data cutoff, June 4, 2021) OS remained significantly longer in the avelumab maintenance group as compared to BSC (HR = 0.76; 95% CI: 0.63-0.92; P = 0.0036). In patients with PD-L1 positive tumors this effect was even more pronounced; median OS 30.9 months versus 18.5 months (HR = 0.69; 95% CI: 0.52-0.90; P = 0.0064) (Powles 2022).

Despite the recent advances in the management of advanced UC with treatments that rely on immunomodulatory mechanisms to target tumors, there is still an unmet medical need for novel approaches to further improve patient clinical outcomes by evaluating rational combinations with avelumab maintenance in the first line treatment of mUC.

2.2.4 Anti-tumor Agents in Combination with Avelumab

The study will start with 3 initial combinations (sacituzumab govitecan, M6223, and NKTR-255) and additional combinations may be added in future. The scientific rationale for these combinations is discussed in Section 4.2.

2.2.4.1 Sacituzumab Govitecan Background

Sacituzumab govitecan is the first-in-class TROP-2-directed antibody conjugated to a topoisomerase inhibitor and is approved by the US FDA for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received 2 or more prior systemic therapies, at least one of them for metastatic disease.

On the 14 October 2021, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization in the European Union for sacituzumab govitecan to treat adult patients with unresectable or metastatic triple-negative breast cancer.

Furthermore, sacituzumab govitecan received accelerated approval by the FDA in patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.

The accelerated approval for sacituzumab govitecan for previously treated advanced mUC was based on data from the TROPHY-U-01 study (IMMU132-006), with an observed 27.7% ORR and 7.2 months median duration of response (n = 112, 31 responders; TRODELVY Prescribing Information). Results for the secondary outcomes were 5.4 months mPFS, 10.9 months mOS (n = 113; Tagawa 2021).

2.2.4.2 M6223 Background

M6223 binds specifically to T-cell immunoreceptor with TIGIT and inhibits the interaction of TIGIT with its ligands, CD155 and CD112. Dual blockade of TIGIT and PD-L1 is expected to lead to a synergistic effect to restore the anti-tumor immune response, as TIGIT modulates a key immunomodulatory pathway distinct from the PD-1/PD-L1 axis and is co-expressed with PD-1 on immune cell subsets. CCI [redacted]

2.2.4.3 NKTR-255 Background

NKTR-255 is a novel immunotherapeutic anticancer drug candidate that consists of recombinant human interleukin-15 (rhIL-15) covalently bound to a 40 kilodalton (kDa) PEG moiety. NKTR-255 binds to IL-15Rα and IL-2/IL-15R βγ subunits and has the potential to maintain the full spectrum of IL-15 biology, including sustained pharmacodynamic effects of both NK cells and CD8+ memory T cells. CCI [redacted].

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of avelumab, sacituzumab govitecan, M6223, and NKTR-255 may be found in Section 6.5, and the corresponding Investigator Brochures (IBs).

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

Based on the available data after the primary analysis results, the schedule of assessments has been reduced to avoid collecting data that will not be analyzed after implementation of this protocol amendment and to reduce participant and study site burden. Safety monitoring will be maintained.

2.3.1 Risk Assessment

Participants will be closely monitored for the risks detailed in Table 4.

Table 4 Risk Assessment Table

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Avelumab		
Immune-related adverse events (irAEs)	The overall incidence and severity of irAEs is found to be consistent across avelumab studies, and similar to the known safety profile of other approved anti-PD-L1 agents. Refer to IB.	See Appendix 5 for irAE management. Regular laboratory tests on parameters indicative for autoimmune disorders, such as TSH, will be performed as detailed in the Schedule of Activities (Section1.3).

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Pre-existing autoimmune disease (AID): in patients with pre-existing AID, data from observational studies suggest that the risk of immune-mediated adverse reactions following immune-checkpoint inhibitor therapy may be increased compared to the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.	
Infusion-related reactions (IRRs)	IRRs, including cytokine release syndrome, have been identified as important risks for avelumab. Refer to IB.	See Section 6.5.
Study Intervention: Sacituzumab govitecan		
Neutropenia	Sacituzumab govitecan can cause severe or life-threatening neutropenia. Refer to IB.	See Section 6.5.
Diarrhea	Diarrhea occurred in patients treated with sacituzumab govitecan, including Grade 3 to 4 diarrhea. In some cases it was observed that diarrhea led to dehydration and subsequent acute kidney injury. Refer to IB.	See Section 6.5.
Hypersensitivity and infusion-related reactions	Sacituzumab govitecan can cause severe and life-threatening hypersensitivity. Anaphylactic reactions have been observed in clinical trials with sacituzumab govitecan. Refer to IB.	See Section 6.5.
Nausea and Vomiting	Sacituzumab govitecan is emetogenic. Chemotherapy induced nausea/vomiting occurred in patients treated with sacituzumab govitecan, including Grade 3 to 4 nausea/vomiting. Refer to IB.	See Section 6.5
[redacted]		

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
CCI		

2.3.2 Benefit Assessment

Avelumab has been approved as maintenance treatment of patients with locally advanced or metastatic UC that has not progressed with first line platinum-containing chemotherapy in the US, EU and other countries. Developing new combinations with avelumab for patients with mUC may extend the known benefit of avelumab monotherapy in 1L maintenance setting and delay possible subsequent treatment with more toxic 2L chemotherapy. Combinations for patients in 1L maintenance may enable further improvement in overall survival demonstrated in the avelumab JAVELIN Bladder 100 study.

2.3.3 Overall Benefit: Risk Conclusion

The safety risk of avelumab in combination with other agents will be closely monitored and treated appropriately as per the usual algorithms for combination agents. Given the anticipated additive or synergistic benefit of avelumab in combination with sacituzumab govitecan, M6223, and NKTR-255, the overall benefit to risk is considered favorable (see Section 4.2.1 and Section 4.3).

3 Objectives and Endpoints

Table 5 Study Objectives and Endpoints

Objectives	Endpoints	Further Estimand Attributes
Primary		
To evaluate PFS of maintenance treatment with avelumab treatment combination regimens compared to maintenance avelumab monotherapy.	PFS as defined from date of randomization to PD according to RECIST v1.1 as assessed by Investigator or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or randomization.	**Population:** Participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with first line platinum-containing chemotherapy. **Treatment:** Maintenance treatment with avelumab treatment combination regimens compared to maintenance avelumab monotherapy. **Strategy for handling intercurrent events:** • Death within 2 scheduled tumor assessments after last evaluable assessment or randomization will be considered as event (composite strategy). • Discontinuation of treatment: The endpoint will be analyzed regardless of whether or not treatment has been discontinued (treatment-policy strategy). • Start of subsequent anticancer treatment: Tumor assessments after start of subsequent anticancer treatment will not be considered for analysis (hypothetical strategy). **Population level summary:** hazard ratio.
To evaluate the safety and tolerability of avelumab combination regimens.	Occurrence of TEAEs, treatment- related AEs, and AESIs as per Qualitative Toxicity Scale (NCI-CTCAE 5.0).	
Secondary		
To evaluate OS of maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy followed by subsequent anticancer treatment.	OS as measured by time from randomization to death.	**Population:** Participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with first line platinum-containing chemotherapy. **Treatment:** Maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy.

Objectives	Endpoints	Further Estimand Attributes
		Strategy for handling intercurrent events: The endpoint will be analyzed regardless of whether or not the following intercurrent events had occurred (treatment-policy strategy): • Treatment discontinuation. • Start of subsequent anticancer therapy. **Population level summary:** hazard ratio.
To evaluate OR of maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy.	OR according to RECIST v1.1 assessed by Investigator.	**Population:** Participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with first line platinum-containing chemotherapy. **Treatment:** Maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy. **Strategy for handling intercurrent events:** • Discontinuation of treatment: The endpoint will be analyzed regardless of whether or not treatment has been discontinued (treatment-policy strategy). • Start of subsequent anticancer treatment: Tumor assessments after start of subsequent anticancer treatment will not be considered for analysis (while not treated with subsequent anticancer therapy strategy). • Progression according to RECIST v1.1 (while not progressed strategy). **Population level summary:** Objective response rate, odds ratio.
To evaluate DoR of maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy.	DoR according to RECIST v1.1 assessed by Investigator defined as time from first documentation of objective response to PD or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or randomization.	**Population:** Participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with first line platinum-containing chemotherapy and confirmed OR according to RECIST v1.1. **Treatment:** Maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy. **Strategy for handling intercurrent events:** Same strategies as defined for PFS.

Objectives	Endpoints	Further Estimand Attributes
		Population level summary: Median DoR.
To collect PK concentration data of avelumab, M6223, SG (derived from total SN-38 and unconjugated SN-38), and NKTR-255 to contribute to respective PopPK analyses and exposure-response analyses.	Concentration will be listed and descriptively summarized as appropriate. Population PK and exposure-response results will be reported separately in a standalone report, as it may also include data from other studies.	
CCI [redacted]	CCI [redacted]	
To evaluate the effect of maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy on disease related physical symptoms during treatment.	Change from baseline score of NCCN FACT FBISI-18 DRS-P at Week 13 visit.	**Population:** Participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with first line platinum-containing chemotherapy. **Treatment:** Maintenance treatment with avelumab combination regimens compared to maintenance avelumab monotherapy. **Strategy for handling intercurrent events:** • Discontinuation of treatment: The endpoint will be analyzed according to the hypothetical strategy, i.e. as if participants were still on randomized treatment at Week 13 visit. • Death: The endpoint will be analyzed according to the hypothetical strategy, i.e. as if participants were still alive and on randomized treatment at Week 13 visit. **Population level summary:** Difference in least-squares means of the change from baseline DRS-P score at Week 13 visit based on a MMRM.


CCI

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; CCI; DoR = duration of response; DRS-P = disease related symptom-physical subscale; CCI; MMRM = mixed effects model for repeated measures; NCCN FACT FBISI-18 = National Comprehensive Cancer Network functional assessment of cancer therapy bladder symptom index; NCI-CTCAE = Northern Cancer Institute-Common Terminology Criteria for Adverse Events; CCI; OR = objective response; OS = overall survival; PD = progressive disease, CCI; PFS = progression-free survival; PK = pharmacokinetics; CCI; RECIST v1.1= Response Evaluation Criteria in Solid Tumors, version 1.1; SG = sacituzumab govitecan; TEAE = treatment-emergent adverse event; CCI; CCI

4 Study Design

4.1 Overall Design

Study Design	Parallel Phase II
Control Method	Active comparator
Single or Multicenter	Multicenter
Control Group	Maintenance avelumab monotherapy (control group from actual randomized participants and external data from the JAVELIN Bladder 100 study)
Study Population Type	Untreated, unresectable locally advanced or metastatic UC
Level and Method of Blinding	Open label
Bias Minimalization Method(s)	• Stratified randomization • Study team will not have access to treatment group aggregated data analysis during the study.
Study Intervention Assignment Method	1:2:2:2 randomization into Group A (control), B, C, and D based on the stratification factor of visceral metastases or not at baseline. • Group A: avelumab 800 mg once every 2 weeks (Q2W) • Group B: sacituzumab govitecan 10 mg/kg Q1W on Days 1 and 8 of 21-day treatment cycles in combination with avelumab 800 mg Q2W • Group C: CCI [redacted] • Group D: CCI [redacted]
Involvement of Special Committee(s):	Yes, see Appendix 2. An internal DMC will evaluate safety and tolerability of avelumab in the proposed combinations throughout the trial. They will start to review all available accumulated safety, clinical, and PK data in an unblinded fashion after the data cutoff, which is defined as 5 weeks after last participant was randomized into the safety run-in phase, 6 participants each to Groups B, C, and D, and 3 participants to Group A.
Total Duration of Study Participation per Participant	Screening: up to 28 days Intervention Period • Groups A, B C, and D: until unacceptable toxicity EOT: 7 days after last treatment intervention Safety follow up: 30 and 90 days post EOT Long-term follow up: every 12 weeks thereafter Permitted visit windows are detailed in the schedule of activities.
Provisions for Study Extension or Entry into Roll-Over Studies	Not applicable.
Adaptive Aspects of Study Design	Not applicable.

Abbreviations: DMC = Data Monitoring Committee; EOT = end of treatment; UC = urothelial cancer.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Combination Drugs

The rationales for the 3 initial combinations (sacituzumab govitecan, M6223 and NKTR-255) as well as for potential future pathways are detailed below.

4.2.1.1 Sacituzumab Govitecan

TROP-2 is an epithelial cell surface antigen highly expressed in UC and is a potential target for ADC aiming to displace platinum-based chemotherapy. Sacituzumab govitecan is the first-in-class TROP-2 ADC and has generated promising data in 2L UC (27% ORR). On 13 April 2021 sacituzumab govitecan received accelerated approval in the US for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor in the US. It is also indicated for the treatment of adult patients with metastatic triple-negative breast cancer who have received at least 2 prior therapies for metastatic disease.

The first ADC (enfortumab vedotin-targeting Nectin-4) was developed and approved as monotherapy in previously treated UC. Initial results from the combination of enfortumab vedotin with pembrolizumab in locally advanced/mUC suggest that ADC agents in combination with PD-1/PD-L1 blockade could play an important role in locally advanced/metastatic UC.

Therefore, the combination of avelumab with sacituzumab govitecan for an investigation in maintenance treatment of mUC is supported by recent safety and efficacy data from both agents independently, with potential to further improve the clinical outcome in patients with mUC.

While combinations of immune checkpoint inhibitors (ICIs) with chemotherapeutic agents have shown to improve outcomes in some indications, including non-small lung cancer (NSCLC), in patients with advanced or metastatic UC, the addition of an ICI (pembrolizumab or atezolizumab) to first line platinum-based chemotherapy did not significantly improve efficacy (Powles 2021). However, in a switch maintenance setting and patients who have not progressed on first line platinum-based chemotherapy, treatment with avelumab significantly improved OS.

We hypothesize that in the maintenance setting, the combination of avelumab with sacituzumab govitecan (SG) has the potential to further improve outcomes for patients. This is supported by nonclinical data studying the combination of topoisomerase I inhibitors with immune -based therapies in solid tumors. SN38 has been shown to increase the sensitivity of melanoma cells to T-cell-mediated killing (McKenzie 2018). Further, in syngeneic mouse model, liposomal irinotecan combined with an anti-PD-L1 antibody or anti-PD1 antibody was shown to have enhanced tumor control, and greater prolongation of survival compared to any of these agents alone (McKenzie 2018). Similar results regarding tumor growth were observed using irinotecan in a syngeneic mouse model using the FM3A murine mammary cancer cell line (Iwai 2018). In this study, irinotecan treatment was shown to have significant effects on the immune system, i.e. increase in interferon gamma (IFNγ) production in the draining lymph nodes, increases in

CD8+ T cells and CD4+ T cells in the lymph nodes and tumor; decrease Foxp3+CD4+ Tregs tumors and lymph nodes as well as transient upregulation of both major histocompatibility complex (MHC) Class I and PD-L1 on the tumor cells. In a recent study, topotecan treatment was shown to increase the efficacy of a cancer vaccine in mice and to alter the immune microenvironment including an increase in intratumoral CD8+ T cells and an improved ratio of CD8+ T/Treg (Lee 2021).

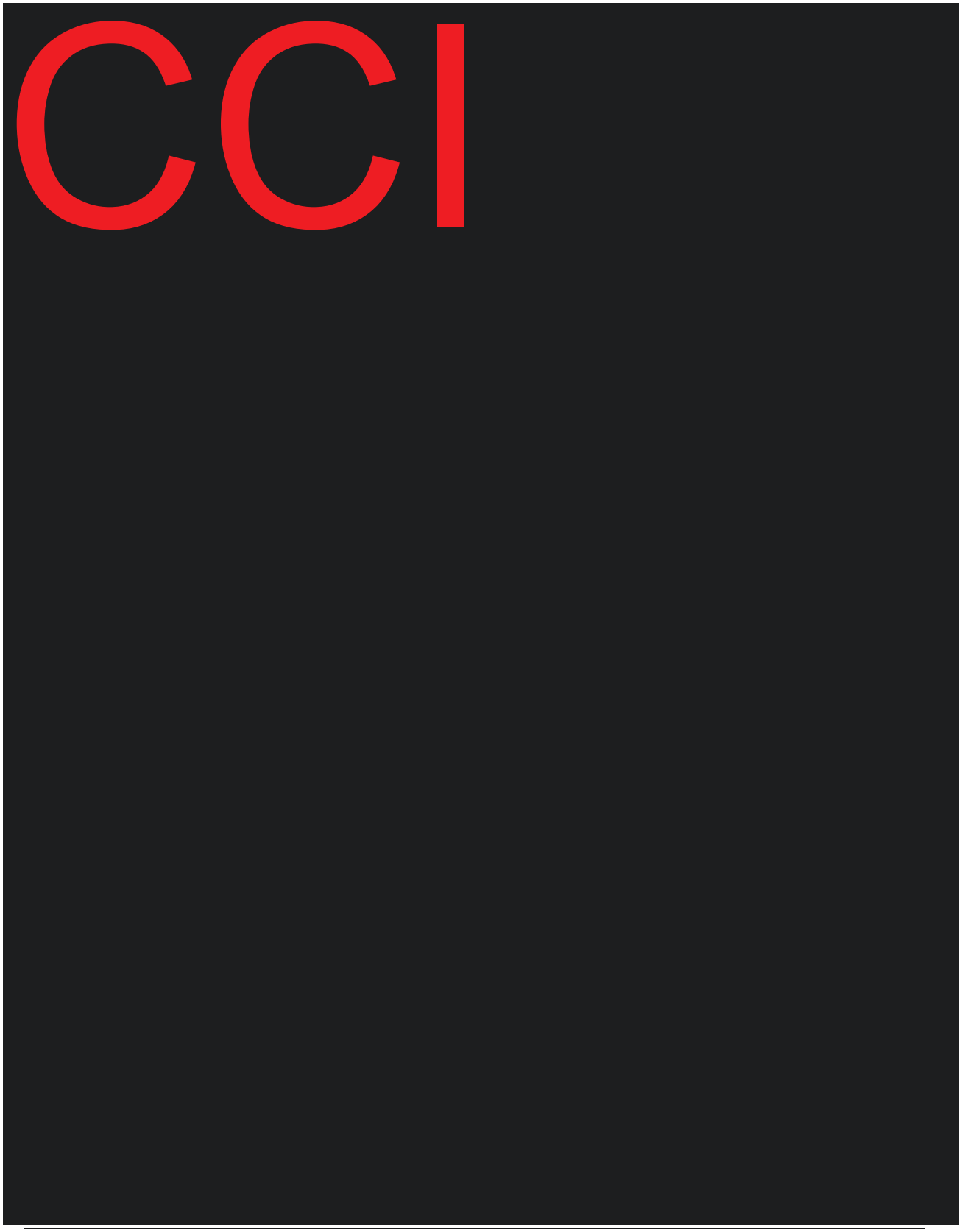
The clinical efficacy of avelumab + SG in UC is further supported by results of enfortumab vedotin (EV, another ADC) with pembrolizumab that has shown promising activity and durability, with a manageable safety profile in cisplatin ineligible patients with locally advanced or metastatic UC (Rosenberg 2020).

For an overview of adverse reactions in patients receiving sacituzumab govitecan, please refer to the IB (Trodelvy IB). While SG has no known immune-mediated toxicity except for hypersensitivity and infusion-related reactions (TRODELVY USPI), there are other potentially overlapping toxicities such as diarrhea. Both SG and avelumab can cause diarrhea, in case of avelumab as a result of immune-related colitis. In the combination arm, participants will be closely monitored for these toxicities. Instructions for the management of diarrhea is provided in Section 6.5.2.

4.2.1.2 M6223

M6223-muIgG2c showed dose-dependent anti-tumor activity in the MC38 model in B-huTIGIT knock-in mice. Consistent increases in body weight and acceptable visual wellness inspections across all groups suggests that each treatment was well tolerated by the mice. Further studies showed peak plasma concentration of M6223-muIgG2c at 24 h following a single i.p. dose at all doses of monotherapy treatment. After maximum plasma concentration (C_{max}), dose-dependent monophasic elimination was observed. At 2.5 mg/kg, M6223-muIgG2c sufficiently decreased unoccupied TIGIT on Tregs for at least 14 days.

The combination of M6223-muIgG2c and avelumab (anti-PD-L1) or bintrafusp alfa (anti-PD-L1/TGFβ) in the MC38 model significantly enhanced anti-tumor activity and extended survival compared with monotherapies (M6223 IB).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Based on the clinical experience of other TIGIT targeted agents in combination with anti-PD-(L)1 therapies, the combination of M6223 with avelumab is expected to have a safety profile comparable to avelumab alone. In the randomized, controlled Phase II CITYSCCAPE study in PD-L1-positive first line metastatic NSCLC of the anti-TIGIT antibody tiragolumab in combination with atezolizumab (anti-PD-L1), the combination was generally well tolerated, showing similar rates of all Grade 3 or more all-cause adverse events when combining the 2 immunotherapies compared with atezolizumab alone. Immune-mediated AEs were more frequent with tiragolumab+atezolizumab compared to atezolizumab but were primarily Grade 1 to 2 and were manageable (Rodríguez-Abreu 2020). In a study with the anti-TIGIT antibody vibostolimab combined with pembrolizumab (anti-PD-1), the combination was well tolerated in patients with advanced NSCLC, either naive or refractory to PD-1/PD-L1 inhibition (Niu 2020, Ahn 2020).

M6223 efficacy data is still preliminary, though no significant anti-tumor effect is expected from anti-TIGIT monotherapy, based on the clinical experience of other TIGIT targeted agents tiragolumab and vibostolimab as monotherapy (Rodríguez-Abreu 2020, Niu 2020, Ahn 2020). Out of 20 patients treated with M6223 with evaluable efficacy data, so far 7 patients had stable disease as best overall response. No complete or partial responses have been observed.

The proposed investigational combination of avelumab with M6223 for maintenance treatment of mUC is supported by safety and efficacy data for avelumab as monotherapy and for M6223 safety data as monotherapy. Regarding additive toxicities, both M6223 and avelumab have the potential to cause infusion-related reactions and based on mechanistic grounds of co-blocking immune checkpoints, there is the potential for the combination to increase the risk of irAEs. Appropriate risk mitigation measures and careful safety monitoring strategies are implemented in the protocol.

4.2.1.3 NKTR-255

NKTR-255 stimulation with or without human IgG induced NK cell proliferation in a dose-dependent manner CCI The EC50 values for NKTR-255 treated groups were approximately 18-fold higher compared to rhIL-15 treated groups. Combination with human IgG increased the maximum response in NKTR-255 treated groups without affecting the EC50, similar to rhIL-15. These data demonstrate that NKTR-255 induces cell proliferation in human primary NK cells, and that this ability of NKTR-255 is enhanced by CD16 cross-linking which triggers antibody-dependent cellular cytotoxicity (ADCC).

In nonclinical animal models of efficacy, NKTR-255 demonstrated enhanced therapeutic efficacy of tumor targeted antibodies with an ADCC mechanism in animal models of efficacy. The properties of NKTR-255 to boost NK cell proliferation and activation translated into enhanced efficacy in combination treatments with 2 different tumor directed antibodies that function through an ADCC mechanism (i.e. daratumumab [anti-human CD38 antibody] and rituximab [anti-human CD20 antibody]) in a B cell lymphoma mouse model. Furthermore, NKTR-255 also enhanced therapeutic efficacy of cetuximab (anti-epidermal growth factor receptor monoclonal human IgG1 antibody) and trastuzumab (anti-human epidermal growth factor receptor 2 [HER2] monoclonal human IgG1 antibody) in mouse xenograft models of human HNSCC, CRC, NSCLC, and ovarian cancer indicating NKTR-255 combination treatment utility with multiple tumor-targeting antibodies via ADCC.

The nonclinical safety profile established for NKTR-255 is considered adequate to support its use in the planned therapeutic cancer indications in humans either as monotherapy or in combination. No overlapping toxicities have been identified in vivo based on repeat-dose toxicity data with monotherapy or combination. In addition, the toxicity profile of NKTR-255 (systemic inflammation due to expected pharmacology) does not overlap substantially with that of cetuximab (infusion reactions, skin and ocular effects, hypomagnesemia) (Thomas 2005,Fakih 2010).

Additionally, NKTR-255 is currently being investigated in the clinic for the treatment of patients with relapse or refractory (R/R) hematologic malignancies, including multiple myeloma (MM) and NHL in first-in-human (FIH) Phase 1 Study 18-255-02. Study 18-255-02 will also evaluate NKTR-255 in combination with daratumumab in patients with MM and rituximab in patients with indolent NHL. In addition, NKTR-255 is being investigated in combination with cetuximab for the treatment of R/R metastatic head and neck squamous cell carcinoma (HNSCC) and colorectal carcinoma (CRC) in Phase 1b/2 Study 19-255-03. For details, refer to NKTR-255 Investigator's Brochure.

IL-15 signaling has been shown in the clinic to stimulate an array of downstream pathways in immune cells leading to increased cellular growth, decreased apoptosis, and enhanced activation and migration of specific immune cells (Conlon 2015). IL-15 is constitutively expressed by a large number of cell types and tissues, including monocytes, macrophages, dendritic cells, keratinocytes, fibroblasts and nerve cells (Grabstein 1994). The receptor for IL-15 consists of the α subunit and a common βγ subunit that shares the IL-2 receptor responsible for signal transduction (Giri 1995). NKTR-255 was shown to increase numbers, proliferation and function, of NK cells and CD8+ T cells in the clinic.

Several lines of evidence suggest that NK cells play an important role in anti-tumor immunity by directly lysing tumor cells or through participating in ADCC in conjunction with a tumor targeted monoclonal antibody (mAb). NKTR-255 has demonstrated PD effects in NK cell and T-cell expansion and proliferation and has shown synergistic ADCC when combined with mAbs in nonclinical studies, which supported the initiation of the 2 clinical studies (Study 18-255-02 in R/R hematological malignancies and Study 19-255-03 in solid tumors).

Additionally, high levels of NK cell infiltration have been associated with a better prognosis for several solid tumors. NK cells, which are innate mediators of cytotoxicity, are significantly lower in peripheral blood of patients with solid tumors than in healthy individuals (Brittenden 1996). Nonclinical pharmacology studies using NKTR-255 in combination with cetuximab showed synergistic enhancement of anti-tumor efficacy in mouse xenograft models of human HNSCC, CRC and NSCLC. Several lines of evidence also suggest that NK cells play an important role in anti-tumor immunity by directly lysing tumor cells or through participating in ADCC in conjunction with a tumor targeted mAb. Moreover, IL-15 stimulation of NK cells was shown to enhance avelumab-triggered cytokine production and degranulation along with increased lytic activity against tumor cells (Julia 2018). In JAVELIN Bladder 100, immune cell gene signatures have suggested that cell types expressing Fc receptors including NK cells may contribute to outcomes, supporting evaluation of this combination of NKTR-255 with avelumab.

The nonclinical safety profile established for NKTR-255 is considered adequate to support its use in the planned therapeutic cancer indications in humans either as monotherapy or in combination. No overlapping toxicities have been identified in vivo based on repeat-dose toxicity data with monotherapy or combination.

NKTR-255 is being evaluated as monotherapy and in combination with daratumumab or rituximab in a phase 1, open-label, multicenter, dose escalation and dose expansion study of NKTR-255 in relapsed or refractory hematological malignancies (18-255-02) and in a Phase 1b/2 open-label, multicenter, dose escalation and dose expansion study in combination with cetuximab as a salvage regimen for solid tumors (19-255-03). For further information, refer to the NKTR-255 IB (NKTR-255 IB).

4.2.1.4 Potential Future Anti-tumor Agents as Combination Partners with Avelumab

Combinations with avelumab and other agents addressing other relevant pathways may be added in the future. If other combinations are added, the randomization scheme may be adjusted and, depending on the progress of the study, additional participants may be randomized to the control group to allow for an unbiased comparison between the different investigational groups and the control. The following agents may be included:

LAG3 Pathway
The lymphocyte activating gene-3 (LAG-3 or CD233) is an immune checkpoint that is widely expressed on tumor infiltrating lymphocytes (TILs) and cytotoxic T cells. The synergistic activity of LAG-3 and PD-1 provides a promising rationale for a combined blockade of both pathway for an enhanced clinical activity. This has been demonstrated in melanoma patients who were not responding well to initial PD-1 or PD-L1 monotherapy (Lecocq 2020).

NK Cell Therapy
NK cells are sentinels of the anti-tumor response, rapidly recognizing and killing transformed cells without the need for prior sensitization (Bald 2020). A greater abundance of NK cells in the tumor microenvironment has been associated with improved survival in a number of cancer types, including liver, gastric, and breast cancers, as well as melanoma. To boost NK cell numbers in the tumor microenvironment, NK cell transfer-based cancer immunotherapy has been established across a range of early-phase clinical trials Autologous NK cells SNK01 in combination with pembrolizumab in patients with NSCLC 2L demonstrated an ORR of 44.4% in 9 evaluable patients treated with the combination (Kim 2020). In that context, combination of NK cell-based approach and avelumab that carry a native Fc function may potentially enhance anti-tumor activity.

4-1BB Pathway
Costimulatory receptor 4-1BB (CD137/TNFSF9) has an incomparable capacity for both activation and proinflammatory polarization of anti-tumor lymphocytes. 4-1BB agonist mAb have been found to promote survival, expansion, and enhanced effector function of cytotoxic CD8 T cells. In that capacity, tumor targeted 4.1BB agonists (to avoid liver inflammation) can

potentiate anti-tumor of immune checkpoint blocking antibodies such as avelumab as extensively demonstrated in preclinical setting.

LILRB2 Pathway
Leukocyte Immunoglobulin Like Receptor B2 (LILRB2/ILT4) is an immune checkpoint for macrophages - LILRB2 maintains an immuno-suppressive state in macrophages via the binding of its ligands, the classical and non-classical MHC I molecules - Blockade of LILRB2 ligand binding induces an immune activating state in macrophages (proinflammatory cytokines release). In JAVELIN Bladder 100, immune cell gene signatures suggested that myeloid cell types may contribute to disease outcomes. So, macrophages M1-like phenotype shift induced by LILRB2 blockade may lead to enhancement of avelumab anti-tumor immune response.

4.2.2 Rationale for Progression-free Survival as Primary Endpoint

Maintenance treatment with avelumab after chemotherapy is an extension of first line treatment. Progression-free survival was chosen as a clinically meaningful endpoint for UC to assess the efficacy of maintenance treatment for patients who had CR, PR or SD after the completion of 1L standard of care platinum-containing chemotherapy.

This study will support further development of Phase 3 study(s) for avelumab combination(s) as maintenance treatment in this indication.

Since PFS is defined as the time from the randomization until the date of progression or death, this endpoint encompasses information from patients who have maintained and/or enhanced the benefit achieved from the induction of platinum-containing chemotherapy in terms of CR, PR, and SD.

Phase 3 JAVELIN Bladder 100 study reported improved PFS with avelumab maintenance plus BSC as compared to BSC alone:

- PFS by BICR assessment: HR = 0.62 (95% CI: 0.519, 0.751), median 3.7 months (95% CI: 3.5, 5.5) versus 2.0 months (95% CI: 1.9, 2.7)
- PFS by Investigator: HR = 0.52 (95% CI: 0.437, 0.625), median 5.5 months (95% CI: 4.2, 7.2) versus 2.1 months (95% CI: 1.9, 3.0)

Independently, sacituzumab govitecan received accelerated approval by the FDA as 2L treatment for UC with an ORR of 27% (sacituzumab govitecan USPI); M6223 is hypothesized to overcome the mechanism of resistance to avelumab maintenance; NKTR-255 may enhance NK cell-mediated anti-tumor immunity and enhance avelumab mediated ADCC. The additional anti-tumor activity of these compounds when combined with avelumab will be reflected in the PFS endpoint.

4.2.3 Rationale for Hybrid Design and Stratification Factors

The randomization ratio of 1:2:2:2 with fewer participants randomized to the control arm was chosen to complement the control arm with the investigational arm of the JAVELIN Bladder 100 study (NCT02603432). The inclusion of the JAVELIN Bladder 100 data assumes this study similarity with JAVELIN Bladder Medley with regards to the key inclusion and exclusion criteria and treatment regimen (see Section 9.2).

The presence of visceral metastases at baseline was selected as a stratification factor as it was shown to be of prognostic value in the JAVELIN Bladder 100 study based on the Sponsor's plans.

4.3 Justification for Dose

4.3.1 Group A

A fixed dose of 800 mg of avelumab, IV, once every 2 weeks (Q2W) is selected as the study dose for Group A. This dose has been approved as a maintenance treatment of patients with advanced or metastatic UC in USA, EU, and other regions based on efficacy data from JAVELIN Bladder 100 study and a large body of PK, target occupancy, and clinical safety observed in the Phase I to III studies at equivalent weight-based dose (10 mg/kg Q2W). Detailed information on the PK of avelumab in humans can be found in the Investigator's Brochure.

4.3.2 Group B

Sacituzumab govitecan will be administered on Day 1 and Day 8 of continuous 21-day treatment cycles at 10 mg/kg. This is the approved dose of sacituzumab govitecan for the treatment of patients with locally advanced or mUC who have previously received a platinum -containing chemotherapy and either a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.

Avelumab will be administered at 800 mg Q2W, which is the approved dose regimen in IL UC maintenance setting.

Significant drug-drug interaction between avelumab and sacituzumab govitecan is not expected given the 2 monoclonal antibodies rely on different target-mediated clearance mechanisms and elimination of the payload of sacituzumab govitecan, SN-38, is through a mechanism mediated by the CCI [redacted] and not expected to be affected by avelumab with a proteolytic catabolism as a monoclonal antibody.

4.3.3 Group C

M6223 will be administered in combination CCI [redacted]

The dosing rationale of M6223 is supported by safety of M6223 and PK/PD data from an integrated model-based analysis.

4.3.4 Group D


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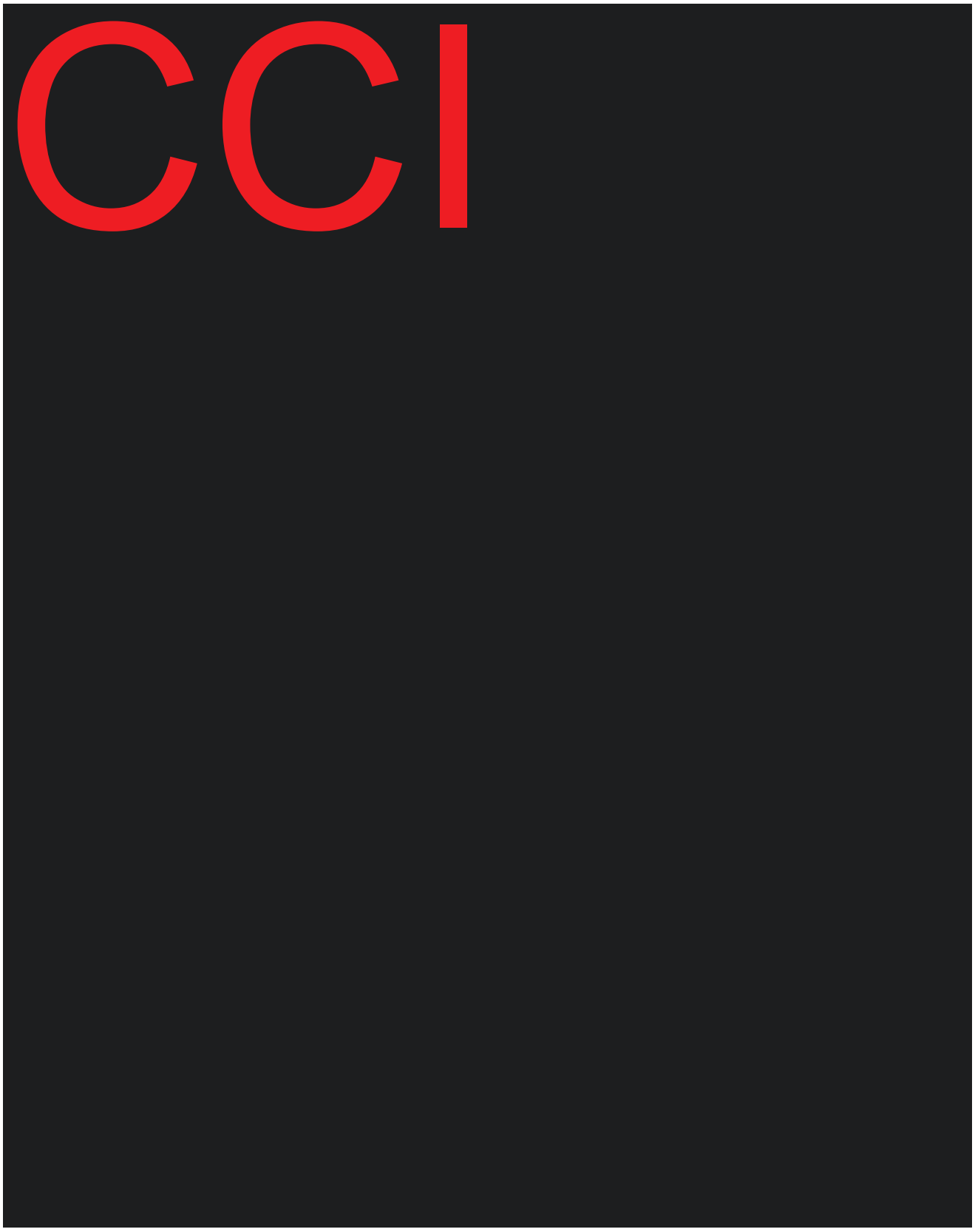
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4.4 End of Study Definition

The end of the study is defined as 2 years after randomization of the last participant or when all participants have terminated study treatment, whichever occurs last; however, the Sponsor may terminate the study at any time once access to study intervention for participants still benefitting is provided (see Section 6.6).

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

The study will be closed after all participants have completed the study, also considering the criteria for discontinuation of study intervention and participant discontinuation / withdrawal in Section 7 and Appendix 2 (study and site closure).

5 Study Population

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

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

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

5.1 Inclusion Criteria

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

Category	Criterion
Age	1. Are ≥ 18 years of age at the time of signing the informed consent.
Type of Participant and Disease Characteristics	2. Has • a. Histologically confirmed, unresectable locally advanced or metastatic urothelial carcinoma. Both transitional cell and mixed transitional/non- transitional cell histologies are allowed, but transitional cell carcinoma must be the predominant histology. • b. Documented Stage IIIA/IIIB with N1-N3, or Stage IV disease (per American Joint Committee on Cancer/International Union for Cancer Control Tumor Node Metastasis system, 8th edition) at the start of first line chemotherapy. 3. Prior 1L chemotherapy must have consisted of at least 4 cycles and no more than 6 cycles of gemcitabine + cisplatin and/or gemcitabine + carboplatin. No other chemotherapy regimens are allowed in this study. (Note: Switch between platinum agents due for toxicity to complete a total of - 4 to 6 cycles first line platinum-based chemotherapy is acceptable). 4. The last dose of first line chemotherapy must have been received no less than 4 weeks, and no more than 10 weeks, prior to randomization in the present study. 5. Participants without progressive disease as per RECIST v1.1 guidelines (i.e. with an ongoing CR, PR, or SD) following completion of 4 to 6 cycles of 1L chemotherapy. Eligibility based on this criterion will be determined by Investigator review of prechemotherapy and post chemotherapy radiological assessments (CT/MRI scans). 6. CCI

Category	Criterion
	 7. Participants who are willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures. 8. Estimated life expectancy of at least 3 months. 9. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1. 10. Adequate bone marrow function, including: a. Absolute neutrophil count (ANC) $\geq$ 1,500/mm^3 or $\geq 1.5 \times 10^9$/L; b. Platelets $\geq$ 100,000/mm^3 or $\geq 100 \times 10^9$/L; c. Hemoglobin $\geq$ 9 g/dL (may have been transfused during the screening period in order to meet inclusionary criteria provided there is no active bleeding). 11. Adequate renal function, defined as estimated creatinine clearance $\geq$ 30 mL/min as calculated using the Cockcroft-Gault equation or by 24-hour urine collection for creatinine clearance or according to the local institutional standard method. 12. Adequate liver function, including: a. Total serum bilirubin $\leq 1.5 \times$ upper limit of normal (ULN); b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ ULN, or, for participants with documented metastatic disease to the liver, AST and ALT levels $\leq 5 \times$ ULN. Patients diagnosed and documented with Gilbert's syndrome are eligible for enrollment.

Category	Criterion
Sex and Contraception/Barrier Requirements	13. All sexes allowed. The Investigator confirms that each participant agrees to use appropriate contraception and barriers, if applicable. The contraception, barrier, and pregnancy testing requirements are below. o **Female participants** o Are **not** pregnant (i.e. have a negative pregnancy test, as required by local regulations, within 24 hours before the first dose of study intervention). o Are **not** breastfeeding. o **Not** a woman of childbearing potential. OR o If a woman of childbearing potential, use a highly effective contraceptive method (i.e. with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 3 for the following time periods: o Before the first dose of the study intervention(s), if using hormonal contraception: o Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses. OR o 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. o During the study intervention period. o After the study intervention period (i.e. after the last dose of study intervention is administered) for at least 6 months after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period. o Additional requirements for pregnancy testing during and after study intervention are in Appendix 3. The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention. 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.

Category	Criterion
	○ **Male participants** Agree to the following during the study intervention period and for at least 3 months after the last dose of study intervention: ○ Refrain from donating fresh unwashed semen PLUS, either ○ Abstain from any activity that allows for exposure to ejaculate. OR ○ Use a male condom: ○ When having sexual intercourse with a woman of childbearing potential, 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. ○ When engaging in any activity that allows for exposure to ejaculate. ○ And up to 3 months after the study intervention is discontinued.
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 ICF and this protocol.
History of HIV, HBV or HBC	15. Participants with known human immunodeficiency virus (HIV) infections are eligible if the following criteria are met: a. If clinically indicated participants must be stable on antiretroviral therapy (ART) for at least 4 weeks and agree to adhere to ART. If not clinically indicated, consult study Medical Monitor. b. Participants with HIV infection should have no evidence of documented multidrug resistance that would prevent effective ART. c. Have an HIV viral load of < 400 copies/mL at Screening. d. If prophylactic antimicrobial drugs are indicated, patient may still be considered eligible upon agreement with the study Medical Monitor. 16. Participants with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infections are eligible if the following criteria are met:

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

5.2 Exclusion Criteria

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

Category	Criterion
Medical Conditions	1. CCI 2. 3. 4.

Category	Criterion
	5. CCI
	6.
	7. Active infection 48 hours before randomization requiring systemic therapy.
	8. CCI
	9. Known prior or suspected hypersensitivity to study drugs or any component in their formulations.
	10. CCI
	11.
	12.

Category	Criterion
	CCI
Prior/Concomitant Therapy	13. Prior adjuvant or neoadjuvant systemic therapy within 12 months of randomization. 14. Prior immunotherapy with IL-2, IL-15, IFN-α, or an anti -PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or CTLA-4 antibody (including ipilimumab), anti-TROP2, anti-TIGIT, any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways, agents targeting Nectin-4, or any of the investigational drugs used in combination with avelumab. 15. CCI 16. 17. Vaccination within 4 weeks of the first dose of study treatment and while on trial is prohibited except for administration of inactivated vaccines (for example, inactivated influenza vaccines) administered ≥ 2 weeks prior first dose of study treatment. All SARS-CoV-2 vaccines approved or authorized by local Health Authorities are allowed.

Category	Criterion
Prior/Concurrent Clinical Study Experience	18. Participation in other studies involving investigational drug(s) within 4 weeks prior to randomization. Observational studies are permitted.
Other Exclusions	19. Participants who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or participants who are Merck employees directly involved in the conduct of the study. 20. For study sites in France, participants under legal protective measure, namely, under guardianship, curatorship, or legal protection are excluded from participation in this study.

5.3 Lifestyle Considerations

No specific lifestyle or dietary restrictions are required throughout the study.

5.3.1 Meals and Dietary Restrictions

No specific restrictions on food and drink are required during the study.

5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoid

No specific restrictions on caffeine, alcohol, tobacco, or cannabinoid use apply during the study.

5.3.3 Activity

Not applicable.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6 Study Intervention(s) and Concomitant Therapies

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.

Treatment administration will start with avelumab and then the combination agent; see Section 6.1 for details.

6.1 Study Intervention(s) Administration

Intervention Name	Avelumab	Sacituzumab Govitecan
Type	Drug - monoclonal antibody.	Antibody drug conjugate that contains SN-38, the active metabolite of irinotecan.
Dose Formulation	Sterile concentrate solution for infusion.	200 mg off-white to yellowish lyophilized powder in a single-dose vial. NOTE: The dose of 180 mg indicated on the label describes the minimum extractable amount of drug per vial.
Unit Dose Strength(s)	Formulated as 20.0 mg/mL solution.	200 mg lyophilized powder in single-dose vials for reconstitution. NOTE: The dose of 180 mg indicated on the label describes the minimum extractable amount of drug per vial.
Dose Amount	Avelumab 800 mg administered as an intravenous infusion as detailed in Table 1, Table 2, and Table 3.	Sacituzumab govitecan 10 mg/kg as detailed in Table 1.
Frequency	Q2W	Q1W on Days 1 and 8 of 21-day treatment cycles.
Route of Administration	Intravenous infusion over 1-hour (−10/+20 minutes).	Intravenous infusion over 3 hours for the first infusion and over 1-2 hours for subsequent infusions if prior infusions were tolerated.
Use	maintenance	Experimental
Investigational Medicinal Product (IMP) and Non-	IMP	IMP

CCI

CCI

Intervention Name	Avelumab	Sacituzumab Govitecan
Investigational Medicinal Product (NIMP)		
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Avelumab will be provided in single-use glass vials, stopper with a rubber septum and sealed with an aluminum polypropylene flip off seal. Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.	Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

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

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

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

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

- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) will not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Study Reference Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Eligible participants will be randomized to one of 4 groups in a 1:2:2:2 ratio as follows:

- Group A: avelumab 800 mg once every 2 weeks (Q2W).
- Group B: sacituzumab govitecan 10 mg/kg Q1W on Days 1 and 8 of 21-day treatment cycles in combination with avelumab 800 mg Q2W.
- Group C: CCI [redacted]
- Group D: CCI [redacted]

The randomization will be stratified by presence of visceral metastases at baseline or not. A unique participant identification number will be used throughout the study.

After confirmation of participant's eligibility and at the last practical moment prior to study intervention administration, participants will be centrally allocated to Group A, B, C, or D in a 1:2:2:2 ratio using an IWRS and per a computer-generated randomization list.

The IWRS will be used to assign unique participant numbers, allocate participants to study intervention group at the randomization visit, and study intervention to participants at each study intervention visit.

Before the study is initiated, the log in information and directions for the IWRS will be provided to each site. The site will contact the IWRS prior to starting study intervention administration for each participant.

6.3.2 Blinding

Blinding Method

The study is open label by the nature of the different treatment groups. The following procedures are put in place to reduce potential bias:

- The study participants will be randomized to one of the specified groups through a central IWRS.
- An independent Statistician will be responsible for determining the data cutoff for the planned interim and primary analysis based on Investigator assessed number of PFS events.
- A rolling review of safety data of participants under treatment will be done in the proposed combinations by a dedicated team composed of safety and medical representatives. To detect and react to occurrence of potential unacceptable toxicities, this review team will have access to participant-level information including the treatment group. Access to any aggregated data analysis by treatment group is not permitted for any study team members until the interim analysis, after which the study team will be unblinded.

Assignment Method Retention

Not applicable as this is an open-label study.

6.3.3 Emergency Unblinding

Not applicable.

6.4 Study Intervention Compliance

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

6.5 Dose Modification

6.5.1 Avelumab

Infusion-related Reactions

To mitigate IRRs, including cytokine release syndrome (CRS), participants must be premedicated with an antihistamine (H1 receptor blocker such as diphenhydramine) and with acetaminophen (paracetamol) approximately 30 to 60 minutes before the first 4 infusions of avelumab, or according to local standards (excluding steroids). Premedication should be

administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. Following the avelumab infusions, patients must be observed for 1 hour post infusion, for the first 4 infusions, for potential infusion-related reactions. For subsequent infusions, participants should be monitored according to local standards. Management of IRRs should follow guidelines set forth in Table 6.

Table 6 Treatment Modification for Symptoms of Infusion-related Reactions Associated with Avelumab

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.[a] Note: if the infusion-related reaction occurs after the infusion please consider decreasing the next avelumab infusion rate by 50% of previous rate [a]
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	• Temporarily discontinue avelumab infusion. • Resume infusion at 50% of previous rate once IRR has resolved or decreased to at least Grade 1 in severity and monitor closely for any worsening.[a] Note: if the infusion-related reaction occurs after the infusion, the next infusion must be performed at 50% of previous rate.[a]
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, 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 avelumab infusion immediately and disconnect infusion tubing from the participant. • Participants have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

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

a Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions.

Immune-related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur and might require dosing modification, interruption or discontinuation. Important identified risks for avelumab are 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), immune-related rash and other immune-related events (myositis, myocarditis, Guillain-Barré syndrome, hypopituitarism, uveitis, pancreatitis, myasthenia gravis/myasthenic syndrome, sclerosing cholangitis, arthritis, polymyalgia rheumatica, Sjogren's syndrome, neutropenia, and gastritis). Refer to the most recent IB for any potential updates in irAEs. For more information on irAEs see Section 8.3.5.2.

6.5.2 Sacituzumab Govitecan

Common adverse reactions of sacituzumab govitecan are:

- diarrhea,
- neutropenia and febrile neutropenia,
- hypersensitivity and infusion-related reactions, and
- nausea/vomiting.

Diarrhea

Diarrhea is a potential overlapping toxicity for both, sacituzumab govitecan and avelumab. Sacituzumab govitecan may cause early (immediately after infusion) and late diarrhea (greater than 24 hours after infusion up to a few weeks after dosing), which may be difficult to differentiate from diarrhea caused by avelumab as a result of immune-related colitis. Treatment of diarrhea should follow guideline as shown in Table 7.

Table 7 Management of Diarrhea in the Group B (Avelumab + Sacituzumab Govitecan)

Severity of Diarrhea	Initial Management	Follow-up Management
Grade 1 Diarrhea: < 4 stools/day over Baseline.	• Continue avelumab and sacituzumab govitecan therapy. • Symptomatic treatment (e.g., loperamide 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves).	• Close monitoring for worsening symptoms. • Educate participant to report worsening immediately. • If worsens treat as Grade 2, 3 or 4.

Severity of Diarrhea	Initial Management	Follow-up Management
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with activities of daily living (ADL).	• Withhold avelumab and sacituzumab govitecan therapy. • Initiate supportive management with fluid and electrolyte substitution and antidiarrheal.	If improves to Grade ≤ 1: • Resume avelumab and sacituzumab govitecan therapy at the original dose. If persists > 5 to 7 days or recurs: • Treat as Grade 3 or 4.
Grade 3 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL.	• Withhold avelumab and sacituzumab govitecan for Grade 3. • Start with 1.0 to 2.0 mg/kg/day prednisone IV or equivalent until symptoms resolve. • Add prophylactic antibiotics for opportunistic infections. • Consider lower endoscopy.	If improves: • Continue steroids until Grade ≤ 1, then taper over 1 month; resume avelumab and sacituzumab govitecan therapy (with 25% dose reduction for sacituzumab) following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Recurrent Grade 3 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL.	• Permanently discontinue avelumab. • Withhold sacituzumab govitecan for recurrent Grade 3 diarrhea at the time of scheduled treatment administration.	• When diarrhea resolved to ≤ Grade 1 resume sacituzumab govitecan with a dose reduction to 50% • If diarrhea recurs despite 50% dose reduction of sacituzumab govitecan, permanently discontinue.
Grade 4 Life-threatening consequences; urgent intervention indicated	• Permanently discontinue avelumab and sacituzumab govitecan for Grade 4. • Admit patient when clinically indicated; patients managed as outpatients should be very closely monitored. • Consider lower GI endoscopy if symptoms.	• Administer 1-2 mg/kg/d methylprednisolone or equivalent until symptoms improve to Grade 1, and then start taper over 4-6 weeks • Consider early infliximab 5-10 mg/kg if symptoms refractory to corticosteroid within 2-3 days.

If the Investigator suspects that the underlying cause for diarrhea might be autoimmune colitis then additional workup of blood and stool (culture, *Clostridium difficile*, parasite, cytomegalovirus or other viral etiology, ova and parasite) should be performed. Testing for lactoferrin and calprotectin and imaging (e.g., CT scan of abdomen and pelvis and gastrointestinal endoscopy with biopsy) should be considered. For management of immune-related colitis see Section 8.3.5.2.

Neutropenia

Neutropenia, including febrile neutropenia, is a common adverse reaction of sacituzumab govitecan. Sacituzumab govitecan can also cause severe or life-threatening neutropenia. Therefore, the blood cell count shall be monitored periodically during the treatment. Sacituzumab govitecan should be withhold for absolute neutrophile count below 1500/mm^3 on Day 1 of any cycle or neutrophil count below 1000/mm^3 on Day 8 of any cycle until resolved to ≤ Grade 1. In case of Grade 4 neutropenia, both drugs should be interrupted and resumed once the participant has recovered. Granulocyte colony-stimulating factor should be administered as clinically indicated.

The administration of granulocyte colony-stimulating factor as primary and secondary prophylaxis is strongly recommended in patients at increased risk of febrile neutropenia, eg, older patients (in particular aged 65 years and older), patients with previous neutropenia, poor performance status, organ dysfunction (including renal, liver, or cardiovascular dysfunction), or multiple comorbid conditions.

In participants with febrile neutropenia, anti-infective treatment shall be initiated without delay. Initial management of neutropenia ≥ Grade 3 should follow sacituzumab govitecan guideline as described in Table 8. If repeat episodes of ≥ Grade 3 neutropenia occur despite a 50% dose reduction in sacituzumab govitecan and continued prophylactic growth factor support or neutropenia fails to resolve to ≤ Grade 1 within 3 weeks despite growth factor support, additional medical investigation should be initiated.

Nausea/vomiting

As sacituzumab govitecan is emetogenic, premedication with a 2 or 3 drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK-1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting is recommended. Corticosteroids should be administered at the minimum effective dose.

Withhold sacituzumab govitecan for Grade 3 nausea or Grade 3 to 4 vomiting at the time of scheduled treatment administration and resume with additional supportive measures when resolved to ≤ Grade 1.

Table 8 provides guidelines on the dose modifications for severe (non-)-neutropenic adverse reactions.

Table 8 Sacituzumab Govitecan Dose Modifications for Adverse Reactions

Adverse Reaction	Occurrence	Dose Modification
Severe Neutropenia		
Grade 4 neutropenia ≥ 7 days or less if clinically indicated, OR Grade 3 to 4 febrile neutropenia OR	First	25% dose reduction and administer granulocyte-colony stimulating factor (G-CSF) as soon as clinically indicated.

Adverse Reaction	Occurrence	Dose Modification
At time of scheduled treatment, Grade 3 to 4 neutropenia which delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1.	Second	50% dose reduction administer G-CSF as soon as clinically indicated.
	Third	Discontinue Treatment administer G-CSF as soon as clinically indicated.
At time of scheduled treatment, Grade 3 to 4 neutropenia which delays dosing beyond 3 weeks for recovery to ≤ Grade 1.	First	Discontinue treatment administer G CSF as soon as clinically indicated.
Severe Non-Neutropenic Toxicity		
Grade 4 non-hematologic toxicity of any duration, OR	First	25% dose reduction.
Any Grade 3 to 4 nausea, vomiting due to treatment that is not controlled with antiemetics agents, OR Other Grade 3 to 4 non-hematologic toxicity persisting > 48 hours despite optimal medical management, OR At time of scheduled treatment, Grade 3 to 4 non-neutropenic hematologic or non-hematologic toxicity, which delays dose by 2 or 3 weeks for recovery to ≤ Grade 1.	Second	50% dose reduction.
	Third	Discontinue treatment.
In the event of Grade 3 to 4 non-neutropenic hematologic or non-hematologic toxicity, which does not recover to ≤ Grade 1 within 3 weeks.	First	Discontinue treatment.

Hypersensitivity/Infusion-related Reactions

Anaphylactic reactions have been observed in clinical trials with sacituzumab govitecan and can be severe and life-threatening in nature. In order to mitigate infusion-related reactions, participants must be premedicated with an antihistamine (H1 receptor blocker such as diphenhydramine) and with acetaminophen (paracetamol) approximately 30 to 60 minutes before the administration of any dose of sacituzumab govitecan. The first infusion of sacituzumab govitecan must be administered over 3 hours and the patients observed for signs or symptoms of infusion-related reactions. If the first infusion of sacituzumab govitecan is well tolerated, subsequent infusions can be administered over 1 to 2 hours.

Whereas premedication is recommended for all doses of sacituzumab govitecan, it is only mandatory before the first 4 infusions of avelumab, or according to local standards (excluding steroids). Premedication should be administered for subsequent avelumab infusions based upon clinical judgment and presence/severity of prior infusion reactions.

On days of co-administration of avelumab and sacituzumab govitecan, avelumab will be administered first. There should be a gap of 30 minutes between the end of the avelumab and start of sacituzumab govitecan administration to allow assessment of potential infusion-related reactions. Additional premedication before the second infusion can be considered if the time between administration of the premedication of the first infusion and the start of the second infusion is longer than 4 hours.

Management of IRRs should follow guidelines set forth in Table 9.

Table 9 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, continue sacituzumab govitecan infusion. Decrease the avelumab infusion rate by 50% and monitor closely for any worsening[a]. Note: if the infusion-related reaction occurs after the avelumab infusion please consider decreasing the next infusion rate by 50% of previous rate[a].
Grade 2 – moderate • Therapy or infusion interruption indicated but if responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Temporarily discontinue sacituzumab govitecan and avelumab infusion. Increased monitoring of vital signs as medically indicated as participants are deemed medically stable by attending Investigator. If symptoms resolve quickly or decrease to at least Grade 1, resume infusion at 50% of original rate of sacituzumab govitecan and 50% of previous rate of avelumab with close monitoring of any worsening. Otherwise dosing should be stopped until resolution of symptoms with mandated premedication for the next schedule[a]. Note: If the infusion-related reaction occurs after the infusions, the next administrations must be performed at 50% of original rate of sacituzumab govitecan and 50% of previous rate of avelumab[a].
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, 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 sacituzumab govitecan and avelumab infusions 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 Sacituzumab govitecan/avelumab treatment and must not receive any further Sacituzumab govitecan/avelumab 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, sacituzumab govitecan and avelumab discontinuation is mandated.

[a] Once the avelumab or sacituzumab govitecan infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, both must remain decreased for all subsequent infusions.

For all types and grades of infusion reactions, details about drug physical constitution, method of preparation and infusion must be recorded.

As a routine precaution, all participants must be observed for 1 hour post end of infusion in an area with resuscitation equipment and emergency agents for the first 8 weeks on-treatment. If no

IRRs are observed during the first 8 weeks, the mandated 1-hour post infusion observation time is no longer required but it is recommended that patients should be closely monitored for at least 30 minutes after completion of each infusion or according to local standards.


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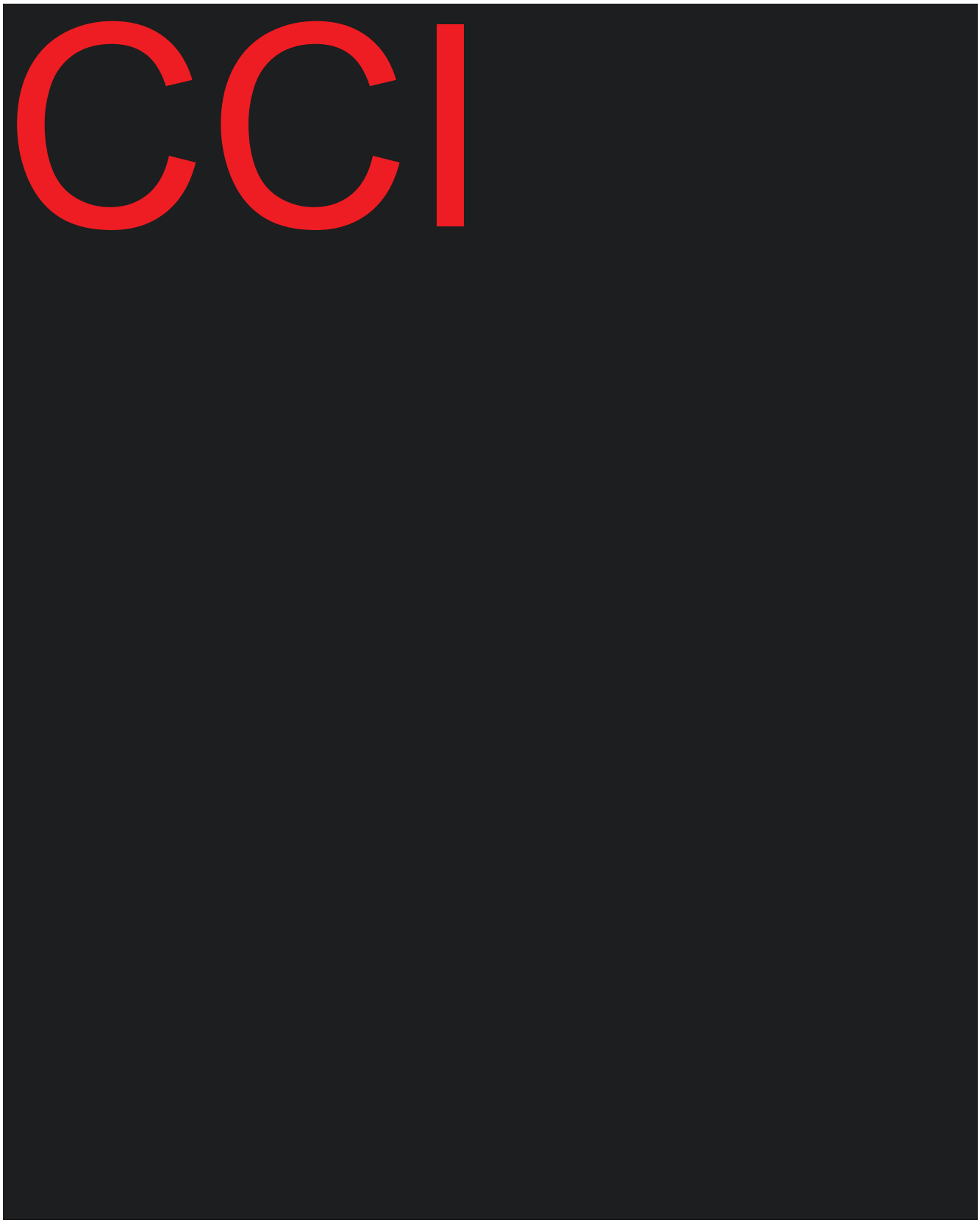
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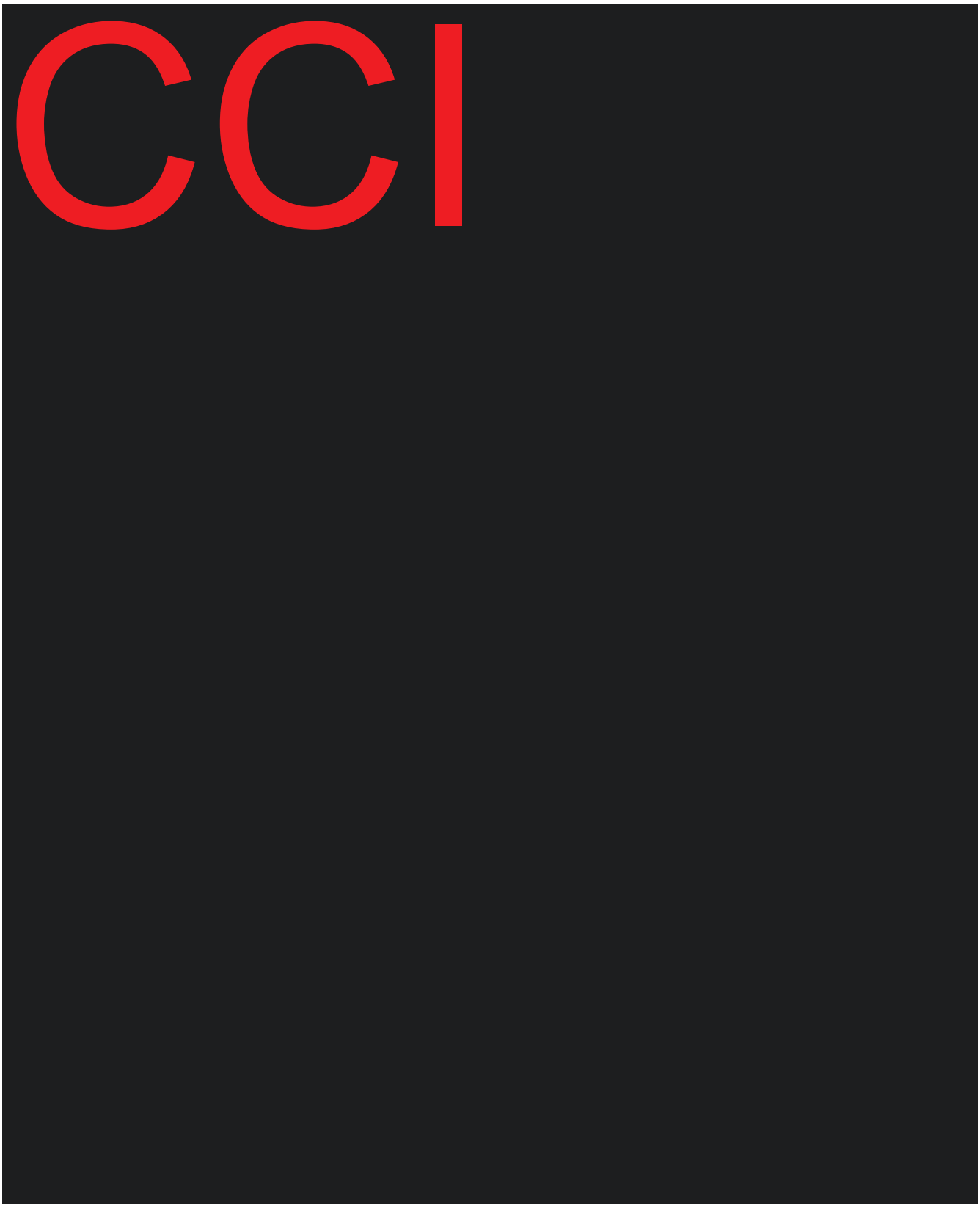
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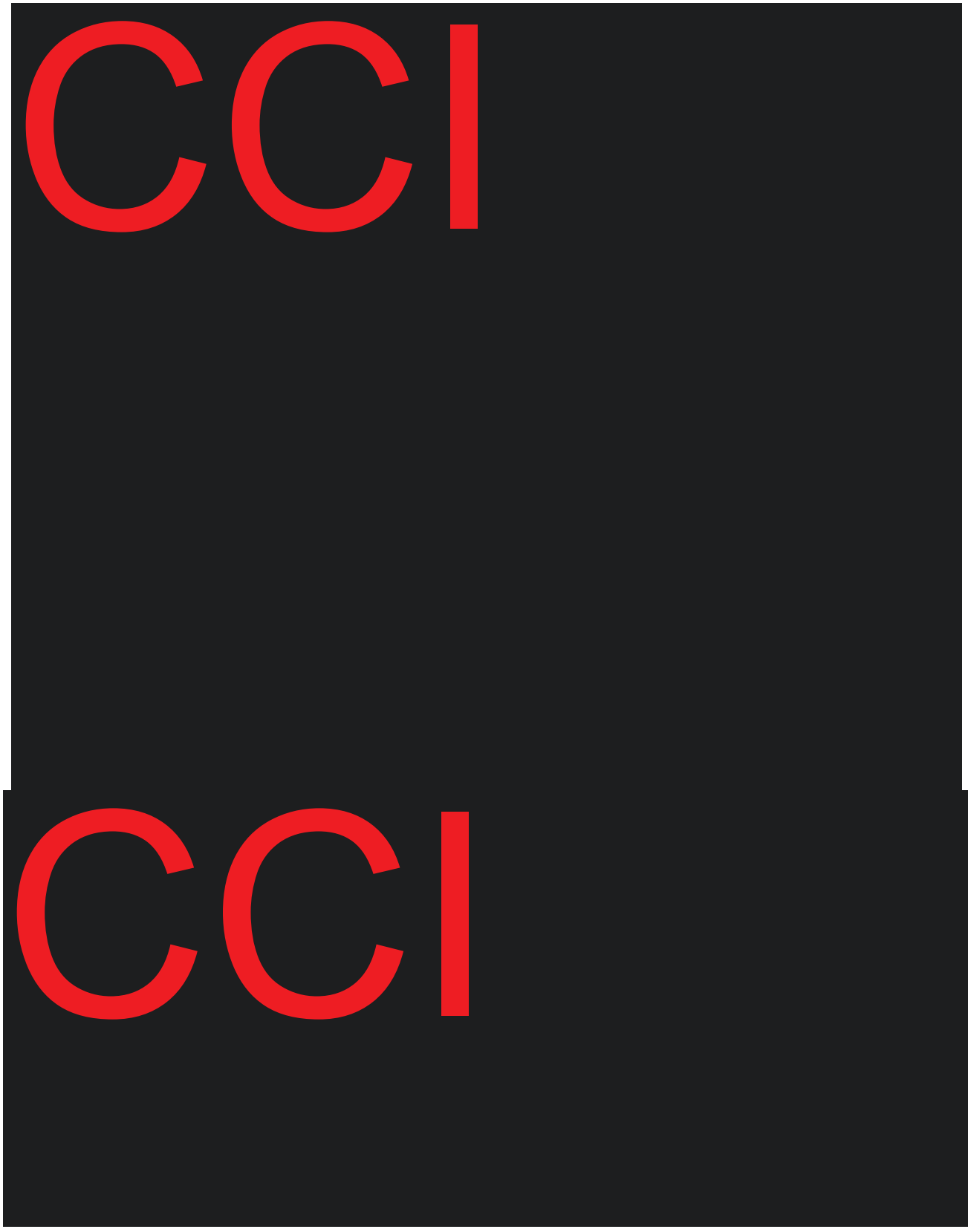
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6.7 Treatment of Overdose

For this study, any dose of avelumab, sacituzumab govitecan, M6223, or NKTR-255 greater than that specified in the protocol will be considered an overdose.

The Investigator will use his/her clinical judgment to manage any overdose, considering the symptoms and any site procedures or standards. Even if not associated with an AE or a SAE, any overdose is recorded in the eCRF and reported to global patient safety in an expedited

manner. Overdoses are reported on a SAE and Overdose Report Form, following the procedure in Appendix 4.

6.8 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.

6.8.1 Rescue Medicine

Proximity to an Intensive Care Unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available for use in the treatment of IRRs.

If hypersensitivity reaction occurs, the participant must be treated according to the best available medical practice (Working Group of the Resuscitation Council [United Kingdom]: emergency treatment of anaphylactic reactions). Participants should be instructed to report any delayed reactions to the Investigator immediately. In addition, all hypersensitivity reactions are to be reported in a timely manner.

6.8.2 Permitted Medicines

The only permitted medicines are the following:

- Other drugs to be used for prophylaxis, premedication for avelumab and sacituzumab govitecan, treatment of hypersensitivity reactions, and treatment of fever or flu-like symptoms are described in 6.8.4.
- Rescue medications may be administered due to anticipated adverse reactions or anticipated emergency situations.
- Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intraocular, or inhalation) are acceptable. For exception regarding prophylactic use in Group B see clarification below.
- Any additional concomitant therapy that becomes necessary during the study, and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

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.

6.8.3 Prohibited Medicines

All participants are prohibited from receiving other drugs containing irinotecan or its active metabolite SN-38 and the following therapies while receiving study treatment:

- Any other anticancer (cytotoxics, biological therapy or other targeted therapy) or investigational agents.
- Other experimental pharmaceutical products.
- Immunotherapy, immunosuppressive drugs (i.e. chemotherapy or systemic corticosteroids except for premedication with sacituzumab govitecan, short-term treatment of allergic reactions, or for the treatment of irAEs). Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection) are allowed.
- Vaccination within 4 weeks of the first dose of study treatment and while on trial is prohibited except for administration of inactivated vaccines (for example, inactivated influenza vaccines) administered ≥ 2 weeks prior first dose of study treatment. All SARS-CoV-2 vaccines approved or authorized by local Health Authorities are allowed.
- Growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor).
  - Exception 1: the use of growth factors for prophylaxis (primary and secondary) and the treatment of neutropenia and febrile neutropenia in relation to toxicity to sacituzumab govitecan.
  - Exception 2: the use Erythropoietin and darbepoetin alpha or similar drugs may be prescribed at the Investigator's discretion.
- Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin).

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Clarifications About Steroid Use: Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes. Furthermore, as with all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit of the proposed study treatment. However, studies with anti-CTLA4 agents indicate that short-term use of steroids may be employed without compromising clinical outcomes. Therefore, the use of steroids during this trial is restricted as follows for participants receiving avelumab:

- Therapeutic use: for the treatment of IRRs and short-term treatment of irAEs, steroids are permitted according to the modalities indicated in Table 4.

- Physiologic use: steroid replacement for adrenal insufficiency at doses equivalent to ≤ 10 mg prednisone daily is acceptable.
- Prophylactic use, e.g., for the prevention of acute IRRs, is prohibited, except prophylactic use prior to CT or MRI. In Group B, prophylactic use of corticosteroids is also permitted for the prevention of nausea and vomiting. Investigators should use their judgment and use corticosteroids at the lowest effective dose level that is still effective in reducing emesis in participants.
- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection) are permitted.

6.8.4 Other Interventions

Premedication for hypersensitivity reactions is permitted. Details regarding other permitted medicines are mentioned in Sections 6.8.2 and 6.5.

For prophylaxis of flu-like symptoms, indomethacin or comparable nonsteroidal anti-inflammatory drug dose (e.g., ibuprofen or naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of avelumab infusion. Alternative treatments for fever (e.g., acetaminophen [paracetamol]) may be given to participants at the discretion of the Investigator.

In order to mitigate IRRs, participants must be premedicated with an antihistamine (H1 receptor blocker such as diphenhydramine) and with acetaminophen (paracetamol) approximately 30 to 60 minutes as described in Section 6.5.

In Group B, further premedication should be considered to mitigate nausea and vomiting which are frequently observed in participants treated with sacituzumab govitecan. To reduce emesis, premedicating with a 2 or 3 drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK1 receptor antagonist, as well as other drugs as indicated) should be considered. If corticosteroids are used as prophylaxis, Investigators should use their judgment and use corticosteroids at the lowest effective dose level that is still effective in reducing emesis in participants.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

If premature termination of 1 agent occurs due to toxicity, the other agent may be continued per protocol schedule.

If study intervention is permanently discontinued due to disease progression or clinical deterioration, the participant will remain in the study to be evaluated for survival long-term

follow up. The SoA indicates data to be collected at the time of discontinuation of study intervention and follow up and for any further evaluations that need to be completed.

Reasons for study intervention permanent discontinuation may include:

- Disease progression as assessed by Investigator.
- Global deterioration of health status requiring discontinuation.
- Unacceptable toxicity.
- Pregnancy.
- Occurrence of an exclusion criteria, which is clinically relevant and affects the participant's safety.
- 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.
- Withdrawal of consent from further treatment with one, or for participants randomized to one of the combination arms, all investigational treatments, or from further study participation.
- Use of a prohibited concomitant drug where the predefined consequence is withdrawal from the study intervention if considered necessary by the Investigator or the Sponsor.
- Significant protocol violation.
- Lost to follow up.
- Permanent unavailability of study intervention due to discontinuation of manufacturing and further drug development.

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

- Pregnancy: any female participant who becomes pregnant while participating in the study will be withdrawn from the study immediately (Section 8.3.4).

- If the administration of a prohibited concomitant medication becomes necessary during the study, study intervention may need to be discontinued. The Medical Monitor will be contacted first to discuss whether study intervention will be discontinued.

7.1.2 Temporary Discontinuation

Refer to Section 6.5 for information on temporary study intervention discontinuation.

7.1.3 Rechallenge

Not applicable for this study.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may discontinue from the study at any time, at their own request or at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of study discontinuation, 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 revokes consent for the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- A participant has the right at any time to request destruction of any biological samples taken. The Investigator will document this in the site study records and the eCRF and inform the Sponsor. The samples will be destroyed.

7.3 Lost to Follow up

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

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

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed “lost to follow up”, the Investigator or designee will make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant’s last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant’s general practitioner or caretaker (where allowed by local regulations) for information. These contact attempts will be documented in the participant’s medical record.
- If the participant continues to be unreachable, he/she will be deemed as “lost to follow up.”
- The date of death may be collected from public records or by other means where allowed by local law/regulations.
- A participant is not considered as “lost to follow-up” until after study completion and the study site has been unable to reach them despite multiple attempts during the study.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA.
- No protocol waivers or exemptions are allowed.

- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations will be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2.
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Where allowed by local law/regulations, samples collected during this clinical study may be transferred to a biobank and used for future research outside the clinical protocol when additional consent for this purpose is given. Transfer to the biobank will be documented and any testing of coded biobank samples will not be reported in the CSR.
- The long-term storage of samples after study completion for future research may be performed will all sample types collected in the study (e.g., PK, pharmacokinetic, immunogenicity, pharmacogenomic, and biomarkers, including genetic testing) if the participant consents to optional future medical research.

8.1 Efficacy Assessments and Procedures

Tumor evaluation will be determined locally according to RECIST v1.1 (Eisenhauer 2009). As the database lock for the primary analysis for this study will have occurred prior to this protocol amendment, with the implementation of this protocol amendment (Protocol Version 5.0), tumor assessments will be performed according to local practice guidelines until discontinuation of study treatment.

Radiographic images used for the determination of disease progression will be evaluated per Investigator assessment, which will determine whether the criteria for tumor response or progression according to RECIST v1.1 have been met, as well as determine the time point for overall response and date of disease progression according to RECIST v1.1 for each participant. These images (including the pre and post 1L platinum therapy) will be collected by an Imaging Research Organization, then quality checked and stored for a possible later independent review of imaging. The CT/MRI scans will be collected until PD is assessed by the Investigator according to RECIST v1.1 regardless of initiation of subsequent anticancer therapy.

After progression of disease and if clinically feasible, a subsequent scan at least 4 weeks after initial assessment of progression should be collected to confirm progression. In case of disease intervention continuation beyond confirmed progression, additional images should be collected in accordance with imaging schedule as long as the participant continues on study therapy.

Tumor assessments will include all known or suspected disease sites. Images will include chest, abdomen, and pelvis CT or MRI scans.

Brain imaging (e.g., MRI) is required at baseline for participants who have a history of brain metastases or for whom brain metastases are suspected during screening. Brain must be included in subsequent tumor assessments if a participant has brain metastases at baseline; otherwise, brain will only be evaluated when clinically indicated.

Bone lesion(s) identified at baseline by chest, abdomen, and pelvis CT or MRI scans will be subsequently reassessed by CT or MRI as per the tumor assessment schedule. Bone scan imaging will only be performed during study as clinically indicated (e.g., participant describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases), at the time of complete response (CR) confirmation if considered local standard of care.

The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. In general, lesions detected at baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

Both pre chemotherapy and post chemotherapy scans must have been performed and be readily available during screening and for image central collection, if participant is randomized. The post chemotherapy confirmatory scan for eligibility must be performed within 28 days prior to the date of randomization to assess response status following first line chemotherapy. This scan will also be used as the baseline scan for tumor assessments in this study.

Treatment decisions will be made by the Investigator based on the Investigator's assessment of tumor status. The CT/MRI scans will be collected until PD is assessed by the Investigator according to RECIST v1.1. regardless of initiation of subsequent anticancer therapy. For all participants and if clinically feasible, a subsequent scan at least 4 weeks after the initial assessment of progressive disease should be collected to confirm progression. Additional radiological tumor assessments should also be conducted whenever disease progression is suspected (e.g., symptomatic deterioration).

For efficacy determination, tumor responses to treatment will be based on the evaluation of the response of target, non-target, and new lesions according to RECIST v1.1 (all measurements should be recorded in metric notation, as described in RECIST v1.1) as per Investigator assessment.

At baseline, tumor lesions will be categorized in target and non-target lesions as described in RECIST v1.1. Measurable or evaluable lesions that have been previously irradiated will not be considered target lesions unless an increase in size has been observed following completion of radiation therapy.

Any CR or PR should be confirmed with repeat imaging performed at least 4 weeks after initial documentation of response.

Participants who withdraw from the trial for clinical or symptomatic deterioration before radiological documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort should be made to confirm a clinical diagnosis of PD by imaging. If discontinuation occurs due to progression and a definitive diagnosis/radiographic confirmation is not made at the time of discontinuation, a second imaging scan may be allowed for confirmation of progression. If progression at the second imaging scan is not confirmed and the participant wishes to restart, the participant will be allowed to continue receiving treatment as long as they meet the criteria for continuation of treatment beyond progression.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, electrocardiograms, and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3. Due to the combined administration of treatments in this study, it is important that the Investigator carefully review and attempt to differentiate causality of AEs.

8.2.1 Physical Examinations

A complete physical examination will be conducted at Screening and EOT as indicated in the SoA (Section 1.3). At other visits a signs and symptom-orientated physical examination will be conducted as indicated in the SoA (Section 1.3) and documented in the eCRF.

- A complete physical examination will include, at a minimum, assessments of the head/neck, extremities, eyes, ears, nose, throat, cognitive status, general appearance, dermatological, pulmonary, cardiovascular, gastrointestinal, genitourinary, lymphatic, neurologic and musculoskeletal systems.
- A brief physical examination (i.e. a signs and symptom-orientated physical examination) will include, at a minimum, assessments of those symptoms that are tailored to the participant's symptoms.
- Investigators will pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

Vital signs should be taken before other study procedures (e.g., blood draws study drug premedication) with the participant in the seated position after the participant has been sitting quietly for at least 5 minutes

- Blood pressure and participant's position; pulse; respiratory rate; temperature and location of measurement, weight, and height (at Screening only) will be measured and recorded.
- Blood pressure and pulse measurements will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and measured with an automated device. Manual techniques will be used only if an automated device is not available.

8.2.3 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically measures heart rate, PR, RR, QRS, QT, and QTcF.

Electrocardiograms will be recorded after the participant has been in a supine position breathing quietly for at least 5 minutes.

8.2.4 Clinical Safety Laboratory Assessments

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

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

The tests will be performed by local laboratory.

The Investigator will review each laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE, unless it does not meet the AE definition, as specified in Appendix 4. The laboratory reports will be filed with the source documents.

Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at monthly intervals during study intervention administration.

Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at the end of the relevant systemic exposure of the study intervention plus an additional 30 days and correspond with the time frame for female participant contraception in Section 5.1 (Inclusion Criteria).

Additional serum or urine pregnancy testing may be conducted at any time during the study to establish the absence of pregnancy, at the Investigator's discretion or if local regulations require them.

8.2.5 Performance Status

ECOG performance status will be assessed at Screening to assess eligibility (Section 5), and then reassessed according to the SoA (Table 1, Table 2, and Table 3).

8.2.6 Data Monitoring Committee

An internal DMC will be formed for this study to monitor interim safety and disease activity data after the safety run-in period and on a regular basis to ensure ongoing surveillance of participant safety and to monitor the conduct of the study to protect its integrity, including recommendations about additional monitoring measures or risk mitigation procedures that may be deemed necessary to protect the study participants. All internal DMC members will have experience in the conduct of clinical studies. Details regarding internal DMC roles, responsibilities, activities, and possible recommendations will be provided in a separate DMC charter.

After the primary analysis, the Sponsor's routine safety surveillance will continue on a regular basis.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

- The definitions of an AE, a SAE, and SUSARs are in Appendix 4.
- The Investigator and any qualified designees (e.g., Sub-Investigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up all AEs or AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study, as specified in Section 8.3.2.
- Requests for follow up will usually be made via the Sponsor or CRO-designated study team member, although in exceptional circumstances the Global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE and SUSAR reports are in Appendix 4.
- All AEs and SAEs will be collected from the signing of the ICF until the follow up visit at the time points specified in the SoA (Section 1.3). Beyond this reporting period, any new unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed.

- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.
- Investigators are not obligated to actively solicit information on AEs or SAEs after the end of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.1 Method of Detecting Adverse Events and Serious Adverse Events

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

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

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

8.3.2 Follow up of Adverse Events and Serious Adverse Events

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

8.3.3 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.

- SUSARs shall be reported to regulatory agencies, as soon as possible but no later than 7 calendar days after first knowledge by the Sponsor that a case qualifies as fatal and life-threatening (refer to Appendix 4).
- SUSARs shall be reported to regulatory agencies, as soon as possible but no later than 15 calendar days after first knowledge by the Sponsor that a case qualifies as nonfatal and nonlife-threatening (refer to Appendix 4).

Individual Case Safety Reports will be prepared for suspected unexpected serious adverse reactions (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 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 2.3.

8.3.4 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 6 months after the last dose of the study intervention for female participants or until 3 months after the last dose of the study intervention for female partners of male participants.

If a pregnancy is reported, the Investigator will record the pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy and will follow the procedures specified below for collection of pregnancy information.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Adverse pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered and reported as SAEs. A spontaneous abortion (occurring at < 22 weeks gestational age) or stillbirth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.

The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date for a healthy newborn. In case of a congenital anomaly or other illness of the newborn, follow up will continue until the illness has resolved or there is a definite outcome of the event.

Any post study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as specified in Section 8.3.3. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.5 Adverse Events of Special Interest and Other Specific Adverse Events

While avelumab and sacituzumab govitecan are established products with known safety profiles, only limited safety data in humans are available for M6223 and NTKR-255, as well as for the combinations of avelumab with either of the 3 products.

In this study, the following events are defined as adverse events of special interest (AESI[s]):

- Infusion-related reactions (M6223, and sacituzumab govitecan and NKTR-255)
- Immune-related adverse events (avelumab and M6223)
- Thromboembolic events (M6223)
- Cytokine release syndrome (NKTR-255)
- CCI [redacted]

AESIs are serious or nonserious AEs that are of clinical interest and should be closely followed. The method of AESI recording and reporting of serious AEs will follow the guideline for AE recording and reporting (refer to Appendix 4).

In addition to an internal DMC, who will be fully unblinded, safety data will also be evaluated in a rolling fashion on a regular basis by a dedicated team composed of safety and medical representatives during the safety run-in and throughout the entire trial (see Section 6.3.2).

In general, this team has the responsibility to review all available safety data. Special focus will be set on the following adverse events, regardless of meeting criteria for an adverse event of special interest:

- Any unexpected/unlabeled toxicities Grade ≥ 3 and SAEs, regardless of causality

- Adverse Events assessed as related to any of the IMPs by the Investigator:
  - Any Grade ≥ 3 hematologic AE (not laboratory) lasting ≥ 7 days despite of medical intervention
  - Any Grade ≥ 3 non-hematologic toxicity (not laboratory) lasting ≥ 7 days despite of medical intervention
  - Grade ≥ 3 nausea, vomiting and diarrhea lasting ≥ 3 days despite optimal supportive care
  - Any Grade 4 laboratory value if:
    - The abnormality leads to hospitalization, or
    - The abnormality persists for ≥ 7 days
  - CCI [redacted]

8.3.5.1 Infusion-related Reactions

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

Possible IRRs are defined based on following Preferred Terms (PTs) and temporal relationship criteria. Events are divided into reactions versus signs and symptoms:

Reactions include the PTs Infusion-Related Reaction, drug-hypersensitivity, hypersensitivity, Type-1-hypersensitivity, anaphylactic reaction, and cytokine release syndrome. These PTs should be considered when the onset is on the day of study drug infusion (during or after the infusion) or within 1 day thereafter.

- Signs and symptoms of IRRs include the PTs pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain and urticaria. These PTs should be considered, if the onset occurs on the day of study drug infusion (during or after the infusion) and resolves within 2 days after onset.

8.3.5.2 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 workup, including possible etiologies such as neoplastic, infectious, metabolic, toxin, etc. Serologic, histologic (biopsy), and/or immunologic workup should be performed as indicated to evaluate the differential diagnosis and/or support an immune-mediated cause.

For the management of irAEs, the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines (Schneider 2021), the NCCN Clinical Practice Guidelines in Oncology (NCCN 2022) and/or guidelines presented in the avelumab and M6223 IBs, as applicable, should be considered. It is recommended to involve the Medical Monitor at first incidence and as needed for follow-up.

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 equivalent) 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, see ASCO guideline tables in Appendix 5.

8.3.5.3 Thromboembolic Events

Thromboembolic events will be considered as an AESI for M6223.

8.3.5.4 Cytokine Release Syndrome

Cytokine release syndrome, regardless of grade, will be considered as an AESI for NKTR-255. Fever after the first 3 days following administration of NKTR-255, without other clinical signs and symptoms of CRS, is not classified as an AESI.

CCI [redacted]

CCI [redacted]

8.4 Pharmacokinetics

The following PK parameters will be calculated, and additional parameters may be added when appropriate:

Symbol	Definition
C_{eoi}	The observed concentration at the end of the infusion period.
C_{trough}	The concentration observed at the end of a dosing interval immediately before next dosing.

Avelumab, M6223, sacituzumab govitecan, and NKTR-255 PK sampling were collected according to the SoA of Protocol Version 4.0 (Tables 4, 5, and 6). As of the implementation of the current protocol Amendment (Version 5.0), no further PK samples will be collected; therefore, the sample collection tables have been deleted.

Blood Samples for PK

- Samples are collected only where allowed by local law/regulations.
- Whole blood samples ranging from approximately 3.5 to 4 mL per drug per collection time point (maximum 7.5 mL per arm per time point) will be collected for detection of avelumab, M6223, sacituzumab govitecan, and NKTR-255 (refer to the Laboratory Manual for complete collection instructions). Collection time points are specified in the Schedule of Activities (Section 1.3). The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration. The sampling timing may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The bioanalysis of PK samples will be performed using validated assay methods.
- Where allowed by local law/regulations, remaining samples collected for analysis of PK may also be used to evaluate immunogenicity or exploratory biomarkers during or after the study.
- Details on processes for collection and handling of these samples are in the Central Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

Concentrations of avelumab, M6223, sacituzumab govitecan, and NKTR-255 will be listed and descriptively summarized as appropriate. Population PK and exposure-response results will be reported separately in a standalone report, as it may also include data from other studies.

8.5 Pharmacogenetics

Participation is optional and a specific pharmacogenetics ICF will have to be signed by the participant who chooses to participate. The Sponsor will be permitted to link the samples to the individual clinical and laboratory outcomes of the investigational treatment in order to enable scientific analyses. The samples will not be utilized to obtain information about individual genetic risks not related to neoplasms or drug effects as described above. Genetic data obtained

during the analysis of the samples may not be reported back to the individual or to his/her healthcare providers. Participants can request the destruction of their sample at any time.

Samples are collected only where it is allowed by local law/regulations.

Where local regulations and IRB/IEC allow, a blood sample of approximately 6 mL will be collected for DNA analysis from consenting participants. Collection time is specified in the SoA. Optional pharmacogenetic samples will be collected from patients enrolled in all 4 groups to support biomarker testing (see section below) and will also be used for CCI [redacted]

In the event of DNA extraction failure, a replacement sample for pharmacogenetic testing may be requested from the participant. Additional informed consent will not be required to obtain a replacement sample.

Appendix 7 provides further information on pharmacogenetic research.

8.6 Biomarkers

Collection of biological samples for other biomarker research is also part of this study; they are collected only where allowed by local law/regulations. The following participant samples for biomarker research will be collected from all participants in this study. Collection times are specified in the SoA of Protocol Version 4.0 (Tables 4, 5 and 6). As of the implementation of the current protocol Amendment (Version 5.0), no further biomarker samples will be collected; therefore, the sample collection tables have been deleted.

The collection of biological samples for exploratory biomarker analysis is not applicable in China.


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Details on processes for collection and handling of these samples are included in the Central 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 the study are specified in the respective ICF.

8.7 Immunogenicity Assessments

Blood samples were collected for immunogenicity assessment according to the SoAs of Protocol Version 4.0 (Tables 4, 5, and 6). As of the implementation of the current protocol Amendment (Version 5.0), no further immunogenicity samples will be collected; therefore, the sample collection tables have been deleted.

- Samples are collected only where allowed by local law/regulations.
- Whole blood samples of approximately 5 mL per drug per collection time point (maximum 10 mL per arm per time point) will be collected for detection of antibodies against avelumab, Sacituzumab, M6223 and NKTR-255 in serum. Collection time points are specified in the Schedule of Activities (Section 1.3).
- The detection of ADA will be performed using validated assay methods. Confirmed positive antibodies may be further characterized.
- Where allowed by local law/regulations, remaining samples collected for analysis of ADA antibodies may also be used to evaluate drug concentration or exploratory biomarkers during or after the study.
- Details on processes for collection and handling of these samples are in the Central Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.
- Pharmacokinetics and immunogenicity samples collected for drug at the same time point can be used interchangeably if the dedicated sample has insufficient quantity, as the participant (if age is appropriate as per local regulations) and/or his/her parent(s)/legally authorized representative(s) will have consented to all collections and tests.

8.8 Health Economics

Not applicable.

8.9 Patient Reported Outcomes

Patient reported outcomes will include the NCCN FACT, FBlSI-18, CCI [redacted] to assess overall wellbeing. Participants completed these assessments at the timepoints specified in the SoAs of Protocol Version 4.0 (Tables 1, 2, and 3). As of the implementation of the current protocol Amendment (Version 5.0), no further patient-reported outcome data will be collected; therefore, NCCN FACT, FBlSI-18, CCI [redacted] were removed from the SoAs.

9 Statistical Considerations

Details of the analysis of safety, efficacy, PK, CCI [redacted] data will be presented in the Integrated Analysis Plan (IAP), which will be finalized before the database is locked for analysis.

9.1 Statistical Hypotheses

No formal statistical hypothesis will be tested, as the study is designed to be exploratory.

9.2 Sample Size Determination

Approximately a total of 252 participants will be randomly assigned to study intervention with 1:2:2:2 randomization ratio between Group A (control), B, C, and D.

Hybrid Design

It is planned to extend the control group of approximately 36 randomized participants by data from an external control, i.e. the JAVELIN Bladder 100 study.

Baseline information will be used to check the comparability between the external and the randomized control group. Comparability will be examined no later than the time of the interim analysis as it is expected that study enrollment will be completed at the time of the interim analysis and baseline information is available for all participants. All participants from JAVELIN Bladder 100 fulfilling the in-/exclusion criteria of this study and randomized to the investigational arm of the study (avelumab plus best supportive care) will be included. The baseline covariate data (see IAP for selection of covariates) will be used to define the preference score, i.e. a prevalence adjusted propensity score calculated as the conditional probability of being a participant of the external control in contrast to being a participant of the Medley study given observed baseline covariates (Walker 2013). The JAVELIN Bladder 100 data will be declared suitable to be used as external control if more than 50% of the participants in the combined group of randomized and external data have a preference score between 0.3 and 0.7. This must be true for each set of treatment-control comparison. If suitable, the randomized

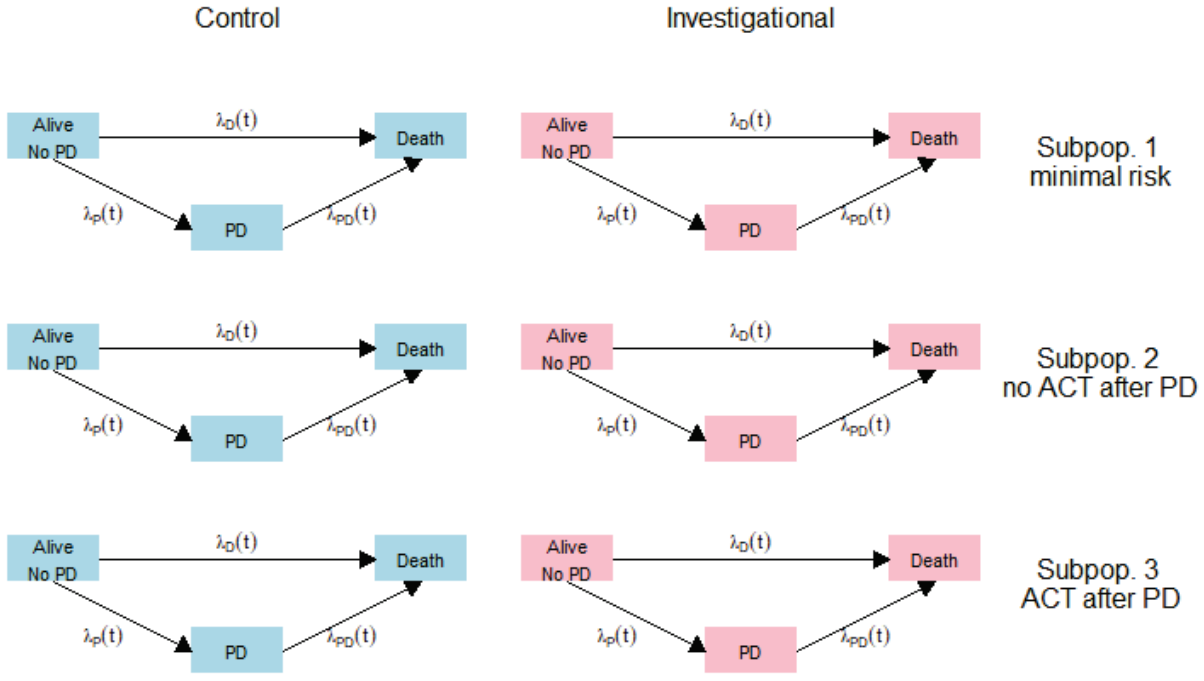
control (Group A) will be finally augmented by the external JAVELIN Bladder 100 data and serve as an extended control group used to compare study endpoints of each of the treatment combinations under investigation (investigational group).

Assumptions and Operational Characteristics

The operational characteristics and respective probabilities of the study are assessed for 2 different scenarios, on the one hand a base-case scenario with approximately 72 participants as control mimicking the case of suitable external data, and on the other hand a scenario with approximately 36 participants, i.e. only the participants randomized to the control arm.

Information from the JAVELIN Bladder 100 study is utilized to make assumptions about efficacy outcomes within the control arm. A subpopulation dependent multi-state model with piecewise constant hazards defines the distribution of PFS and OS time. The subpopulations encompass a minimal risk subpopulation, a subpopulation receiving no (relevant) subsequent anticancer treatment (ACT) after PD and a subpopulation receiving subsequent anticancer treatment after PD.

Figure 8 Schematic Figure of Hazards by Treatment Group and Subpopulation



ACT = anticancer treatment; PD = progressive disease.

Based on the PFS distribution in JAVELIN Bladder 100, a model with piecewise constant hazards for 4 time intervals is considered. For post progression overall survival time 2 additional intervals are specified. Further details on the hazards assumed for each subpopulation and time interval are given in Section 11, Appendix 8.

In the JAVELIN Bladder 100 study, 96% of the PFS events are progressive disease. The avelumab monotherapy PFS curve shows a high risk for progression at the first assessment (around 8 weeks) and a lower risk afterwards. Based on this information, it is assumed that the combination treatments (Group B, C, and D) have the highest potential for improvement at early timepoints.

Four PFS and one OS distributions are investigated to compare the probabilities of success of different possible scenarios (see Table 14 and Figure 9 to Figure 13).

Table 14 Progression-free Survival and Overall Survival Scenarios

Scenario	Abbreviation	Assumptions
Optimistic PFS Scenario	Opt. PFS	Strong positive effect already at the first tumor assessment.
Positive PFS Scenario 1	PFS 1	Positive effect already at the first tumor assessment.
Positive PFS Scenario 2	PFS 2	Positive effect after the first tumor assessment.
No-effect PFS Scenario 3	PFS 3	Almost no effect.
OS Scenario	OS	Positive overall effect.

Abbreviations: OS = overall survival; PFS = progression-free survival.

Figure 9 Optimistic Progression-free Survival Scenario

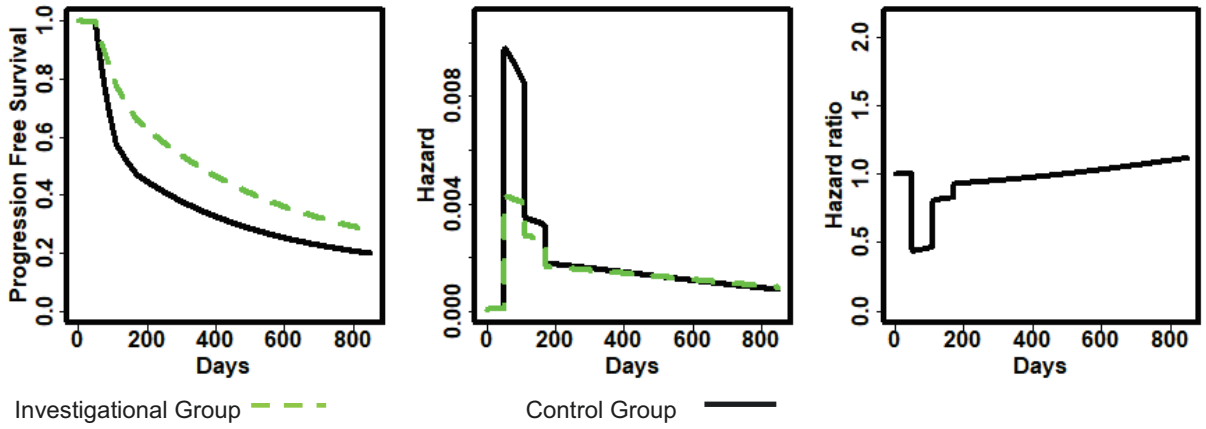


Figure 10 **Positive Progression-free Survival Scenario 1**

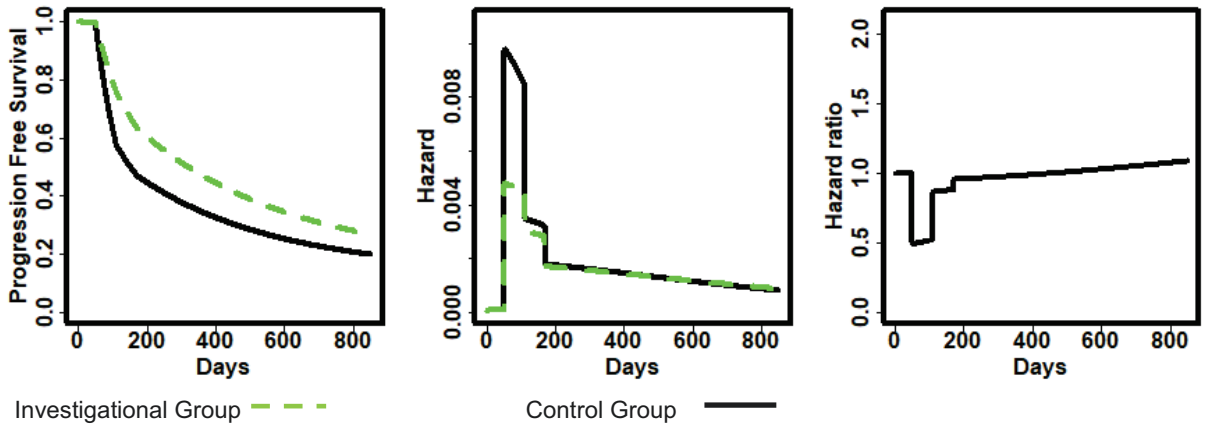


Figure 11 **Positive Progression-free Survival Scenario 2**

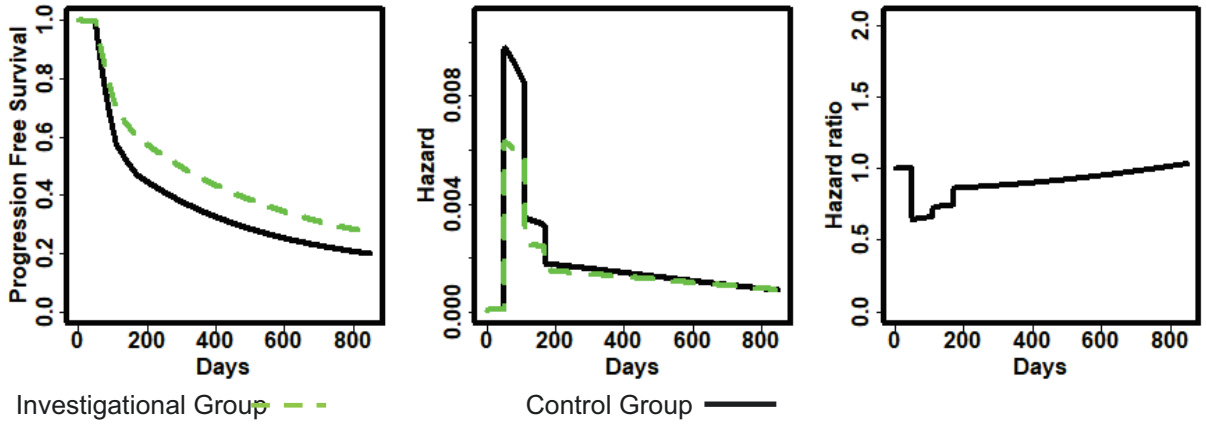


Figure 12 **No-effect Progression-free Survival Scenario 3**

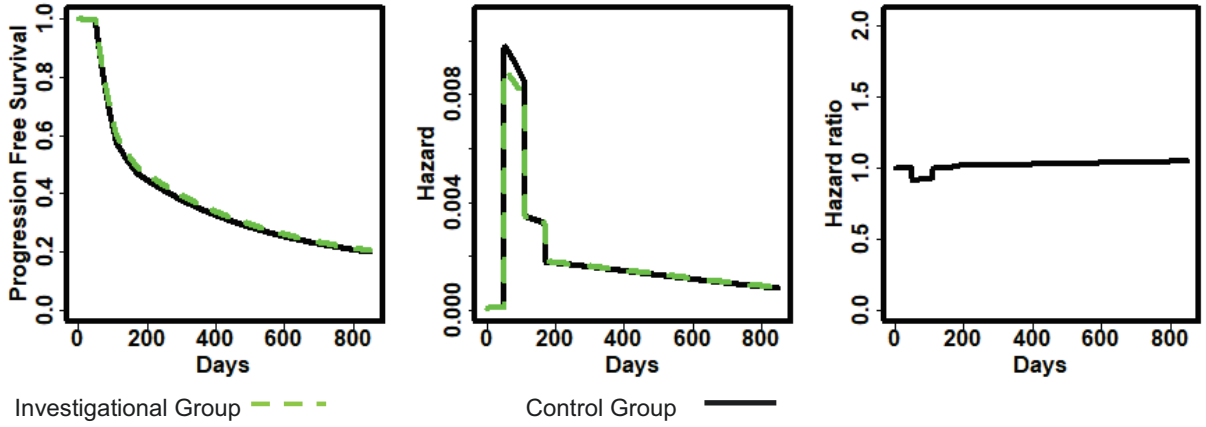
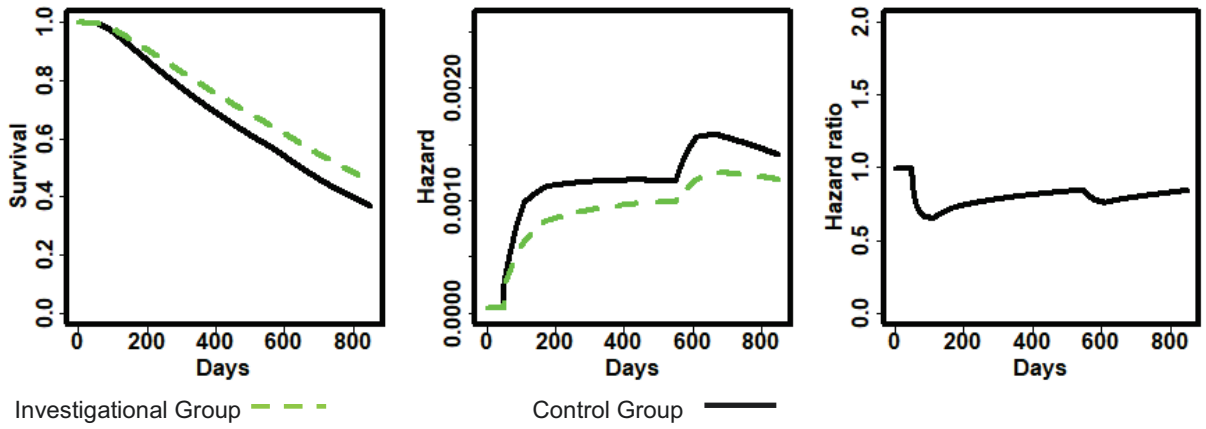


Figure 13 Overall Survival Scenario



To account for the case the JAVELIN Bladder Medley and JAVELIN Bladder 100 study are not comparable (following the decision criteria previously specified), probabilities are presented for 2 cases:

- External control cannot be used, i.e. the actual randomized control group including approximately 36 participants serves as control group.
- External control is suitable (base-case), i.e. the information borrowed can be used to an extent to what would be expected from a 1:1 randomization design.

The success of the study is dependent on efficacy boundaries for PFS as specified in Table 15. The study is successful if at least one investigational arm achieves an observed PFS hazard ratio compared to the control that is equal or below the given boundaries. OS boundaries are added to evaluate the likelihood of observing a positive effect of the combined treatments, but the primary focus of the study is PFS. Considering fixed assumed time points for the respective analyses, i.e. 26 months after first patient-in (FPI) for the interim analysis and 32 months after FPI for the primary analysis, Table 16 and Table 17 below show:

- The number of events per investigational treatment and control comparison (treatment-control).
- The number of events for each investigational treatment arm without events of the control (treatment arm).
- The expected hazard ratio based on the respective scenario assumptions at the time of analysis.

Table 15 Progression-free Survival and Overall Survival Boundaries

	Interim Analysis	Primary Analysis
Progression-free Survival	CCI	
Overall Survival		

Abbreviations: HR = hazard ratio.

CCI

The necessary number of events for the interim and primary analysis, i.e. 56 PFS events per treatment-control comparison (i.e. Group B – Group A, Group C – Group A, and Group D – Group A) at interim and 65 at the primary, are based on the PFS 1 Scenario as it is expected to be most realistic. Note that the necessary number of events is based on the actual randomized participants without considering events from the external data and following,

56 PFS events (see Table 17, PFS 1, interim analysis) per treatment-control comparison and not 78 (see Table 16, PFS 1, interim analysis) are applicable. The same applies to the primary analysis. The interim analysis will be performed when each of the treatment-control comparisons (i.e. Group B – Group A, Group C – Group A, or Group D – Group A) has reached 56 PFS events, the primary analysis will be performed when each of the treatment-control comparisons has reached 65 PFS events.

CCI

A recruitment duration of 24 months is assumed, and for the probability estimations an exponential distributed drop-out mechanism is used to lead to about 15% drop-out rate for PFS and 5% for OS by the time of the primary analysis. The interim analysis is expected at around 26 months after first participant randomized and the primary analysis is estimated to take place at around 32 months after first participant randomized.

Sample size calculations and evaluations were done with R 3.6.3.

9.3 Analysis Sets

The analysis sets are specified below in Table 18.

Table 18 JAVELIN Bladder Medley Analysis Sets

Analysis Set	Description
SCR	All participants, who provided informed consent, regardless of the participant's randomization and study intervention status in the study.
FAS	The FAS will include all randomized participants[a]. Participant will be analyzed according to the treatment assigned at randomization as per the Intention-to-Treat (ITT) principle.
SAF	All participants, who were administered any dose of any study intervention [b]. Analyses will consider participants as treated.
PK	All participants, who receive at least one dose of study intervention, and provide at least one measurable postdose concentration. A measurement below lower limit of quantification is considered a valid measurement. Participants will be analyzed per the actual study intervention they received. All PK analyses will be based on this analysis set.
Immunogenicity	All participants who receive at least one dose of study intervention and have at least one valid ADA result. All ADA analyses will be based on this analysis set.

[a] In case the JAVELIN Bladder 100 data is suitable to extend the control group, the FAS will include all participants from the external data set fulfilling the in-/exclusion criteria defined for this protocol and who were randomized to the investigational arm of the JAVELIN Bladder 100 study (avelumab plus best supportive care).

[b] In case the JAVELIN Bladder 100 data is suitable to extend the control group, the SAF will include all participants from the external data set fulfilling the in-/exclusion criteria defined for this protocol and who were administered any dose of the investigational arm in the JAVELIN Bladder 100 study (avelumab plus best supportive care).

9.4 Statistical Analyses

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 IAP.

Besides the details outlined below, more details will be specified in the IAP finalized before database lock.

Safety and efficacy analyses will be performed on the Safety and Full Analysis Set, respectively, unless specified otherwise.

All analyses are considered exploratory, and the family-wise error rate is not controlled.

9.4.1 Efficacy Analyses

A description of study objective, endpoint and further estimand attributes can be found in Section 3. In case the external control is suitable, propensity scores are used as weights to minimize the impact of confounding factors on the estimation of causal treatment effects (Austin 2013). Each participant from the randomized study will be assigned a weight of 1, while participants from the external control get a propensity score-based weight with the sum of weights adding up to the number of participants in the randomized control arm. The weights will be used for main statistical analysis of PFS and OS.

Efficacy estimand attributes are summarized in Table 19.

Table 19 Efficacy Estimand Attributes

Estimand	Statistical Analysis Methods/Further Estimand Attributes	
	Statistical Category	Statistical Analysis
Primary		
PFS	Main Estimand	• The treatment effect will be evaluated in terms of the hazard ratio and CI, estimated by means of a Cox proportional hazards model, stratified by the randomization strata. Randomization strata will be taken as specified and documented in the IWRS and each stratum will define a separate baseline hazard function.

		• Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics. The estimate of the standard error will be computed using Greenwood's formula. Median PFS and corresponding two-sided 95% CI will be calculated according to Brookmeyer and Crowley (Brookmeyer 1982). • Frequency (number and percentage) of participants with each event type (PD or death) and censoring reasons will be presented by treatment group.
	Sensitivity 1	Rationale: Evaluate robustness of treatment effect with regard to stratification. Sensitivity analysis: Estimand as defined for main analysis, except for the following change: Population level summary: Unstratified estimation of HR.
	Sensitivity 2	Rationale: Explore interaction of treatment effect and selected baseline covariates. Sensitivity analysis: Estimand as defined for main analysis, except for the following change: Population level summary: Interaction derived from unstratified Cox-model including treatment effect, baseline covariate, and their interaction (separately for each covariate). Covariates considered will be specified in the IAP.
	Sensitivity 3	Rationale: Explore homogeneity of treatment effect across subgroups defined by selected baseline covariates. Sensitivity analysis: Estimand as defined for main analysis, except for the following change: Population level summary: Treatment effect based on unstratified Cox-model using treatment group as only covariate (separately for each subgroup level). Covariates considered will be specified in the IAP.
	Sensitivity 4	Rationale: Evaluate the robustness of estimand towards the assumption that tumor assessments after several missing scans cannot reasonably be used to determine the time point of progression. Sensitivity analysis: Estimand as defined for main analysis, except for the following change: Population level summary: all RECIST confirmed PDs and deaths are taken into account, i.e. events after 2 or more missing tumor assessments are included.
	Supplementary 1	Rationale: Evaluate whether the study intervention improves PFS irrespective of subsequent anticancer treatment administered before PD. Supplementary analysis: Estimand as defined for main analysis, except for the following change: Intercurrent event strategy: Tumor assessments after start of subsequent anticancer treatment will be considered for analysis (treatment-policy strategy).

Secondary		
OS	Main estimand	• The treatment effect will be evaluated in terms of the hazard ratio and CI, estimated by means of a Cox proportional hazards model, stratified by the randomization strata. Randomization strata will be taken as specified and documented in the IWRS and each stratum will define a separate baseline hazard function. Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics. The estimate of the standard error will be computed using Greenwood's formula. Median OS and corresponding two-sided 95% CI will be calculated according to Brookmeyer and Crowley (Brookmeyer 1982). • Frequency (number and percentage) of participants with an event (death) and censoring reasons will be presented by treatment group.
	Sensitivity 1	Rationale: Evaluate robustness of treatment effect regarding stratification. Sensitivity analysis: Estimand as defined for main analysis, except for the following change: Population level summary: Unstratified estimation of HR.
	Sensitivity 2	Rationale: Explore interaction of treatment effect and selected baseline covariates. Sensitivity analysis: Estimand as defined for main analysis, except for the following change: Population level summary: Interaction derived from unstratified Cox-model including treatment effect, baseline covariate, and their interaction (separately for each covariate). Covariates considered will be specified in the IAP.
	Sensitivity 3	Rationale: Explore homogeneity of treatment effect across subgroups defined by selected baseline covariates. Sensitivity analysis: Estimand as defined for main analysis, except for the following change: Population level summary: Treatment effect based on unstratified Cox-model using treatment group as only covariate (separately for each subgroup level). Covariates considered will be specified in the IAP.
OR	Main estimand	• Objective response rate together with exact 95% Clopper-Pearson CI. • Odds ratio estimated based on Cochran-Mantel-Haenszel method (taking into account strata according to IWRS data) and 95% CI. • Frequency (number and percentage) of participants with best overall response of CR, PR, SD, PD, non-CR/non-PD, and NE.
DoR	Main estimand	• Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics. The estimate of the standard error will be computed using Greenwood's formula. Median PFS and corresponding two-sided 95% CI will be calculated according to Brookmeyer and Crowley (Brookmeyer 1982).
DRS-P	Main estimand	• Difference in least-squares means of the change from baseline DRS-P score at Week 13 visit between the treatment groups will be estimated by a MMRM model with fixed effect terms: treatment group, visit as categorical variable, treatment-visit-interaction, randomization strata (from IWRS), and participant as random effect. Two-sided 95% CIs will be provided. • Data will be used as collected and no explicit imputations will be performed for missing data up to visit Week 13.

	Supplementary 1	Rationale: Evaluate the treatment effect of study intervention on the DRS-P at visit W13 considering both intercurrent events, i.e. discontinuation of treatment and death, as poor outcomes. Supplementary analysis: Estimand as defined for main analysis, except for the following change: Intercurrent event strategy: The intercurrent events • Discontinuation of treatment • Death will be handled according to the composite strategy. Estimator: A common poor outlier (e.g. 0) will be imputed for the missing DRS-P values for all dropouts after an intercurrent event (either due to discontinuation of treatment or death) followed by a between-treatment comparison using quantile regression. Population level summary: Difference in median change from baseline DRS-P score at Week 13 visit between the treatment groups.
	Supplementary 2	Rationale: Evaluate the treatment effect of study intervention on the DRS-P considering data after discontinuation of treatment are missing at random as in main estimand, and the intercurrent event of death is a poor outcome. Supplementary analysis: Estimand as defined for main analysis, except for the following change: Intercurrent event strategy: • Discontinuation of treatment: The endpoint will be analyzed according to the hypothetical strategy, i.e. as if participants were still on randomized treatment at Week 13 visit. • Death: The endpoint will be analyzed according to a composite strategy, i.e. after the intercurrent event occurs, scores will be replaced by the worst possible DRS-P score until and including Week 13 visit.
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Abbreviations: CI = confidence interval; CR = complete response; DRS-P = disease-related physical symptoms; HR = hazard ratio; IAP = interim analysis plan; IWRS = interactive web response system; MMRM = mixed model repeated measures; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

9.4.2 Safety Analyses

Participants will be analyzed according to the actual treatment they receive. Safety estimand attributes are summarized in Table 20.

Table 20 Safety Estimand Attributes

Estimand	Statistical Analysis Methods/Further Estimand Attributes
Occurrence of TEAEs and treatment - related AEs	The definitions, procedures for recording, evaluating, follow up, and reporting of AEs are described in Appendix 4. AEs will be coded according to the latest available version of the MedDRA. Missing classifications concerning study intervention relationships will be considered related to the study interventions. Analysis will be based on TEAEs, which are events with onset dates during the on-treatment period, or events with onset dates before the on-treatment period and worsening during the on-treatment period.
Laboratory Values	Baseline values are defined as the last value prior to first administration of study intervention. Only on-treatment values will be summarized. Laboratory values will be graded using NCI-CTCAE (Version 5.0), if applicable. Nongradable parameters will be classified as normal, high, or low. Summary statistics will be provided for: • Absolute values. • Change from baseline. • Worst on-treatment grade. Shift tables (baseline versus worst on-treatment) will be displayed. Further details of safety analyses (including AEs, clinical laboratory assessments, vital signs, physical examination, and ECOG PS) will be provided in the IAP.

Abbreviations: AE = adverse event; CTCAE = common terminology criteria for adverse events; ECOG PS = Eastern Cooperative Oncology Group performance status; MedDRA = medical dictionary for regulatory activities; TEAE = treatment-emergent adverse event.

9.4.3 Other Analyses

Details on the PK, immunogenicity, CCI [redacted] analyses will be in the IAP that will be finalized before database lock. Integrated analyses across studies will be presented separately from the main CSR.

Participant characterization for ADAs will be tabulated across the participants. For ADA treatment-emergent participants, listings will be prepared for ADA results, TEAEs, efficacy measures, and drug concentrations in serum. Details will be provided in the IAP.

9.4.4 Sequence of Analyses

Planned analyses are outlined in Table 21.

Table 21 Sequence of Analysis

Analysis	Timing	Reporting	Resulting Actions
Safety Run-in Evaluation	Cutoff 5 weeks after 21 participants (3 to Group A, 6 to each of the other 3 groups) have been randomized.	Safety data analysis to internal DMC (unblinded).	Internal DMC recommendation to proceed/adjust/stop study.
Regular Safety Analyses	Every 3 months after safety run-in evaluation.	Safety data analysis to internal DMC (unblinded).	Internal DMC recommendation to proceed/adjust/stop study.
Interim Analysis	When 56 PFS events have been observed in each of the treatment-control comparisons.	Safety and efficacy data analysis to internal DMC (unblinded).	Internal DMC recommendation to proceed/adjust/stop study.
Primary Analysis	When 65 PFS events have been observed in each of the treatment-control comparisons.	Primary safety and efficacy data analysis.	Not applicable.
Final Analysis	Two years after the last participant randomized (06 June 2026).	OS and safety update.	Not applicable.

Abbreviations: DMC = Data Monitoring Committee; OS = overall survival; PFS = progression-free survival.

10 References

Ahn MJ, J. Niu DW, Rasco KD, Mileham KF, Chung HC, Vaishampayan UN et al. 1400P Vibostolimab, an anti-TIGIT antibody, as monotherapy and in combination with pembrolizumab in anti-PD-1/PD-L1-refractory NSCLC, Annals of Oncology, 2020; 31(S4): S887.

Austin 2013 https://doi.org/10.1002/sim.5984

CCI

Brittenden J, Heys SD, Ross J, Eremin O. Natural killer cells and cancer. Cancer. 1996 Apr 1;77(7):1226-43.

Brookmeyer R. and Crowley, J. (1982) A confidence interval for the median survival time. Biometrics, 38, 29-41. doi:10.2307/2530286

Conlon KC, Lugli E, Welles HC et al. Redistribution, hyperproliferation, activation of natural killer cells and CD8 T cells, and cytokine production during first-in-human clinical trial of recombinant human interleukin-15 in patients with cancer. J Clin Oncol. 2015;33(1):74-82.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European Journal of Cancer 2009; 45(2): 228-247.

Fakih M, Wong R. Efficacy of monoclonal antibody EGFR inhibitiors for the treatment of metastatic colorectal cancer. Current Oncol. 2010; 17(Suppl 1): S3-17.

CCI

Giri JG, Kumaki S, Ahdieh M, et al. Identification and cloning of a novel IL-15 binding protein that is structurally related to the alpha chain of the IL-2 receptor. EMBO J. 1995 ;14(15):3654-63.

CCI

GLOBOCAN. IARC. Bladder Fact Sheet: GLOBOCAN. https://gco.iarc.fr/today/data/factsheets/cancers/30-Bladder-fact-sheet.pdf

Grabstein KH, Eisenman J, Shanebeck K et al. Cloning of a T cell growth factor that interacts with the beta chain of the interleukin-2 receptor. Science. 1994;264(5161):965-8.

Iwai T, Sugimoto M, Wakita D, Yorozu K, Kurasawa M, Yamamoto K. Topoisomerase I inhibitor, irinotecan, depletes regulatory T cells and up-regulates MHC class I and PD-L1 expression, resulting in a supra-additive anti-tumor effect when combined with anti-PD-L1 antibodies. Oncotarget 2018; 9(59):31411-31421.

Julia EP, Amante A, Pampena MB, Mordoh J and Levy EM. Avelumab, an IgG1 anti-PD-L1 Immune Checkpoint Inhibitor, Triggers NK Cell-Mediated Cytotoxicity and Cytokine Production Against Triple Negative Breast Cancer Cells. Front. Immunol, 2018; 9:2140.

CCI

Lawrance R, Degtyarev E, Griffiths P, et al. What is an estimand & how does it relate to quantifying the effect of treatment on patient-reported quality of life outcomes in clinical trials? J Patient Rep Outcomes. 2020;4:68.

CCI

Lee JM, Shin KS, Koh CH, et al. Inhibition of topoisomerase I shapes antitumor immunity through the induction of monocyte-derived dendritic cells [published online ahead of print, 2021 Jul 3]. Cancer Lett. 2021;520:38-47.

Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188–195.

Lee DW, Santomasso BD, Locke FL, et al. ASBMT consensus grading for cytokine release syndrome and neurological toxicity associated with immune effector cells. Biol Blood Marrow Transpl. 2019; 25; 625-638.

McKenzie JA, Mbofung RM, Malu S, et al. The Effect of Topoisomerase I Inhibitors on the Efficacy of T-Cell-Based Cancer Immunotherapy. J Natl Cancer Inst. 2018; 110(7): 777-786.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Management of Immunotherapy-Related Toxicities. NCCN April 2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

NCCN Guidelines for Bladder Cancer (NCCN Guidelines®) v3.2021. Available at: https://www.nccn.org/guidelines/guidelines-process/transparency-process-and-recommendations/GetFileFromFileManager?fileManagerId=12152.

Niu, A. Nagrial, M. Voskoboynik, H.C. Chung, D.H. Lee, M-J. Ahn, T.M. Bauer, A. Jimeno, V. Chung, K.F. Mileham, E. Chartash, D. Chen, J. Healy, M. Rajasagi, C. Maurice-Dror, 1410P Safety and efficacy of vibostolimab, an anti-TIGIT antibody, plus pembrolizumab in patients with anti-PD-1/PD-L1-naive NSCLC, Annals of Oncology, 2020; 31(S4): S891-S892.

Powles T, Csőszi T, Özgüroğlu M, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021; 22(7): 931-945.

Powles T, Park SH, Voog E, et al. Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (UC): Long-term follow-up results from the JAVELIN Bladder 100 trial. J Clin Oncol 2022;40(6_suppl):487.

Rodríguez-Abreu D, Johnson ML, Hussein MA, et al. Primary analysis of a randomized, double-blind, phase III study of the anti-TIGIT antibody tiragolumab (tira) plus atezolizumab (atezo) versus placebo plus atezo as first line (1L) treatment in patients with PD-L1-selected NSCLC (CITYSCAPE). Program and abstracts of the 2020 Annual Meeting of the American Society of Clinical Oncology; May 29 - June 2, 2020; Virtual. Abstract 9503.

Rosenberg JE, Flaig TW, Friedlander TW, Milowsky MI, Srinivas S et al. Study EV-103: Preliminary durability results of enfortumab vedotin plus pembrolizumab for locally advanced or metastatic urothelial carcinoma. J Clin Oncol 2020; 38(6): S441.

Romee R, Cooley S, Berrien-Elliott MM, et al. First-in-human phase 1 clinical study of the IL-15 superagonist complex ALT-803 to treat relapse after transplantation. Blood. 2018;131(23):2515-2527.

Saginala K. Epidemiology of Bladder Cancer Med Sci (Basel). 2020 Mar; 8(1): 15. Published online 2020 Mar 13.

Sharma s, Ulahannan S, Garrido-Laguna I, et al. Initial result from a phase 1a/b study of Etigilimab (OMP-313M32), and anti-T-cell immunoreceptor with Ig and ITIM domains (TIGIT) antibody, in advanced solid tumors. Poster presentation, VK/SS Honor Health Research Institute, Scottsdale, AZ KNM/SU Stephenson Cancer Center at the University of Oklahoma, Oklahoma City and Sarah Cannon Research Institute, Nashville, TN. NBM Duke University, Durham, NC IGL University of Utah, Salt Lake City, UT AK/LF OncoMed Pharmaceuticals, Redwood City, CA JB Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN. 2018.

Schneider BJ, Nadoo J, Santomasso B, et al; Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO Guideline Update, J Clin Oncol 2021;39:4073-4126.

Tagawa ST, Balar AV, Petrylak DP, et al. TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors. J Clin Oncol. 2021;39(22):2474-2485. doi: 10.1200/JCO.20.03489. Epub 2021 Apr 30.

Thomas M. Cetuximab: adverse event profile and recommendations for toxicity management. Clinical J Oncol. 2005; 9(3): 332-8.

von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23(21):4602-8.

Walker A, Patrick A, Lauer M, Hornbrook M, Marin M, Platt R, Roger V, Stang P, Schneeweiss S. A tool for assessing the feasibility of comparative effectiveness research. Comparative Effectiveness Research. 2013;3:11-20 https://doi.org/10.2147/CER.S40357

Working Group of the Resuscitation Council [United Kingdom]: emergency treatment of anaphylactic reactions. Emergency treatment of anaphylactic reactions: Guidelines for healthcare providers. January 2008.

11 Appendices

Appendix 1 Abbreviations

ACC	American College of Cardiology
AChR	Acetylcholine Receptor
ACT	Anticancer Treatment
ACTH	Adrenocorticotropic Hormone
ADA	Antidrug Antibodies
ADC	Antibody Drug Conjugate
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Events of Special Interest
AHA	American Heart Association
AID	Autoimmune disease
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody
ANC	Absolute Neutrophil Count
ANCA	Antineutrophil Cytoplasmic Antibodies
AST	Aspartate Aminotransferase
ATG	Antihymocyte Globulin
BAL	Bronchoalveolar Lavage
BCG	Bacille Calmette-Guérin
BICR	Blinded Independent Central Review
BSA	Body Surface Area
BSC	Best Supportive Care
BNP	B-type Natriuretic Peptide
CBC	Complete Blood Count
CCP	Citrullinated Protein Antibody
CFR	US Code of Federal Regulations
CI	Confidence Interval

CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
CMV	Cytomegalovirus
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CR	Complete Response
CRO	Clinical Research Organization
CRP	C-reactive Protein
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CT	Computed tomography
CTR	Clinical Trials Regulation
CTPA	Computed Tomography Pulmonary Angiography
CV	Cardiovascular
CXR	Chest X-ray
DIC	Disseminated Intravascular Coagulation
DIHS	Drug-Induced Hypersensitivity Syndrome
DKA	Diabetic Ketoacidosis
DLCO	Diffusing Capacity of Lung for Carbon Monoxide
DLT	Dose Limiting Toxicity
DM	Diabetes Mellitus
DMARD	Disease-Modifying Antirheumatic Drug
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
DRE	Disease Related Events
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DRS-P	Disease Related Symptom-Physical Subscale
DVT	Deep Vein Thrombosis
EBV	Epstein-Barr Virus

ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Score
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture/Collection
EEG	Electroencephalogram
EMA	European Medicines Agency
EMG	Electromyography
EMS	Emergency Medical Services
EOI	End of Infusion
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome
ER	Extended Release
ESC	European Society of Cardiology
ESR	Erythrocyte Sedimentation Rate
EudraCT	European Clinical Trials Database
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
CCI	[redacted]
FIH	First in Humans
FPI	First Patient-in
FSH	Follicle-Stimulating Hormone
FT4	Free thyroxine
GCP	Good Clinical Practice
GCSF	Granulocyte Colony Stimulating Factor
GH	Growth Hormone
GI	Gastrointestinal
GPI	Glycosylphosphatidylinositol
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus

HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
HSV	Herpes Simplex Virus
IA	Interim Analysis
IAP	Integrated Analysis Plan
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICPI	Immune Checkpoint Inhibitor
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILT	Immunoglobulin like Transcript
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
IRR	Infusion-related Reaction
CCI	[redacted]
ITT	Intention-to-Treat
IV	Intravenous
IVIG	Intravenous Immunoglobulin
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase

LH	Luteinizing Hormone
LLN	Lower Limit of Normal
LMWH	Low-Molecular-Weight Heparin
MCC	Merkel Cell Carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MGFA	Myasthenia Gravis Foundation of America
MMRM	Mixed-effect Model for Repeated Measures
MRI	Magnetic resonance imaging
mTNBC	Metastatic triple-negative breast cancer
NA	Not Applicable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NCS	Nerve Conduction Study
NIF	Negative Inspiratory Force
NIMP	Non-Investigational Medicinal Product
NK	Natural Killer
NSAID	Nonsteroidal Anti-inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PB	Peripheral Blood
PCP	Pneumocystis Pneumonia
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic, Progressive Disease
PE	Physical Examination
PEG	Polyethylene glycol
PEX	Plasma Exchange
PFS	Progression-free Survival
PK	Pharmacokinetic

PNH	Paroxysmal Nocturnal Hemoglobinuria
PPI	Protein Pump Inhibitor
PR	Partial Response
PRO	Patient Reported Outcome
PT	Prothrombin Time
PTT	Partial Thromboplastin time
PTU	Propylthiouracil
CCI	[redacted]
QTcF	Corrected QT interval by Fridericia' formula
QTL	Quality Tolerance Limits
RBC	Red Blood Cell Count
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumor
RF	Rheumatoid Factor
RPR	Rapid Plasma Reagin
SCAR	Severe Cutaneous Adverse Reactions
SAE	Serious Adverse Event
SAF	Safety
SD	Stable Disease
SFU	Safety Follow up
SG	Sacituzumab Govitecan
SJS	Stevens-Johnson Syndrome
SoA	Schedule of Activities
SoC	Standard of care
SSKI	Potassium Iodide
SUSAR	Suspected Unexpected Serious Adverse Reactions
T4	Thyroxine
TB	Tuberculosis
TEAE	Treatment-emergent Adverse Event
TEN	Toxic Epidermal Necrolysis

TIGIT	T-cell-immuno-receptor with Ig and ITM domains
TIL	Tumor Infiltrating Lymphocytes
TME	Tumor Microenvironment
TNF	Tumor Necrosis Factor
TPO	Thyroid Peroxidase
TSH	Thyroid-stimulating Hormone
TSI	Thyroid-stimulating Immunoglobulin
TTE	Transthoracic Echocardiogram
TTP	Thrombotic Thrombocytopenic Purpura
UC	Urothelial Carcinoma
ULN	Upper Limit of Norma
UK	United Kingdom
US	United States
UTI	Urinary Tract Infection
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential
CCI	[redacted]
VC	Vital Capacity
VKA	Vitamin K Agonist

Appendix 2 Study Governance

Financial Disclosure

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

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative (where allowed by local laws and regulations) and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants or their legally authorized representative (where allowed by local laws and regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act requirements, where applicable; and the IRB/IEC or study center.
- The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent will also sign the ICF.
- If the ICF is updated during their participation in the study, participants will be re-consented to the most current, approved version.
- 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.
- As this study includes optional pharmacogenetic examinations, including collection and storage of biological samples, participants may consent to a separate pharmacogenetic analysis, the process of which will need to be documented in the participant's medical records.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor will inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the

participant and pregnant partners (if applicable), who will be required to give consent for their data to be used, as specified in the informed consent.

- The participant will be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

This clinical study will be sponsored by Merck Healthcare KGaA Darmstadt, Germany for sites outside of the US and Canada and EMD Serono Research & Development Institute, Inc., Billerica, MA, US for sites in the US and Canada.

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.

An internal DMC will perform specific study-related activities as detailed in each committee's charter (see Section 8.2.6).

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

Details of structures and associated procedures will be defined in a separate Pharmacy 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 CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations including as Regulation [EU] No 536/2014
- The protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) will be submitted to an IRB/IEC for review and approve 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 protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

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

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

Clinical Study Insurance and Compensation to Participants

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

Clinical Study Report

After completion of the primary analysis of the study, the Sponsor will write a clinical study report in consultation with the Coordinating Investigator. Any additional data generated after the primary analysis cut-off date (e.g. OS data, additional AEs documented, subsequent therapy) will be summarized in a CSR addendum once no further data will be acquired (see Section 9.4.4).

Publication

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

Dissemination of Clinical Study Data

After completion of the study, a CSR will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 and will be submitted in accordance with local regulations.

Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff who had been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study intervention and therefore may be disclosed as required to other clinical Investigators, to the 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 CRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Operations Manual.
- The Investigator will maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- QTLs will be predefined in the Project Management Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring),

methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan.

- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.
- Study Monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

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

Study and Site Start and Closure

The study start date is when the first participant signs the Informed Consent Form.

Study and Site Closure

The Investigator may initiate site closure at any time, provided there is reasonable cause, and enough notice is given in advance of the intended closure.

Reasons for the early closure of a study site by the Sponsor or Investigator may include:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further development (including subsequent stop of production) of any of the investigational compounds (M6223, NKTR-255, SG, avelumab) compounds provided by the Sponsor for this study
- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any third-party service providers of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow up.

Appendix 3 Contraception and Barrier Requirements

Woman of Childbearing Potential (WOCBP):

A woman is of childbearing potential (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.

Postmenopause:

Postmenopause is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or HRT. However, in the absence of 12months of amenorrhea, confirmation with more than 1 FSH measurement is required.
- A female on HRT and whose menopausal status are 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.

Permanent Sterilization:

For this study, permanent sterilization includes:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

For individuals 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.

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- IUD
- IUS
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or due to a medical cause)

  Azoospermia is a highly effective contraceptive method provided the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

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

Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - Oral
  - Injectable
- Sexual abstinence: a highly effective method **only** if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Barrier Methods (to be used in addition to a highly effective method)

- Male or female condom with or without spermicide

Cap, diaphragm, or sponge with spermicide

Notes:

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

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

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

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

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

AE Definition

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline and are judged to be more severe than expected for the participant's condition are considered clinically significant in the medical and scientific judgment of the Investigator (i.e. not related to progression of underlying disease, but may be leading to study intervention discontinuation). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or a SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or a SAE if they fulfill the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Unless judged by the Investigator to be more severe than expected for the participant's condition, any clinically significant abnormal laboratory findings, other abnormal safety assessments that are associated with the underlying disease, the disease/disorder being studied within the expectedness for participant's condition, as judged by the Investigator. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) will not be reported as AEs/SAEs, unless the participant's general condition is more severe than expected for his/her condition and/or unless the outcome is fatal within the AE reporting period, as defined in Section 8.3.

SAE Definition

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

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

a. Results in death

b. Is life-threatening

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

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

c. Results in persistent disability/incapacity

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

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

d. Is a congenital anomaly/birth defect

e. Other situations:

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

Recording and Follow up of AE and/or SAE

AE and SAE Recording

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

Assessment of Intensity

The Investigator is required to grade the severity/intensity of each AE and SAE reported during the study.

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

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

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

The 5 general grades are:

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

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

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

Assessment of Causality

- The Investigator will assess the relationship between study intervention and each AE/SAE occurrence:
- Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention. A reasonable alternative explanation will be available.
- Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator will document in the medical notes that he/she has reviewed the AE/SAE and assessed causality.
- There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. To meet the reporting timeline, the causality assessment is not required for the initial report.
- The Investigator may change his/her causality assessment after considering follow up information and send a SAE follow up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow up of AEs and SAEs

- The Investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the Sponsor/designee to elucidate the nature and/or causality of the AE or SAE, as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to Sponsor/designee within 24 hours of receipt of the information.

SUSAR Definition

A SUSAR is an adverse reaction that meets three criteria: suspected, unexpected, and serious; Suspected: There is a reasonable possibility that the drug caused the adverse drug reaction; Unexpected: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. the RSI, see glossary term contained within the Investigator's Brochure or alternative documents according to applicable regulatory requirements; Serious: See Appendix 4 for SAE definition.

Reporting of SAEs

SAE Reporting by an Electronic Data Collection Tool

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

SAE Reporting by a Paper Form

- SAE reporting on a paper report form may be used in single center studies in addition to the standard electronic CRF and as a back-up method for an EDC system failure. The form includes completion instructions for the Investigator, names, addresses, and telephone and fax numbers. All information from the paper form will be transcribed into the electronic form as soon as the system becomes available.
- Facsimile transmission (fax to mail) of the paper form or any follow up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the form within 24 hours after becoming aware of the event.
- Additional documents (e.g., laboratory reports, autopsy report, hospital discharge letter) and relevant pages from the CRF may be required in addition (e.g. medical history, concomitant medication). The data provided will be consistent with the information in the CRF.

Reporting of AESIs

- For a nonserious AESI, the site will complete the specific AESI report form and notify the Sponsor immediately (within 24 hours), using the same process for reporting SAEs, as specified above.
- For a serious AESI, the site will complete an SAE report form, using the SAE reporting process, specified above.

Reporting of Pregnancies

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

Appendix 5 The Recommendations for irAE Management, in Accordance with the American Society of Clinical Oncology Clinical Practice Guidelines (Schneider 2021)

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1.0. Recommendations for Identification, Evaluation, and Management of Cutaneous Toxicities

Immune-related cutaneous AEs are characterized as inflammatory dermatoses, bullous dermatoses, and severe cutaneous adverse reactions (SCARs), according to the CTCAE.[1] The median time to onset of skin toxicities is 4 weeks but can range broadly from 2 to 150 weeks.[2-4] Rash or inflammatory dermatitis irAEs encompass erythema multiforme, lichenoid, eczematous, psoriasiform, morbilliform, and palmo-plantar erythrodysesthesia, or hand-foot syndrome. Presenting symptoms related to immune therapy-induced rash or inflammatory dermatitis can vary but often include itch with or without rash, new or worsening skin lesions, including macules, papules, or plaques, and loss of skin pigmentation. For bullous dermatoses, presenting symptoms may also include new or worsening skin lesions, including bullae, persistent urticaria, or erosions on the skin or mucosal surfaces. SCAR includes Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis (although note that acute generalized exanthematous pustulosis is not always severe), and drug reaction with eosinophilia and systemic symptoms or drug-induced hypersensitivity syndrome. Presenting symptoms related to immune therapy-induced SCAR may include fever, widespread rash, skin pain, skin sloughing, facial or upper-extremity edema, pustules, blisters, or erosions.

See Table A 1 for a complete set of recommendations, definition of grades, and additional considerations for cutaneous toxicities.

Table A 1 Cutaneous Toxicities

Cutaneous Toxicities	
1.1. Rash or Inflammatory Dermatitis	
Workup and evaluation Pertinent history and physical examination including examination of the oral mucosa, assessment for blister formation, and assessment of BSA involved. Review full list of participant medications to rule out other drug-induced cause for photosensitivity. Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, including prior or other recent cancer therapies, or a skin condition linked to another systemic disease or unrelated primary skin disorder. Recent or new complete blood count and comprehensive metabolic panel (if needed for skin differential diagnosis). Consider referral to dermatologist if autoimmune skin disease is suspected. Consider skin biopsy. Consider clinical monitoring with use of serial clinical photography.	
Grading (grading according to CTCAE criteria is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration).	**Management**

G1: Rash covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness.	▪ Continue ICPi. ▪ Treat with topical emollients and/or mild-moderate potency topical corticosteroids. ▪ Counsel participants to avoid skin irritants.
G2: Rash covering 10% to 30% BSA with or without symptoms (e.g. pruritus, burning, and tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms.	▪ Consider holding ICPi and monitor weekly for improvement. If skin toxicity is not improved after 4 weeks, then regrade toxicity as G 3. ▪ In addition, treat with topical emollients, oral antihistamines, and medium-to-high potency topical corticosteroids. ▪ Consider initiating prednisone (or equivalent) at dosing 0.5 to 1 mg/kg, tapering over 4 weeks. In participants with pruritis without rash, consider topical anti-itch remedies (e.g. refrigerated menthol and pramoxine).
G3: Rash covering > 30% BSA with moderate or severe symptoms; limiting self-care ADL.	▪ Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming. ▪ Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids. May also consider phototherapy to treat severe pruritus. ▪ Initiate oral prednisone or equivalent (1 mg/kg/d) tapering over at least 4 weeks. ▪ Once downgraded to ≤ G1 and prednisone (or equivalent) below 10 mg/d, clinicians may consider resuming ICPi therapy with close monitoring and follow-up with dermatology in certain cases such as psoriasis. ▪ In participants with pruritis without rash, may treat with gabapentin, pregabalin, aprepitant, or dupilumab.
G4: Severe consequences requiring hospitalization or urgent intervention indicated or life-threatening consequences.	▪ Immediate hold ICPi. ▪ May admit participant immediately with direct oncology involvement and with an urgent consult by dermatology. ▪ Systemic steroids: IV methylprednisolone (or equivalent) dosed at 1 to 2 mg/kg with slow tapering when the toxicity resolves. ▪ Monitor closely for progression to SCAR. ▪ Consider alternative antineoplastic therapy over resuming ICPis if the skin irAE does not resolve to ≤ G1. If ICPis are the participant's only option, consider restarting once these side effects have resolved to a G1 level with close dermatology follow-up.

1.2. Bullous Dermatoses

Workup and evaluation
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. Dermatology consultation for consideration of skin biopsy and direct immunofluorescence. Further serologic workup, such as ELISA testing or indirect immunofluorescence, may be pursued. Primer on monitoring for complicated cutaneous adverse drug reactions Review of systems: skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements.

Physical examination includes 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, and facial or distal extremity swelling (may be signs of DIHS/DRESS); see **Section 1.3**. Assess for pustules or blisters or erosions in addition to areas of dusky erythema, which may feel painful to palpation.	
Grading	**Management**
G1: Asymptomatic or blisters covering < 10% BSA and no associated erythema	▪ If blisters are < 10% BSA, are asymptomatic and noninflammatory (such as the case with friction blisters or pressure blisters), cessation of ICPi is not necessary and only observation or local wound care is warranted. ▪ When symptomatic bullae or erosions, which are deroofed vesicles or bullae, are noted on the skin or mucosal surfaces, the cutaneous irAE is considered at least G 2. ▪ See G 2 management recommendations.
G2: Blistering that affects CCI and requires intervention based on diagnosis not meeting criteria for > G 2. Blisters covering 10% to 30% BSA.	▪ Hold ICPi therapy and consult with dermatology for steroid-sparing options, workup, 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 on the skin after the blister has popped or if the roof of the blister easily sloughs off. ▪ Initiate class 1 high-potency topical steroid, e.g. clobetasol, betamethasone, or equivalent, and reassess every 3 days for progression or improvement. ▪ Low threshold to initiate treatment with prednisone (or equivalent) at 0.5 to 1 mg/kg/d dosing and taper over at least 4 weeks. ▪ Monitor participants closely for progression to greater BSA involvement and/or mucous membrane involvement. Consider following participants closely using serial photography.
G3: Skin sloughing covering > 30% BSA with associated pain and limiting self-care ADL.	▪ Hold ICPi therapy and consider admitting participant. ▪ Administer IV methylprednisolone (or equivalent) 1 to 2 mg/kg and when appropriate convert to oral steroids, tapering over at least 4 weeks. ▪ If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic steroids and transition to steroid-sparing options (e.g. IVIG and rituximab), as an alternative approach to treating the irAE. ▪ Consult with dermatology to determine appropriateness of resuming ICPi once symptoms improve.
G4: Blisters covering > 30% BSA with associated fluid or electrolyte abnormalities.	▪ Permanently discontinue ICPi. ▪ Admit participant immediately and place under supervision of a dermatologist. ▪ Administer IV methylprednisolone (or equivalent) 1 to 2 mg/kg and when appropriate convert to oral steroids, with tapering over at least 4 weeks. ▪ If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic steroids and treat with steroid-sparing options, as an alternative approach to treating the irAE (e.g. IVIG and rituximab).

1.3. SCAR

Workup and evaluation

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 DIFF, liver, and kidney function tests; consider UA in the context of DRESS to assess for associated nephritis in addition to the blood work. If the participant is febrile, blood cultures should be considered as well. Skin biopsies to assess for full-thickness epidermal necrosis, as is seen in SJS or TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses or other drug reactions, such as AGEP.

Follow participants closely using serial clinical photography.

If mucous membrane involvement or blistering is noted on the skin, consider early admission to a burn center for further monitoring and management.

Follow primer on monitoring for complicated cutaneous adverse drug reactions from **Section 1.2.**

Grading	**Management**
All grades	In cases of suspected SJS or any mucous membrane involvement (not including isolated stomatitis), discontinue ICPi treatment and consult dermatology. Monitor closely for improvement regardless of grade.
G1 and G2: NA	For the SCAR adverse reactions, there are no G1 or G2 categories. If limited BSA is involved with bullae or erosions, there should remain high concern that this reaction will progress to G3 or G4.
G3: Skin sloughing covering < 10% BSA with mucosal involvement-associated signs (e.g. erythema, purpura, epidermal detachment, and mucous membrane detachment).	▪ Hold ICPi therapy and consult with dermatology. ▪ Admit to burn unit and/or consult wound services with attention to supportive care including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection. ▪ 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 methylprednisolone (or equivalent) 0.5 to 1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks. ▪ Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered. The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immune-directed toxicity. Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS or drug hypersensitivity syndrome. ▪ 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, otolaryngology, urology, or gynecology as appropriate).

G4: Skin erythema and blistering or sloughing covering ≥ 10% BSA with associated signs (e.g. erythema, purpura, epidermal detachment, and mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (e.g. liver function test elevations in the setting of DRESS or DIHS).	▪ Permanently discontinue ICPi. ▪ Admit participant 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, or otolaryngology). ▪ Initiate IV methylprednisolone (or equivalent) 1 to 2 mg/kg, tapering when toxicity resolves to normal. ▪ IVIG or cyclosporine may also be considered in severe or steroid-unresponsive cases. ▪ Consider pain or palliative consultation and/or admission in participants presenting with DRESS manifestations.

Abbreviations: ADL = activity of daily living; AGEP = acute generalized exanthematous pustulosis; BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; DIFF = differential test; DIHS = drug-induced hypersensitivity syndrome; DRESS = drug reaction with eosinophilia and systemic symptom; ELISA = enzyme-linked immunosorbent assay; ICPi = immune checkpoint inhibitor; ICU = Intensive Care Unit; irAE = immune-related adverse event; IV = intravenous; IVIG = intravenous immune globulin = NA = not available; CCI [redacted]; SCAR = severe cutaneous adverse reaction; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; UA = urinalysis.

2.0. Recommendations for Identification, Evaluation, and Management of Gastrointestinal Toxicities

Gastrointestinal toxicities reported with ICPi use include colitis, hepatitis, gastritis, and enterocolitis. The median time to onset of GI toxicities is 6 weeks, with a wide range of 1 to 107.5 weeks.[3,4] Presenting symptoms related to ICPi-induced colitis may include abdominal pain, nausea, diarrhea, blood and mucous in the stool, and fever. Presenting symptoms related to ICPi-induced hepatitis may include jaundice, nausea or vomiting, anorexia, pain on the right side of the abdomen, dark urine (tea-colored), bleeding, or bruising more easily than normal.

Refer to Table A2 for a complete set of recommendations, definition of grades, and additional considerations for GI toxicities.

Table A 2 Gastrointestinal Toxicities

2.0 GI Toxicities	
2.1. Colitis	
Workup and evaluation G2 Workup of blood (CBC, CMP, and TSH) and stool (culture, *C. diff*, parasite, CMV, or other viral etiology, O&P if appropriate) should be performed for the initial presentation, and also considered for immunosuppressant refractory cases. Consider testing for fecal lactoferrin (for participant stratification to determine who needs more urgent endoscopy) and calprotectin (to follow-up on disease activity). Screening labs (HIV, hepatitis A and B, and TB testing), repeated annually in participants who require biologic treatment, e.g. infliximab or vedolizumab for > 1 year until treatment is completed. Consider reviewing concomitant medications that could alter the gut microbiome and their indications for prolonged use (e.g. proton pump inhibitors, antibiotics, and probiotics). Imaging, e.g. CT scan of abdomen and pelvis for colitis-related symptoms (abdominal pain and bleeding) to rule out colitis-related complications, including typhlitis and bowel perforation or abscess. GI endoscopy or colonoscopy with biopsy for participants who have positive stool inflammatory markers or colitis-related symptoms should be considered as there is evidence showing the presence of ulceration in the colon can predict steroid-refractory course,[5] which may require early infliximab. Repeat colonoscopy may be considered for cases G ≥ 2 for disease activity monitoring to document complete remission, especially if there is a plan to resume ICPi. Mucosal healing on repeat endoscopy and/or fecal calprotectin level ≤ 116 µg/g can be considered the treatment target to guide decisions on when to stop biologic treatment and when to resume ICPi therapy.[5,6,7] G3 to 4 Complete all recommendations as above and consider inpatient care.	
Grading (based on CTCAE for diarrhea, as most often used clinically)	**Management**
All participants	▪ Counsel all participants 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, or constipation. ▪ For G ≥ 2, consider permanently discontinuing CTLA-4 agents and may restart PD-1 or PD-L1 agents if participants recover to G ≤ 1; concurrent immunosuppressant maintenance therapy should be considered only if clinically indicated in individual cases.
G1: Increase of < 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 G 1 or resolves. ▪ May also include supportive care with medications such as loperamide if infection has been ruled out in participants with diarrhea only and not colitis-related symptoms as a temporary measure. ▪ Monitor for dehydration and recommend dietary changes. ▪ Participant should be closely monitored by phone or electronic medical system for symptoms changes by clinical providers every 3 days or more frequently if needed until stabilized. ▪ May obtain gastroenterology consult for prolonged G1 cases and consider endoscopy with biopsies.

G2: Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared with baseline	▪ Hold ICPi at least until recovery to G1 – see last bullets. ▪ May also include supportive care with medications such as loperamide if infection has been ruled out in participants with diarrhea only and not colitis-related symptoms as a temporary measure. ▪ Consider consult with gastroenterology for G ≥ 2. ▪ Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent until symptoms improve to G1, and then start taper over 4 to 6 weeks. ▪ Consider adding narrower-spectrum or more potent agents, including anti-TNF (infliximab) or anti-integrin (vedolizumab) antibody to participants whose colitis is corticosteroid-refractory (ie, no decrease by 1 grade in 72 hours) or dependent or with high-risk endoscopic features on initial endoscopy examination. ▪ When symptoms improve to G ≤ 1, taper corticosteroids over 4 to 6 weeks; may consider shorter tapers in participants also treated with biologics. ▪ Endoscopic evaluation with EGD or colonoscopy is highly recommended for cases G ≥ 2 to stratify participants for early treatment of biologics based on the endoscopic findings. ▪ Resuming ICPi after symptoms improve to G ≤ 1 may be considered when steroid taper is completed, risk and benefits reviewed if maintained on biologics, and/or if endoscopic and histologic remissions are achieved. Fecal calprotectin ≤ 116 µg/g may be considered as a surrogate for endoscopic and histologic remission. [7] ▪ Resuming PD-1/PD-L1 agent is associated with lower risk of flare-up; however, CTLA-4 inhibitor can still be considered in selected cases, such as in participants who have not yet responded or whose response is deemed inadequate.
G3: Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared with baseline; and limiting self-care ADL	▪ Follow G2 recommendations as listed, with the following additions for G3: ▪ Administer corticosteroids (initial dose of 1 to 2 mg/kg/d prednisone or equivalent) until symptoms improve to G1, and then start taper over 4 to 6 weeks. Consider IV methylprednisolone, especially if concern for concurrent upper GI inflammation. ▪ Consider early introduction of infliximab or vedolizumab in addition to steroids in participants with high-risk endoscopic features[a] on initial endoscopy examination or inadequate response to steroids (persistent symptoms after 3 days). ▪ Consider hospitalization for participants with dehydration or electrolyte imbalance. ▪ Consider repeat colonoscopy in participants who are immunosuppression-refractory. Should consider permanently discontinuing CTLA-4 agents.

G4: Life-threatening consequences; urgent intervention indicated	▪ Follow G2 to G3 recommendations as listed, with the following additions for G4: ▪ Permanently discontinue treatment. ▪ Should provide inpatient care. ▪ 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 biologics (infliximab or vedolizumab) if inadequate response to steroids after 3 days. ▪ Consider lower GI endoscopy if symptoms are refractory, despite treatment or there is concern of new infections.
Additional considerations May consider fecal microbiota transplant,[8,9] JAK inhibitor tofacitinib,[10] or IL-12-blocking antibody ustekinumab[11] in participants who are refractory to the previous immunosuppressants. Participants with both irAE-related hepatitis and irAE-related colitis are less common, and management may include permanently discontinuing ICPi and offering other immunosuppressant agents (e.g. prednisone and mycophenolate) that work systemically for both conditions. Infliximab is contraindicated for hepatic irAE. Currently, enteritis and/or gastritis alone as the cause of GI toxicity is uncommon and endoscopy with biopsy is recommended as the evaluation tool. It may be managed similarly to colitis including steroid and/or biologics etc.	
2.2. Hepatitis	
Workup and evaluation: Monitor participant for abnormal liver blood tests: AST, ALT, and bilirubin before each infusion and/or consider weekly if G 1 LFT elevations. No treatment is recommended for G 1 LFT abnormality. Review medications and supplements that may cause hepatotoxicity and rule out abnormal liver enzymes from development or progression of liver metastases. Liver biopsy should be considered if the participant is steroid-refractory or if concern for other differential diagnoses that would alter medical management. For G ≥ 2 Workup for other causes of elevated liver enzymes (e.g. viral hepatitis, alcohol history, iron studies, thromboembolic event, or potential liver metastasis from primary malignancy) by doing blood work and imaging (ultrasound and cross-sectional imaging). If suspicion for primary autoimmune hepatitis is high, can consider ANA/ASMA/ANCA. If participants with elevated ALKP alone, GGT should be tested. For isolated elevation of transaminases, consider checking CK for other etiologies.	
Grading	**Management**
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. ▪ Consider monitoring labs 1 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. ▪ Participants should be advised to stop unnecessary medications and any known hepatotoxic drugs. Temporarily hold other potentially hepatotoxic oncologic agents. ▪ For G2 hepatic toxicity, may administer steroid (0.5 to 1 mg/kg/d prednisone) or equivalent if no improvement is seen after 3 to 5 days. ▪ Increase frequency of monitoring to every 3 days. ▪ If inadequate improvement after 3 days, consider adding mycophenolate mofetil. ▪ May initiate steroid taper when symptoms improve to G ≤ 1 and may resume ICPi treatment when steroid ≤ 10 mg/d. Taper over at least 1 month. ▪ Consider hepatology consult for G2 and above. ▪ May resume if recover to G ≤ 1 on prednisone ≤ 10 mg/d.
G3: AST or ALT 5 to 20 x ULN and/or total bilirubin 3 to 10 x ULN, OR symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; and reactivation of chronic hepatitis	▪ Follow G2 recommendations as listed, with the following additions for G3: ▪ Consider permanently discontinuing ICPi if asymptomatic; permanently discontinue if symptomatic. ▪ Immediately start steroid 1 to 2 mg/kg methylprednisolone or equivalents. ▪ If steroid refractory, consider liver biopsy to rule out NASH, tumor, cholestatic variants, other drug-related hepatic inflammation, infection, or other autoimmune entity and consider adding azathioprine[b] or mycophenolate[c] if infectious cause is ruled out. ▪ Labs daily or every other day; consider inpatient monitoring for participants with AST/ALT > 8 x ULN and/or elevated total bilirubin 3 x > ULN. ▪ If no improvement is achieved with steroid or for participants on ICPi therapy combined with a novel agent, with standard CTX, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis. ▪ Steroid taper can be attempted around 4 to 6 weeks when G ≤ 1, re-escalate if needed, optimal duration unclear. ▪ Consider transfer to tertiary care facility if necessary.
G4: AST or ALT > 20 x ULN and/or total bilirubin > 10 x ULN OR decompensated liver function (e.g. ascites, coagulopathy, encephalopathy, and coma)	▪ Follow G3 recommendations as listed, with the following additions for G4: ▪ Administer 2 mg/kg/d methylprednisolone equivalents.
Additional considerations Infliximab is contraindicated for immune-related hepatitis.	

Abbreviations: ADL = activities of daily living; ALKP = alkaline phosphatase; ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; ASMA = anti-smooth muscle antibodies; CK = creatine kinase; CMP = comprehensive metabolic panel; CMV, cytomegalovirus; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; CTLA = cytotoxic T-lymphocyte-associated antigen; CTX = chemotherapy; EGD = esophagogastroduodenoscopy; GGT = gamma-glutamyl transferase; ICPi = immune checkpoint inhibitor; IL = interleukin; irAE = immune-related adverse event; IV = intravenous; JAK = Janus kinase; LFT = liver function tests; NASH = nonalcoholic steatohepatitis; PD-1 = programmed cell death-1; PD-L1 = programmed cell death-ligand1; TB = tuberculosis; TNF = tumor necrosis factor; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

a High-risk endoscopic features include large deep ulceration, multiple ulcers, and extensive colitis beyond left colon.[5,6]

b Anecdotal experience suggests azathioprine may be beneficial in steroid-refractory immune-related hepatitis. If using azathioprine, should test for thiopurine methyltransferase deficiency.

c A case study reports use of mycophenolate mofetil in steroid-refractory immune-related hepatitis with some success.[12]

3.0. Recommendations for Identification, Evaluation, and Management of Lung Toxicities

Pneumonitis is defined as focal or diffuse inflammation of the lung parenchyma, typically identified on computed tomography imaging. There are no symptomatic, pathologic, or radiographic features that are pathognomonic for pneumonitis, although presenting symptoms related to immune therapy-induced pneumonitis may include new or worsening cough, shortness of breath, increased oxygen requirement, chest pain, and/or fever. The median time to onset of pneumonitis is 34 weeks but can range from 1.5 to 127 weeks.[3,13]

Refer to Table A3 for a complete set of recommendations, the definition of grades, and additional considerations for lung toxicities.

Table A 3 Lung Toxicities

Lung Toxicities	
3.1. Pneumonitis	
Workup and evaluation Should include the following: Pulse oximetry and CT chest[14] preferably with contrast if concerned for other etiologies such as pulmonary embolus. For G2 or higher, may include the following infectious workup: nasal swab, sputum culture, and sensitivity, blood culture and sensitivity, urine culture, and sensitivity. COVID-19 evaluation – per institutional guidelines where relevant.	
Grading	**Management**
G1: Asymptomatic; confined to one lobe of the lung or < 25% of lung parenchyma; clinical or diagnostic observations only	▪ Hold ICPi or proceed with close monitoring. ▪ Monitor participants weekly with history and physical examination, pulse oximetry; may also offer chest imaging (CXR, CT) if uncertain diagnosis and/or to follow progress. ▪ Repeat chest imaging in 3 to 4 weeks or sooner if participant becomes symptomatic. ▪ In participants who have had baseline testing, may offer a repeat spirometry or DLCO in 3 to 4 weeks. ▪ May resume ICPi with radiographic evidence of improvement or resolution if held. If no improvement, should treat as G2.
G2: Symptomatic; Involves more than one lobe of the lung or 25% to 50% of lung parenchyma; medical intervention indicated; limiting instrumental ADL	▪ Hold ICPi until clinical improvement to G ≤ 1. ▪ Prednisone 1 to 2 mg/kg/d and taper over 4 to 6 weeks. ▪ Consider bronchoscopy with BAL ± transbronchial biopsy. ▪ Consider empiric antibiotics if infection remains in the differential diagnosis after workup. ▪ Monitor at least once per week with history and physical examination, pulse oximetry, consider radiologic imaging; if no clinical improvement after 48 to 72 hours of prednisone, treat as G3. ▪ Pulmonary and infectious disease consults if necessary.
G3: Severe symptoms; Hospitalization required: Involves all lung lobes or > 50% of lung parenchyma; limiting self-care ADL; oxygen indicated	▪ Permanently discontinue ICPi. ▪ Empiric antibiotics may be considered. ▪ Methylprednisolone IV 1 to 2 mg/kg/d.

G4: Life-threatening respiratory compromise; urgent intervention indicated (intubation)	▪ If no improvement after 48 hours, may add immunosuppressive agent. Options include infliximab or mycophenolate mofetil IV or IVIG or cyclophosphamide. Taper corticosteroids over 4 to 6 weeks.[a] ▪ Pulmonary and infectious disease consults if necessary. ▪ May consider bronchoscopy with BAL ± transbronchial biopsy if participant can tolerate.

Abbreviations: ADL = activity of daily living; BAL = bronchoalveolar lavage; CT = computed tomography; CXR = chest X-ray; DLCO = diffusing capacity of lung for carbon monoxide; ICPi = immune checkpoint inhibitor; IV = intravenous; IVIG = intravenous immune globulin.

[a] Subset of participants may develop chronic pneumonitis and may require longer taper. Chronic pneumonitis is a described phenomenon where the incidence is not known, but < 2%. [15]

4.0. Recommendations for Identification, Evaluation, and Management of Endocrine Toxicities

Immune-related endocrine AEs are characterized by the gland or organ affected and include primary hypothyroidism, thyrotoxicosis, primary adrenal insufficiency, hypophysitis, and diabetes.

The median time to onset of endocrine toxicities is 14.5 weeks with a range of 1.5 to 130 weeks.[3] Presenting symptoms related to immune therapy-induced endocrinopathies vary and may include headache and visual changes, especially visual field changes in pituitary swelling. Presenting symptoms of hypothyroidism can include cold intolerance, dry skin, constipation, weight gain, and/or fatigue. Palpitations, heat intolerance, insomnia, frequent bowel movements, or weight loss may be present with thyrotoxicosis and nausea, vomiting, abdominal pain, weight loss, lightheadedness or orthostasis or syncope, and profound fatigue may be symptoms of adrenal insufficiency. Diabetes or diabetic ketoacidosis (DKA) may present with polyuria or polydipsia, nausea or vomiting, abdominal pain, and/or visual blurring.

Refer to Table A 4 for a complete set of recommendations, definition of grades, and additional considerations for endocrine toxicities.

Table A 4 Endocrine Toxicities

Endocrine Toxicities	
4.1. Thyroid **4.1.1. Primary hypothyroidism**	
Workup and evaluation TSH, with the option of also including FT4, can be checked every 4-6 weeks as part of routine clinical monitoring for asymptomatic participants on ICPi therapy. TSH and FT4 should be used for case detection in symptomatic participants. Low TSH with a low FT4 is consistent with central hypothyroidism. Evaluate as per hypophysitis (see 4.3). Commonly develops after thyrotoxicosis phase of thyroiditis (4.1.2).	
Grading	**Management**
G1: TSH > 4.5 and < 10 mIU/L and asymptomatic	Should continue ICPi with monitoring of TSH (option for FT4) every 4 to 6 weeks as part of routine care.
G2: Moderate symptoms, able to perform ADL. TSH persistently > 10 mIU/L	▪ May continue or hold ICPi until symptoms resolve to baseline. ▪ Consider endocrine consultation for unusual clinical presentations, concern for central hypothyroidism, or difficulty titrating hormone therapy. ▪ Prescribe thyroid hormone supplementation in symptomatic participants with any degree of TSH elevation or in asymptomatic participants with TSH levels that persist over 10 mIU/L (measured 4 weeks apart).[16,17] ▪ Monitor TSH every 6 to 8 weeks while titrating hormone replacement to goal of TSH within the reference range. ▪ FT4 can be used to help interpret ongoing abnormal TSH levels on therapy, as TSH may take longer to normalize. ▪ Once adequately treated, repeat testing every 6 to 12 months or as indicated for a change in symptoms.
G3 to 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 to assist with rapid hormone replacement. ▪ Hospital admission for developing myxedema (bradycardia, hypothermia, and altered mental status). ▪ Inpatient endocrinology consultation can assist with IV levothyroxine dosing, steroids, and supportive care. ▪ If there is uncertainty about whether primary or central hypothyroidism is present, hydrocortisone should be given before thyroid hormone is initiated. ▪ Myxedema coma is a life-threatening emergency requiring admission and a high level of care. ▪ Thyroid supplementation and reassessment as in G2.
Additional considerations For participants without risk factors (ie, < 70 years old, not frail, and without cardiac disease or multiple comorbidities), full replacement can be estimated using ideal body weight for a dose of approximately 1.6 mcg/kg/d. For those older than age 70 years and/or frail participants with multiple comorbidities (including cardiac disease), consider titrating up from a lower starting dose of 25 to 50 µg.	

Elevated TSH can be seen in the recovery phase of thyroiditis. In asymptomatic participants with FT4 that remains in the reference range, it is an option to monitor before treating to determine whether there is recovery to normal within 3 to 4 weeks. Progression or development of symptoms should be treated as per G2.

Development of a low TSH on therapy suggests overtreatment or recovery of thyroid function and dose should be reduced or discontinued with close follow-up.

4.1.2. Thyrotoxicosis

Workup and evaluation

TSH can be checked every 4 to 6 weeks as part of routine clinical monitoring for asymptomatic participants on ICPi therapy.

TSH and FT4 should be used for case detection in symptomatic participants. T3 can be helpful in highly symptomatic participants with minimal FT4 elevations.

Low TSH with a low FT4 is consistent with central hypothyroidism. Evaluate as per hypophysitis (see 4.3).

Consider TSH receptor antibody testing if there are clinical features and suspicion of Graves' disease (e.g. ophthalmopathy and T3 toxicosis).

Grading	Management
G1: Asymptomatic or mild symptoms	▪ Can continue ICPi. ▪ Beta-blocker (e.g. atenolol or propranolol) for symptomatic relief. ▪ Close monitoring of thyroid function every 2 to 3 weeks after diagnosis to catch the transition to hypothyroidism, the most common outcome for transient subacute thyroiditis. ▪ Treat transition to elevated TSH and low FT4 as for primary hypothyroidism (see 4.1.1). ▪ For persistent thyrotoxicosis (> 6 weeks) consider endocrine consultation for additional workup.
G2: Moderate symptoms, able to perform ADL	▪ Consider holding ICPi until symptoms return to baseline. ▪ Consider endocrine consultation. ▪ Beta-blocker (e.g. atenolol or propranolol) for symptomatic relief. ▪ Hydration and supportive care. ▪ For persistent thyrotoxicosis (> 6 weeks) refer to endocrinology for additional workup and possible medical thyroid suppression.
G3 to 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 for all participants. ▪ Beta-blocker (e.g. atenolol or propranolol). ▪ Hydration and supportive care. ▪ Consider hospitalizing participants in severe cases as inpatient endocrine consultation can guide the use of additional medical therapies including steroids, SSKI, or thionamide (methimazole or propylthiouracil) and possible surgery.

4.1. Thyroid

Additional considerations

Thyroiditis is self-limited and the initial hyperthyroidism generally resolves in weeks with supportive care, most often to primary hypothyroidism or occasionally to normal.

Persistent or symptomatic hypothyroidism developing after hyperthyroidism should be treated as above (4.1).

Graves' disease has not been reported with ICPi specifically, but sporadic cases could occur. Graves' disease is generally persistent and is treated with antithyroid medical therapy, radioactive iodine, or surgery. Endocrine consultation is recommended if suspected.

Physical examination findings of ophthalmopathy or thyroid bruit are diagnostic of Graves' disease and should prompt early endocrine referral.

4.2. Adrenal—Primary AI

Workup and evaluation

Evaluate AM levels of ACTH (if > 2x ULN) and cortisol level (if < 3 mg/dL).

Basic metabolic panel (Na, K, CO_2, and glucose).

Renin and aldosterone.

Consider standard-dose ACTH stimulation test for indeterminate results (AM cortisol > 3 mg/dL and < 15 mg/dL).

Evaluate for precipitating cause of crisis such as infection.

Adrenal CT for metastasis or hemorrhage (most common causes of primary AI).

Grading	Management
All grades	Referral to endocrinology. Education on steroid stress dosing, emergency injections, and a medical alert bracelet or necklace, accessory, or system.
G1: Asymptomatic or mild symptoms	▪ Consider holding ICPi until participant is stabilized on replacement hormone. ▪ Endocrine consultation. ▪ Initiate replacement therapy with hydrocortisone (15 to 20 mg in divided doses – see additional considerations). ▪ Titrate hydrocortisone to maximum of 30 mg daily total dose for residual symptoms of AI. ▪ Reduce maintenance dosing for symptoms of iatrogenic Cushing's syndrome (e.g. bruising, thin skin, edema, weight gain, hypertension, and hyperglycemia). ▪ Most primary AI will also require fludrocortisone (starting dose 0.05 to 0.1 mg/d). Adjust based on volume status, sodium level, and renin response (target upper half of the reference range).
G2: Moderate symptoms, able to perform ADL	▪ Consider holding ICPi until participant is stabilized on replacement hormone. ▪ Endocrine consultation. ▪ See in clinic to assess need for hydration, supportive care, and hospitalization. ▪ Initiate outpatient corticosteroid treatment at 2 to 3 times maintenance (e.g. hydrocortisone 30 to 50 mg total dose or prednisone 20 mg daily) to manage acute symptoms. ▪ Initiate fludrocortisone (0.05 to 0.1 mg/d). ▪ Decrease stress dose corticosteroids down to maintenance doses after 2 days. ▪ Maintenance therapy as in G1.

G3 to 4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	▪ Hold ICPi until participant is stabilized on replacement hormone. ▪ Endocrine consultation. ▪ Inpatient management may be needed to provide: Normal saline (at least 2L). IV Stress dose steroids: Hydrocortisone 50 to 100 mg Q 6 to 8 hours initial dosing. ▪ Taper stress dose corticosteroids down to oral maintenance doses over 5 to 7 days. ▪ 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 hypophysitis in Section 4.3 for secondary (central) adrenal insufficiency.

Using hydrocortisone allows for recreation of the diurnal rhythm of cortisol. Typically, 2/3 of the dose is given in the morning and 1/3 in the early afternoon. Long-acting steroids such as prednisone, rather than short-acting hydrocortisone, carry risk of over replacement but can be used in special circumstances, for example, if a participant is not able to adhere to a short-acting steroid regimen. Hydrocortisone 20 mg is equivalent to prednisone 5 mg.

DHEA replacement is controversial, but deficiency can be tested and replacement considered in women with low libido and/or energy who are judged to be otherwise well replaced.

All participants need education on stress dosing for sick days, use of emergency injectables, when to seek medical attention for impending adrenal crisis, and a medical alert bracelet or necklace for adrenal insufficiency to trigger stress dose corticosteroids by emergency medical personnel. Therefore, early endocrinology consultation is appropriate.

Endocrine consultation should be part of planning before surgery or high-stress treatments such as cytotoxic CTX at any time during a participant's care.

4.3. Pituitary – Hypophysitis

Workup and evaluation:

Evaluate ACTH (AM), cortisol (AM), TSH, free T4, and electrolytes.

Consider standard-dose ACTH stimulation testing for indeterminate results (AM cortisol > 3 mg/dL and < 15 mg/dL).

Consider evaluating LH and testosterone in males, FSH, and estrogen in premenopausal females with fatigue, loss of libido and mood changes, or oligomenorrhea.

Consider MRI brain w/wo contrast with pituitary or sellar cuts in all participants with new hormonal deficiencies and particularly those with multiple endocrine abnormalities ± new severe headaches or complaints of vision changes.

Perform MRI brain w/wo contrast with pituitary or sellar cuts for all participants presenting with diabetes insipidus (DI is most commonly from metastatic disease).

Grading	Management
All grades	Referral to endocrinology Education on steroid stress dosing, emergency injections, and a medical alert bracelet or necklace, accessory, or system.

G1: Asymptomatic or mild symptoms	▪ Consider holding ICPi until participant is stabilized on replacement hormones. ▪ Endocrine consultation. ▪ Corticosteroid replacement for adrenal insufficiency with preference for hydrocortisone (15-20 mg in divided doses – see additional considerations Section 4.2). ▪ Initiate other hormone replacement only after any needed adrenal replacement to avoid precipitating adrenal crisis. ▪ Thyroid hormone replacement if needed using dosing as above for primary hypothyroidism, with a goal FT4 in the upper half of the reference range (TSH is not accurate in central hypothyroidism). ▪ Testosterone or estrogen therapy if needed in those without contraindications (e.g. prostate cancer, breast cancer, or history of DVT). ▪ Recommend education on stress dosing, emergency injectable, and a medical alert or necklace accessory or system.
G2: Moderate symptoms, able to perform ADL	▪ Consider holding ICPi until participant is stabilized on replacement hormones. ▪ Endocrine consultation. ▪ Clinic evaluation to assess need for steroids and volume repletion. ▪ Consider oral pulse dose therapy in participants with MRI findings of swelling or threatened optic chiasm compression (prednisone 1 mg/kg/d [or equivalent]). Taper over 1 to 2 weeks and transition to physiologic maintenance therapy once down to 5 mg prednisone equivalent. ▪ Hormonal supplementation as in G1.
G3* to 4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	▪ Hold ICPi until participant is stabilized on replacement hormones. ▪ Endocrine consultation. ▪ Hospitalize or make an ED referral for: Normal saline (at least 2L) or monitored free water replacement if DI. IV Stress dose steroids: Hydrocortisone 50 to 100 mg Q6 to 8 hours initial dosing. Oral pulse dose therapy with Prednisone 1 to 2 mg/kg daily (or equivalent) tapered over at least 1 to 2 weeks to physiologic maintenance in participants with significant swelling on MRI, optic chiasm compression, severe headache, or visual changes. ▪ Taper stress dose corticosteroids down to oral maintenance doses over 5 to 7 days. ▪ Maintenance therapy as in G1.
Additional considerations: Please be aware of the need to start corticosteroids first when planning hormone replacement therapy for multiple deficiencies as other hormones accelerate the clearance of cortisol and can precipitate adrenal crisis. ACTH stimulation can give a false-negative result early in hypophysitis as adrenal reserve declines slowly after pituitary stimulation is lost. In the presence of clinical uncertainty, opt for replacement and test for ongoing need at 3 months. If prednisone or equivalent is started for mild or moderate symptoms, consider lower doses (average daily dose over 2 months of < 7.5 mg) because of report of reduced survival on higher doses.[18]	

All participants need education on stress dosing for sick days, use of emergency steroid injectables, when to seek medical attention for impending adrenal crisis, and a medical alert bracelet for adrenal insufficiency to trigger stress dose corticosteroids by EMS.

Steroid use for other irAEs can cause isolated central adrenal insufficiency with a low ACTH. In a participant with adrenal insufficiency, a recent history of treatment with corticosteroids, and no other central hormone deficiencies, the HPA axis should be tested for recovery after 3 months of maintenance therapy with hydrocortisone.

Laboratory confirmation of AI should not be attempted in participants given high-dose corticosteroids for other irAEs until treatment is ready to be discontinued.

AM cortisol in a participant on corticosteroids is not diagnostic as the measurement of therapeutic steroids in the assay for cortisol varies. Hydrocortisone needs to be held for 24 hours and other steroids for longer before endogenous function is assessed. Consider consulting endocrinology for recovery and weaning protocols using hydrocortisone in participants with symptoms of AI after weaning off corticosteroids.

*Per the Avelumab IB, permanently discontinue avelumab therapy for recurrent Grade ≥ 3 hypophysitis.

4.4. Diabetes

Workup and evaluation

Monitor participants for symptoms of new or worsening DM (polyuria, polydipsia, and fatigue).

Monitor glucose at baseline and with each treatment cycle while on therapy and at follow-up visits for at least 6 months.

Laboratory evaluation in suspected CIADM should include:

Urine and/or serum ketones.

Anion gap on a metabolic panel.

Anti-GAD or anti-islet cell antibodies.

C-peptide levels.

Grading	Management
G1: Asymptomatic or mild symptoms; T2DM with fasting glucose value > ULN to 160 mg/dL (> ULN to 8.9 mmol/L). No evidence of CIADM such as ketoacidosis or laboratory evidence of pancreatic autoimmunity.	▪ Can continue ICPi with close clinical follow-up and laboratory evaluation. ▪ Refer to PCP for additional management or: May initiate oral therapy for those with new-onset T2DM. Intensify medical therapy for those with worsening T2DM.
G2: Moderate symptoms, able to perform ADL; T2DM with fasting glucose value > 160 to 250 mg/dL (> 8.9 to 13.9 mmol/L). No ketoacidosis or metabolic derangements but other evidence of CIADM at any glucose level.	▪ May hold ICPi until glucose control is obtained. ▪ Urgent endocrine consultation for any participant with new-onset CIADM. ▪ Initiate insulin for CIADM (or as default therapy if there is any question about the diagnosis). ▪ Referral to ED or hospital admission if unable to initiate therapy, urgent outpatient specialist evaluation is not available, developing ketoacidosis, or other concern for CIADM.
G3 to 4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL; G3: > 250 to 500 mg/dL (> 13.9 to 27.8 mmol/L); G4: > 500 mg/dL (> 27.8 mmol/L). Ketoacidosis or other metabolic abnormality.	▪ Hold ICPi until glucose control is obtained with reduction of toxicity to G ≤ 1. ▪ Admit for inpatient management of DKA, volume and electrolyte resuscitation, and insulin initiation. ▪ Endocrine consultation for all participants. ▪ Insulin therapy appropriate for all participants.
Additional considerations	

Insulin therapy should be used in any case with significant hyperglycemia pending additional diagnostic workup if mechanism of DM is not known.

Long-acting insulin therapy alone is not sufficient for CIADM because of the absence of pancreatic function after beta-cell destruction.

- Starting total daily requirement can be estimated at 0.3 to 0.4 units/kg/d.
- Half of daily requirements are typically given in divided doses as prandial coverage, while half should be administered as a once-daily long-acting homolog. This requires self-monitoring 4 or more times daily or the use of a continuous glucose monitor.
- Sliding scale insulin can be used in conjunction with multiple daily injection regimens to accommodate the variability in glucose levels.
- Decreased requirements after the initial acute admission for DKA are commonly seen in the so-called honeymoon period.
- Education is critical to learn skills like responding to hypoglycemia, anticipating exercise, monitoring for DKA, or carbohydrate counting, and to transition to technologies such as insulin pumps. Early endocrinology consultation is a high priority for all participants.

T2DM participants will need to increase the frequency of self-monitoring as therapy intensifies and agents that can cause hypoglycemia are added to their regimen.

Steroids can exacerbate postprandial hyperglycemia, and endocrinology consult should be considered for initiating or managing insulin in participants with T2DM being started on high-dose steroids. If insulin is used, the doses generally need to be adjusted again as steroids are tapered down.

Abbreviations: ACTH = adrenocorticotropic hormone; ADL = activities of daily living; AI = adrenal insufficiency; AM = morning; CIADM = checkpoint inhibitor-associated diabetes mellitus; CT = computed tomography; CTX = chemotherapy; DHEA = dehydroepiandrosterone; DI = diabetes insipidus; DKA = diabetic ketoacidosis; DM = diabetes mellitus; DVT = deep vein thrombosis; ED = emergency department; EMS = emergency medical services; FSH = follicle-stimulating hormone; FT4 = free thyroxine; GAD = glutamic acid decarboxylase; GD = Graves' disease; HPA = hypothalamic pituitary adrenal; ICPi = immune checkpoint inhibitor; IV = intravenous; LH = luteinizing hormone; MRI = magnetic resonance imaging; PCP = primary care practitioner; SSKI = potassium iodide; T2DM = type 2 diabetes mellitus; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

5.0. Recommendations for Identification, Evaluation, and Management of Musculoskeletal Toxicities

Immune-related musculoskeletal AEs are characterized as inflammatory arthritis (IA), myositis, and polymyalgia-like syndrome. The median time to onset is 38 weeks but can vary greatly from 1 to 127 weeks.[3] Presenting symptoms related to immune therapy-induced IA may include joint pain accompanied by joint swelling and/or inflammatory symptoms such as stiffness after inactivity or in the morning, lasting more than 30 minutes to 1 hour. It is important to note that improvement of symptoms with NSAIDs or corticosteroids, but not with opioids or other pain medications, may also be suggestive of IA. Presenting symptoms of immune therapy-induced myositis may include muscle pain and weakness. Patients with myositis can also develop myasthenia gravis–like syndrome and/or myocarditis (see cardiovascular and neurologic sections for further details), which can be life-threatening if respiratory muscles or myocardium are involved. Symptoms of polymyalgia-like syndrome related to ICPi therapy include pain and stiffness in proximal upper and lower extremities.

Refer to Table A 5 for a complete set of recommendations, definition of grades, and additional considerations for musculoskeletal toxicities.

Table A 5 Musculoskeletal Toxicities

Musculoskeletal Toxicities	
5.1. Inflammatory arthritis (IA)	
Workup and evaluation 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 or imaging to exclude metastases and evaluate joint damage (erosions) if appropriate. Consider autoimmune blood panel including ANA, RF, anti-CCP, and 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 ultrasound ± MRI imaging of affected joints if clinically indicated (e.g. persistent arthritis unresponsive to treatment, and suspicion for differential diagnoses such as metastatic lesions or septic arthritis). Consider arthrocentesis if septic arthritis or crystal-induced arthritis is suspected. Consider early referral to a rheumatologist, if there is joint swelling (synovitis) or if symptoms persist > 4 weeks. G3 to 4: As for G2. Seek rheumatologist advice and review. Test for viral hepatitis B, C, and latent or active TB test before DMARD treatment. Repeated screening labs annually in participants who require biologic treatment for > 1 year until treatment is completed. Monitoring Participants with IA should be monitored with serial rheumatologic examinations, including inflammatory markers, every 4 to 6 weeks after treatment is instituted.	
Grading	**Management**
All grades	Clinicians should follow reports of new joint pain to determine if IA is present. Question whether symptoms 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	▪ Consider holding ICPi. ▪ Escalate analgesia and consider higher doses of NSAIDS as needed. ▪ If inadequately controlled, initiate prednisone 10 to 20 mg/d or equivalent. ▪ If improvement, slow taper according to response during the next 4 to 6 weeks. If no improvement after initial 4 weeks treat as G3. ▪ If unable to lower corticosteroid dose to below 10 mg/d after 6 to 8 weeks, consider DMARD. ▪ Consider intra-articular steroid injections for large joints. ▪ Referral to rheumatology.

G3 to 4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; and limiting self-care ADL	▪ Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to G ≤ 1. ▪ Initiate oral prednisone 0.5 to 1 mg/kg. ▪ If failure of improvement after 2 weeks or worsening in meantime, consider synthetic or biologic DMARD. Synthetic: methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine alone or in combination. Biologic: Consider anticytokine therapy such as TNFα or IL-6 antagonists. Note: As a caution, IL6 inhibition can cause intestinal perforation.[19] Although this is extremely rare, it should not be used in participants with concomitant immune-related colitis. ▪ Referral to rheumatology.
Additional considerations Early recognition is critical to avoid erosive joint damage. Corticosteroids can be used as part of initial therapy in IA, but because of likely prolonged treatment requirements, physicians should consider starting steroid-sparing agents earlier than one would with other irAEs. Oligoarthritis can be treated early on with intra-articular steroids, consider early referral.	

5.2. Myositis

Workup and evaluation

Complete rheumatologic and neurologic history regarding differential diagnosis and rheumatologic and neurologic examination including muscle strength, and examination of the skin for findings suggestive of dermatomyositis. Muscle weakness is more typical of myositis than pain. Consider pre-existing conditions that can cause similar symptoms.

Blood testing to evaluate muscle inflammation, CK, and aldolase. Transaminases (AST and ALT) and LDH can also be elevated.

Troponin to evaluate myocardial involvement. Other cardiac testing such as ECG and echocardiogram or cardiac MRI (see CV section for further details).

Autoantibody testing to evaluate possible concomitant myasthenia gravis (anti-AChR and antistriational antibodies)

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 (e.g. anti-TIF1g, anti-NXP2, and other myositis autoantibodies as indicated), especially if participant had muscle-related manifestations before receiving ICPi.

Urinalysis for rhabdomyolysis.

Monitoring

CK, ESR, CRP, and aldolase if CK has not been elevated.

G1: Complete examination and laboratory workup as above.

G2: Complete history and examination as above; autoimmune myositis blood panel; EMG, MRI imaging of affected joints. Early referral to a rheumatologist or neurologist.

G3 to 4: As for G2. Urgent referral to a rheumatologist or neurologist.

Grading	**Management**[a]
G1: Mild weakness with or without pain	▪ Continue ICPi. ▪ If CK and/or aldolase are elevated and participant has muscle weakness may offer oral corticosteroids, starting prednisone at 0.5 mg/kg/ day. Offer analgesia with acetaminophen or NSAIDs for myalgia if there are no contraindications. ▪ Consider holding statins.

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 (x 3 ULN or more), initiate prednisone or equivalent at 0.5 to 1 mg/kg/d. ▪ May require permanent discontinuation of ICPi in cases with G2 symptoms if participant had other objective findings of severe muscle involvement such as very elevated enzymes, or extensive involvement as determined by EMG, MRI or histology. ICPi should not be restarted until CK is normal and clinical manifestations of myositis are resolved.
G3 to 4: Severe weakness with or without pain; limiting self-care ADL	▪ Hold ICPi. ▪ Consider hospitalization for participants with severe weakness severely limiting mobility, respiratory, dysphagia, or rhabdomyolysis. ▪ Urgent referral to rheumatologist and/or neurologist. ▪ Initiate prednisone 1 mg/kg/d or equivalent. ▪ For participants with severe compromise, start 1 to 2 mg/kg of methylprednisolone IV or higher dose bolus. ▪ Consider plasmapheresis in participants with acute or severe disease as guided by rheumatology or neurology. ▪ Consider IVIG therapy, noting onset of action is slower. Note: Plasmapheresis immediately after IVIG will remove immunoglobulin. ▪ Consider other immunosuppressant therapy including biologics (e.g. rituximab), TNFα, or IL-6 antagonists if symptoms worsen or if no improvement after 2 weeks. Other synthetic immunosuppressants such as methotrexate, azathioprine, or mycophenolate mofetil could be considered for maintenance[b], or if symptoms and CK levels do not resolve entirely after 4 weeks. Rituximab is used in primary myositis. [20] ▪ Consider permanent discontinuation of ICPi.
Additional considerations Caution is advised with rechallenging. With elevated transaminases, consider differential with immune-mediated hepatitis.	

5.3. Polymyalgia-Like Syndrome

Workup and evaluation G1: Complete rheumatologic history regarding differential diagnosis and examination of all joints and skin. Rarely participants may also develop concomitant GCA. Check for symptoms of temporal arteritis, such as headache, visual disturbances, or jaw claudication. Urgent referral to ophthalmologist if present and consider temporal artery biopsy as permanent visual loss can occur within days of symptom onset. ANA, RF, and anti-CCP. CK to evaluate differential diagnosis of myositis. Inflammatory markers (ESR and CRP). Monitoring: ESR and CRP ≥ G2: Complete history and examination as above; autoimmune tests as required for differential diagnosis. Early referral to a rheumatologist.

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, prednisone < 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 to G ≤ 2. However, note that cases of toxicity returning upon rechallenge have been reported. ▪ Referral to rheumatology. ▪ Should initiate prednisone 40 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a steroid-sparing agent such as synthetic drugs (e.g. methotrexate) or biologic agents (e.g. IL-6 antagonists). Note: As caution, IL-6 inhibition can cause intestinal perforation. Although this is extremely rare, it should not be used in participants with immune-related colitis. ▪ Consider admission of participants with severe symptoms.
Additional considerations IL-6 antagonists may be the preferred steroid-sparing agents for management of polymyalgia-like syndrome as they are already approved for use in participants with GCA.	

Abbreviations: AChR = acetylcholine receptor; ADL = activity of daily living; ANA = antinuclear antibody; CCP = citrullinated protein antibody; CK = creatine kinase; CRP = C-reactive protein; CV = cardiovascular; DMARD = disease-modifying antirheumatic drug; EMG = electromyography; ESR = erythrocyte sedimentation rate; GCA = giant cell arteritis; IA, inflammatory arthritis; ICPi, immune checkpoint inhibitor; IL, interleukin; irAE = immune-related adverse event; IV = intravenous; IVIG = intravenous immune globulin; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; RF = rheumatoid factor; TB = tuberculosis; TNF = tumor necrosis factor; ULN = upper limit of normal.

[a] Participants with myasthenia gravis–like syndrome or myocarditis and concomitant myositis should be hospitalized; see neurologic or cardiovascular sections, respectively, for further information.

[b] Strongly urge maintenance with synthetic immunosuppressants be undertaken in collaboration with rheumatology or neurology.

6.0. Recommendations for Identification, Evaluation, and Management of Renal Toxicities

Immune-related renal toxicities include nephritis or acute kidney injury (AKI). The median time to onset of renal toxicities is 14 weeks but can range from 6.5 to 21 weeks.[3] Presenting symptoms related to immune therapy-induced renal toxicities may include urinary frequency, dark cloudy urine; fluid retention (edema) of face, abdomen and extremities; sudden weight gain; abdominal or pelvic pain; nausea or vomiting; high blood pressure; and/or change in mental status, such as drowsiness.

Refer to Table A 6 for a complete set of recommendations, definition of grades, and additional considerations for renal toxicities.

Table A 6 Renal Toxicities

Renal Toxicities	
Nephritis and renal dysfunction – diagnosis and monitoring	
Clinical presentation[21] and diagnosis	
Definite ICPi-related nephritis or AKI	
Kidney biopsy-confirmed diagnosis compatible with ICPi nephritis or AKI, and after clinical review of risk factors[a].	
Probable ICPi-related nephritis or acute renal failure:	
BOTH of the following: Sustained increase in serum creatinine ≥ 50% on at least 2 consecutive values or need for RRT, after clinical review of risk factors[a].	
Absence of an alternative plausible etiology	
AND at least one of the following:	
Sterile pyuria (≥ 5 WBCs/hpf)	
Concomitant or recent extrarenal irAE-eosinophilia (≥ 500 cells per mL)	
Possible ICPi-related nephritis or acute renal failure:	
BOTH of the following:	
Increase in serum creatinine ≥ 50%	
Need for RRT nephritis or AKI is not readily attributable to alternative causes	
Monitoring	
Monitor participants for elevated serum creatinine before every dose.	
Routine urinalysis is not necessary, other than to rule out UTIs etc.	
For any suspected immune-mediated adverse reactions, exclude other causes (see below). For suspected renal irAE obtain urinalysis, consider referral to nephrology	
For participants receiving combination therapy with ICPis and other agents, assess the potential contribution of the non-iCPI treatment to the renal failure	
Assess for concomitant medications, prescribed and OTC, herbals, vitamins, nephrotoxic agents, or contrast media	
If no potential alternative cause of AKI is identified, then one can assume it is ICPi-related and should forego biopsy	
Swift treatment of autoimmune component is important.	
6.1. Nephritis or acute kidney injury (AKI)	
Grading	**Management**
G1: Creatinine level increase of > 0.3 mg/dL; creatinine 1.5 to 2.0x above baseline	Consider temporarily holding ICPi and/or other potential contributing agents in combination regimens, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status, and UTI) and baseline renal function. A change that is still < 1.5 ULN *could* be meaningful.

G2: Creatinine 2 to 3x above baseline	▪ Hold ICPi temporarily. ▪ Consult nephrology. ▪ Evaluate for other causes (recent IV contrast, medications, and fluid status). If other etiologies are ruled out, administer 0.5 to 1 mg/kg/day prednisone equivalents. ▪ If worsening or no improvement after 1 week, increase to 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue ICPi. ▪ If improved to G ≤ 1, taper steroids over at least 4 weeks. ▪ If no recurrence of CRI discuss resumption of ICPi with participant after taking into account the risks and benefits. Resumption of ICPi can be considered once steroids have been successfully tapered to ≤ 10 mg/d or discontinued.
G3: Creatinine > 3 x baseline or > 4.0 mg/ dL; hospitalization indicated G4: Life-threatening consequences; dialysis indicated; creatinine 6x above baseline	▪ Permanently discontinue ICPi if ICPi is directly implicated in renal toxicity. ▪ Consult nephrology. ▪ Evaluate for other causes (recent IV contrast, medications, fluid status, and UTI). ▪ 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 steroid treatment has been attempted.	

6.2. Nephritis or AKI – Follow-Up

Grading	Management
G1: Creatinine level increase of > 0.3 mg/dL; creatinine 1.5 to 2.0x above baseline	If improved to baseline Resume routine creatinine monitoring.
G2: Creatinine 2 to 3x above baseline	▪ If improved to G1: Taper corticosteroids over at least 4 weeks before resuming treatment with routine creatinine monitoring. ▪ If elevations persist > 7 days or worsen and no other cause found, treat as G3.
G3: Creatinine > 3 x baseline or > 4.0 mg/dL; hospitalization indicated	▪ If improved to G1: Taper corticosteroids over at least 4 weeks. ▪ If elevations persist > 3 to 5 days or worsen, consider additional immunosuppression (e.g. infliximab, azathioprine, cyclophosphamide [monthly], cyclosporine, and mycophenolate).
G4: Life-threatening consequences; dialysis indicated; creatinine 6x above baseline	▪ If improved to G1: Taper corticosteroids over at least 4 weeks. ▪ If elevations persist > 2 to 3 days or worsen, consider additional immunosuppression (e.g. infliximab, azathioprine, cyclophosphamide [monthly], cyclosporine, and mycophenolate).
NOTE. Data adapted from Gupta et al.[21]	

Abbreviations: AKI = acute kidney injury; CRI = chronic renal insufficiency; ICPi = immune checkpoint inhibitor; irAE = immune-related adverse event; IV = intravenous; OTC = over the counter; RRT = renal replacement therapy; ULN = upper limit of normal; UTI = urinary tract infection.

[a] Risk factors include prior or concomitant nephrotoxic agent(s) use and prior or concomitant extrarenal irAEs

7.0. Recommendations for Identification, Evaluation, and Management of Nervous System Toxicities

Neurologic irAEs encompass a broad spectrum of neurologic syndromes including myasthenia gravis or myasthenic syndrome, myasthenia gravis with myositis overlap, aseptic meningitis, encephalitis, Guillain-Barré-like syndrome, and a variety of other peripheral neuropathy phenotypes, and demyelinating disorders.[22] The median time to onset of nervous system toxicities, in general, is 4 weeks and can range from 1 to 68 weeks.[4, 23] Presenting symptoms of myasthenia gravis may include fatigable or fluctuating muscle weakness, ptosis, double vision, dysphagia, dysarthria, facial muscle weakness, and/ or head drop or neck weakness. Guillain-Barre syndrome can present with ascending, progressive muscle weakness, shortness of breath, facial weakness, numbness and tingling in the feet or hands, burning, stabbing, or shooting pain in affected areas, loss of balance, and coordination. As nerves that control involuntary bodily functions are damaged in ICPi-induced autonomic neuropathy, blood pressure, temperature control, digestion, bladder function, and sexual function may be affected and can present as GI difficulties such as new severe constipation or nausea, urinary problems, sexual difficulties, sweating abnormalities, sluggish pupil reaction, and orthostatic hypertension. Aseptic meningitis may present with headache, photophobia, neck stiffness, nausea or vomiting, and occasionally fever. Mental status should be normal, in contrast to encephalitis. Encephalitis symptoms may include confusion, altered mental status, altered behavior, headaches, seizures, weakness, and gait instability. Other potentially immune-related demyelinating diseases include multiple sclerosis, transverse myelitis, acute-disseminated encephalomyelitis, optic neuritis, and neuromyelitis optica.

Refer to Table A 7 for a complete set of recommendations, definition of grades, and additional considerations for nervous system toxicities.

Table A 7 Nervous System Toxicities

Nervous System Toxicities
7.1 Myasthenia Gravis
Workup and evaluation AChR and antistriated muscle antibodies in blood. If AChR antibodies are negative, consider MuSK and LPR4 antibodies in blood – while presence of antibodies is confirmatory, the absence of antibodies does not rule out the syndrome. Pulmonary function assessment with NIF and VC. CPK, aldolase, ESR, and CRP for possible concurrent myositis Consider MRI brain and/or spine depending on symptoms to rule out CNS involvement by disease or alternate diagnosis Troponin, ECG, and consider TTE and/or cardiac MRI to evaluate concomitant myocarditis (see CV section for further details) Electrodiagnostic studies, under neurologic consultation, including neuromuscular junction testing with repetitive stimulation and/or jitter studies, NCS to exclude neuropathy, and needle EMG to evaluate for concomitant myositis

Inflammatory markers (ESR and CRP)

Consider paraneoplastic workup

Review and stop medications with known risk of worsening myasthenia: beta-blockers, IV magnesium, fluoroquinolones, aminoglycosides, and macrolide antibiotics.

Grading	Management
All grades	All grades warrant workup and intervention given potential for progressive MG to lead to respiratory compromise. Inpatient admission may be appropriate at all grades.
No G1	NA
G2: Some symptoms interfering with ADLs. MGFA severity class I (ocular symptoms and findings only) and MGFA severity class II (mild generalized weakness).	▪ Hold ICPi and may resume in G2 participants (MGFA 1 and 2) only if symptoms resolve and steroid taper completed.[24] ▪ Neurology consultation. ▪ Strongly consider inpatient care as participants can deteriorate quickly. ▪ Pyridostigmine starting at 30 mg PO 3 times a day and gradually increase to maximum of 120 mg PO 4 times a day as tolerated and based on symptoms and wean based on improvement. These procedures should be done in close collaboration with the neurologist. ▪ Administer corticosteroids (prednisone 0.5 mg/kg[a] orally daily). Wean based on symptom improvement.
G3 to 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 III-V (moderate to severe generalized weakness to myasthenic crisis)	▪ Follow G2 recommendations as listed, with the following additions for G3 to 4: ▪ Permanently discontinue ICPi. ▪ Admit participant, may need ICU-level monitoring. ▪ Continue steroids, taper should begin 3 to 4 weeks after initiation then wean based on symptom improvement. ▪ Initiate IVIG 2 G/kg IV over 5 days (0.4 G/kg/d) or plasmapheresis x 5 days. ▪ Consider adding rituximab if refractory to IVIG or plasmapheresis. ▪ Frequent pulmonary function assessment. ▪ Daily neurologic review.

7.2. Guillain-Barré syndrome

Workup and evaluation

Neurologic consultation

MRI spine w/wo contrast (rule out compressive lesion and evaluate for nerve root enhancement/thickening)

Lumbar puncture: CSF analysis for cell count and differential, cytology for malignant cells, protein, glucose, and viral/bacterial cultures. Note that CSF typically has elevated protein and often elevated WBC as well, although this is not typically seen in classical Guillain-Barré.

Consider paraneoplastic workup eg ANNA-1 antibody testing

Serum antiganglioside antibody tests for GBS and its subtypes (e.g. anti-GQ1b for Miller Fisher variant associated with ataxia and ophthalmoplegia).

Flow cytometry in participants with hematologic malignancies

Electrodiagnostic studies (NCS and EMG) to evaluate polyneuropathy

Pulmonary function testing (NIF or VC)

Frequent neuro checks

Grading	Management
All grades warrant workup and intervention given potential for progressive GBS to lead to respiratory compromise. Note, there is no G1 toxicity.	
No G1	NA
G2: Moderate: some interference with ADLs, symptoms concerning to participant. G3 to 4: Severe: limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms.	▪ Discontinue ICPi. ▪ Neurology consultation. ▪ 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. Note: plasmapheresis immediately after IVIG will remove immunoglobulin. ▪ Corticosteroids are usually not recommended for idiopathic GBS; however, in ICPi-related forms, a trial is reasonable (methylprednisolone 2 to 4 mg/kg/d), followed by slow steroid taper. Pulse steroid dosing (methylprednisolone 1 g daily for 5 days) may also be considered for G3 to 4 along with IVIG or plasmapheresis. After pulse steroids, taper steroids over 4 to 6 weeks. ▪ Frequent neuro checks and pulmonary function monitoring. ▪ Monitor for concurrent autonomic dysfunction. ▪ Nonopioid management of neuropathic pain, for example, pregabalin, gabapentin, or duloxetine. ▪ Treatment of constipation/ileus.
Additional considerations Extreme caution with rechallenging for severe cases after complete resolution of symptoms and tapered off immunosuppression	

7.3. Peripheral Neuropathy

Workup and evaluation

G1

Consider neurology consultation to guide neuropathy phenotype determination and workup Serum testing for reversible neuropathy causes: HbA1c, vitamin B12, TSH, vitamin B6, folate, serum protein electrophoresis, and immunofixation, CPK

Consider additional testing guided by neuropathy phenotype: ANA, ESR, CRP, ANCA, anti-smooth muscle, SSA/SSB, RNP, anti-dsDNA, ganglioside ab, anti-MAG, anti-Hu (ANNA-1 ab), thiamine, Lyme, hepatitis B or C, and HIV

Consider MRI spine w/wo contrast

G2: In addition to the above

MRI spine advised, MRI brain if cranial nerve involvement, and MRI plexus if concern for plexus involvement

Consider lumbar puncture: CSF analysis for cell count and differential, cytology for malignant cells, protein, glucose, and viral or bacterial cultures.

Consider EMG or NCS

G3 to 4: go to GBS algorithm

Grading	Management
G1: Mild: no interference with function and symptoms not concerning to participant. 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 ADLs, symptoms concerning to participant (ie, pain but no weakness or gait limitation).	Hold ICPi and resume once return to G ≤ 1. Initial observation OR initiate prednisone 0.5 to 1 mg/kg/d (if progressing from mild). Gabapentin, pregabalin, or duloxetine for pain.
G3 to 4: Severe: limiting self-care and aids warranted, weakness limiting walking or respiratory problems (ie, leg weakness, foot drop, and rapidly ascending sensory changes). Severe may be GBS and should be managed as such.	Permanently discontinue ICPi. Admit participant. Neurology consultation. Initiate IV methylprednisolone 2 to 4 mg/kg/d and proceed as per GBS management.

7.4. Autonomic neuropathy

Workup and evaluation

An evaluation by neurologist or relevant specialist depending on organ system, with testing that may include:

Screen for other causes of autonomic dysfunction: diabetic screen, adrenal insufficiency, HIV, paraproteinemia, amyloidosis, and botulism; consider chronic diseases such as Parkinson's and other autoimmune screen.

Orthostatic vital signs.

Consider electrodiagnostic studies (NCS and EMG) to evaluate for concurrent polyneuropathy.

Consider paraneoplastic autoimmune dysautonomia antibody testing (e.g. antiganglionic AChR, ANNA-1, and N-type voltage-gated calcium channel antibodies).

Grading	Management
G1: Mild: no interference with function and symptoms not concerning to participant.	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 ADLs, symptoms concerning to participant.	▪ Hold ICPi and resume once return to G ≤ 1 and off prednisone if used. ▪ Initial observation OR initiate prednisone 0.5 to 1 mg/kg/d (if progressing from mild). ▪ Neurology consultation.
G3-4: Severe: limiting self-care and aids warranted.	▪ Permanently discontinue ICPi. ▪ Admit participant. ▪ Initiate methylprednisolone 1 g daily x 3 days followed by oral steroid taper. ▪ Neurology consultation.

7.5. Aseptic Meningitis

Workup and evaluation

MRI brain w/wo contrast with pituitary or sellar cuts protocol.

AM cortisol, ACTH to rule out adrenal insufficiency.

Strongly consider lumbar puncture with CSF analysis for opening pressure, cell count and differential, cytology for malignant cells that could indicate leptomeningeal metastases, protein, glucose, gram stain, viral or bacterial cultures, PCR for HSV, and other viral PCRs depending on suspicion.

May see elevated WBC in CSF with normal glucose, normal culture, and gram stain. May see reactive lymphocytes, neutrophils, or histiocytes on cytology.

Grading	Management
G1: Mild: no interference with function and symptoms not concerning to participant. Note: any cranial nerve problem should be managed as moderate	▪ Hold ICPi and discuss resumption with participant only after taking into account the risks and benefits.[25] ▪ Consider neurology consult.

G2: Moderate: some interference with ADLs, symptoms concerning to participant (ie, pain but no weakness or gait limitation). G3 to 4: Severe: limiting self-care and aids warranted	▪ Consider empiric antiviral (IV acyclovir) and antibacterial therapy until CSF results. ▪ Once bacterial and viral infection negative, may closely monitor off corticosteroids or consider oral prednisone 0.5 to 1 mg/kg/day or IV methylprednisolone 1 mg/kg/day if moderate or severe symptoms. ▪ Steroids can be tapered after 2 to 4 weeks, monitoring for symptom recurrence. ▪ Consider hospitalization for G3 to 4.

7.6. Encephalitis

Workup and evaluation

Neurologic consultation.

MRI brain w/wo contrast may reveal T2/FLAIR changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal. Lumbar puncture with CSF analysis for opening pressure, cell count and differential, cytology for malignant cells that could indicate leptomeningeal metastases, protein, glucose, gram stain, viral or bacterial cultures, PCR for HSV and other viral PCRs depending on suspicion, oligoclonal bands, autoimmune encephalopathy, and paraneoplastic panels.

May see elevated WBC with lymphocytic predominance and/or elevated protein.

EEG to evaluate for subclinical seizures.

Serum studies: Chem panel, CBC, ESR, CRP, ANCA (if suspect vasculitic process), thyroid panel including TPO and thyroglobulin, am cortisol and ACTH, GQ1b antibodies (Bickerstaff encephalitis and rhomboencephalitis), celiac antibody panel, and paraneoplastic and autoimmune encephalitis panels.

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 participant. Note: any cranial nerve problem should be managed as moderate. G2: Moderate: some interference with ADLs, symptoms concerning to participant (ie, pain but no weakness or gait limitation). G3 to 4: Severe: Limiting self-care and aids warranted	▪ Hold ICPi and discuss resumption with participant 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/d. ▪ Neurology consultation. ▪ If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids (methylprednisolone 1 g IV daily for 3 to 5 days) plus IVIG 2 g/kg over 5 days (0.4 g/kg/d) or plasmapheresis. ▪ Taper steroids following acute management over at least 4 to 6 weeks. ▪ If positive for autoimmune encephalopathy or paraneoplastic antibody or limited or no improvement, consider rituximab in consultation. ▪ Admit participant for G3 to 4.

7.7. Demyelinating Diseases, Including Multiple Sclerosis, Transverse Myelitis, ADEM, ON, and NMO

Workup and evaluation

Neurologic consultation.

Ophthalmic or neuro-ophthalmic evaluation if ocular involvement

MRI with contrast of brain, orbit, cervical, and thoracic spinal cord (tailor to examination finding).

Lumbar puncture with CSF analysis including autoimmune encephalitis panel and oligoclonal bands, CNS demyelinating disease antibodies (aquaporin 4 and myelin oligodendrocyte glycoprotein), and viral PCRs especially JCV PCR to exclude progressive multifocal leukoencephalopathy.

Serum studies: B12, HIV, RPR, ANA, Ro/La, TSH, aquaporin-4 IgG, paraneoplastic panel or anti-HU and anti-CRMP5-CV2, thyroid panel including TPO and thyroglobulin, am cortisol and ACTH, and paraneoplastic and autoimmune encephalitis panels. Evaluation for urinary retention and constipation. EEG to evaluate for subclinical seizures. Although less common, biopsy may provide definitive evidence of CNS demyelination.	
Grading	**Management**
G1: Asymptomatic or mild symptoms; clinical or diagnostic observations only	▪ Intervention not indicated. ▪ Continue immunotherapy unless symptoms worsen or do not improve.
G2: Moderate symptoms; minimal, limiting age-appropriate instrumental ADL	▪ Stop ICPi. ▪ Neurology consultation. ▪ Start prednisone 1 mg/kg daily and taper over 1 month. ▪ Rule out infection.
G3: Severe or medically significant symptoms but not immediately life-threatening; limiting self-care ADL	▪ Permanently discontinue ICPi. ▪ Neurology consultation. ▪ Nonopioid management of neuropathic pain, for example, pregabalin, gabapentin, or duloxetine. ▪ Admit participant for methylprednisolone pulse dosing 1 g/d and consider IVIG[b] or plasmapheresis if no improvement or symptoms worsen after 3 days.[c]
G4: Life-threatening consequences	▪ Permanently discontinue ICPi. ▪ Neurology consultation. ▪ ICU-level inpatient care. ▪ Start methylprednisolone pulse dosing 1 g/d and consider IVIG or plasmapheresis if no improvement or symptoms worsen after 3 days.[c]

Abbreviations: AChR = acetylcholine receptor; ACTH = adrenocorticotropic hormone; ADEM = acute disseminated encephalomyelitis; ADL = activity of daily living; AM = morning; ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibodies; ANNA-1 = antineuronal nuclear antibody type 1; CPK = creatine phosphokinase; CRP = C-reactive protein; CV = cardiovascular; dsDNA = double stranded DNA; EMG, = electromyography; ESR = erythrocyte sedimentation rate; FLAIR = fluid-attenuated inversion recovery; GBS = Guillain-Barré syndrome; HSV = herpes simplex virus; ICPi = immune checkpoint inhibitor; ICU = Intensive Care Unit; IV = intravenous; IVIG = intravenous immune globulin; JCV = John Cunningham virus; LPR4 = lipoprotein-related 4; MAG = myelin-associated glycoprotein; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; MRI = magnetic resonance imaging; MuSK = muscle-specific kinase; NA = not applicable; NCS = nerve conduction study; NIF = negative inspiratory force; NMO = neuromyelitis optica; ON = optic neuritis; PCR = polymerase chain reaction; PO = by mouth; RNP = ribonucleoprotein; RPR = rapid plasma reagin; SSA, Sjögren's syndrome A; SSB = Sjögren's syndrome B; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone; TTE = transthoracic echocardiogram; VC =vital capacity.

[a] The divergence from 1 mg/kg in the setting of MG is because of the potential short-term exacerbation of MG with high-dose steroid.

[b] IVIG 2 g/kg, administered in divided doses per package insert.

[c] Plasmapheresis immediately after IVIG will remove immunoglobulin.

8.0. Recommendations for Identification, Evaluation, and Management of Hematologic Toxicities

Immune-related hematologic toxicities encompass a spectrum of conditions including hemolytic anemia, acquired thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome, aplastic anemia, lymphopenia, immune thrombocytopenia (ITP), and acquired hemophilia A. The median time to onset of hematologic toxicities in general is 5.7 weeks but can range from 1 to 84 weeks.[26,27] Patients with immune therapy-induced hemolytic anemia may present with weakness, paleness, jaundice, dark-colored urine, fever, and heart murmur. Immune-related TTP can present as fever, mild renal failure, and neurologic manifestations such as seizures, hemiplegia, and visual disturbances. Presenting symptoms related to immune therapy-induced hemolytic uremic syndrome may 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, and/or swelling of the face, hands, feet, or the entire body. Immune therapy-induced aplastic anemia may include fatigue, shortness of breath, rapid or irregular heart rate, pallor, unexplained or easy bruising, bleeding, skin rash, dizziness, headache, and fever. Lymphopenia induced by ICPi therapy may present as fever, cough, runny nose, enlarged lymph nodes, painful joints, skin rash, and/or night sweats. Immune therapy-induced ITP may present as easy or excessive bruising, petechiae, usually on the lower legs, bleeding from the gums or nose, and blood in urine or stool. Acquired hemophilia A can present with subcutaneous bleeding and/or muscle, GI, genitourinary, and retroperitoneal bleeding.

Refer to Table A 8 for a complete set of recommendations, definition of grades, and additional considerations for hematologic toxicities.

Table A 8 Hematologic Toxicities

Hematologic Toxicities
8.1. Hemolytic Anemia
Workup and evaluation
History and physical examination (with special consideration of history of new drugs, insect, spider, or snake bites)
Blood chemistry, CBC with evidence of anemia, macrocytosis, evidence of hemolysis on peripheral smear. LDH, haptoglobin, bilirubin, reticulocyte count, and free hemoglobin
DIC panel, which could include PT or INR or PTT, and infectious causes
Autoimmune serology
PNH screening
Direct and indirect bilirubin, direct agglutinin test, and if no obvious cause, bone marrow analysis, and cytogenetic analysis to evaluate MDS
Evaluation for viral or bacterial (mycoplasma etc) causes of hemolysis studies
Protein electrophoresis and cryoglobulin analysis
Workup for BM failure syndrome if refractory including B12, folate, copper, parvovirus, iron, and thyroid, infection

Glucose-6-phosphate dehydrogenase level Evaluation of common drug causes (ribavirin, rifampin, dapsone, interferon, cephalosporins, penicillins, NSAIDs, quinine or quinidine, fludarabine, ciprofloxacin, lorazepam, and diclofenac) Assessment of methemaglobinemia	
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; < 6.2 to 4.9 mmol/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 participant. ▪ Hematology consult. ▪ Prednisone 1 to 2 mg/kg/d (oral or IV equivalent depending on symptoms or speed of development). ▪ 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 participant to a safe hemoglobin range (7 to 8 g/dL in stable, noncardiac inpatients). ▪ Should offer participants supplementation with folic acid 1 mg daily.
G4: Life-threatening consequences; urgent intervention indicated	▪ Permanently discontinue ICPi. ▪ Admit participant. ▪ Hematology consult. ▪ IV prednisone corticosteroids 1 to 2 mg/kg/d. ▪ If no improvement on or if worsening on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, cyclosporine, infliximab, MMF, or ATG. ▪ RBC transfusion per existing guidelines. Discuss with blood bank team before transfusions that a participant with possible ICPi SAE is in the hospital.
Additional considerations Monitor hemoglobin levels weekly until the steroid tapering process is complete. Thereafter, less frequent testing is needed.[28]	
8.2 Acquired TTP	
Workup and evaluation History with specific questions related to drug exposure (e.g. CTX, sirolimus, tacrolimus, oxymorphone, antibiotics, and quinine) Hematology consult Physical examination, peripheral smear to check for schistocytes ADAMTS13 activity level and inhibitor titer LDH, haptoglobin, reticulocyte count, bilirubin, and urinalysis to rule out other causes Prothrombin time, activated partial thromboplastin time, and fibrinogen Blood group and antibody screen, and direct antiglobulin test Consider CT or MRI brain, echocardiogram, electrocardiogram Cytomegalovirus serology	

Note: this disorder is usually associated with severe drop in platelets and hemolysis or anemia precipitously (microangiopathy)	
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 or morbidity. ▪ Initially, the participant 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 participant only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting ICPi therapy. ▪ Administer 0.5 to 1 mg/kg/d prednisone.
G3: Laboratory findings with clinical consequences (G3 thrombocytopenia, anemia, and renal insufficiency > 2) G4: Life-threatening consequences, (e.g. CNS hemorrhage or thrombosis or embolism or renal failure)	▪ Hold ICPi and discuss resumption with participant only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting ICPi therapy. ▪ In conjunction with hematology, initiate therapeutic PEX according to existing guidelines with further PEX dependent on clinical progress.[29-32] ▪ Administer methylprednisolone 1 g IV daily for 3 days, with the first dose typically administered immediately after the first PEX. For participant who has an initial platelet count response, discontinue PEX. ▪ May offer rituximab. ▪ Consider caplacizumab if ADAMTS13 activity level is < 10 IU/dL or < 10% of normal, with an inhibitor or elevated anti-ADAMTS13 IgG. [29] ▪ If no exacerbation within 3 to 5 days after stopping PEX, taper steroids over 2 to 3 weeks, complete course of rituximab (if receiving), and discontinue caplacizumab (if receiving).[30]

8.3 HUS

Workup and evaluation

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 or MMA

Complement testing C3, C4, and CH50 (complement inhibitory antibodies for suspected familial)

Evaluate reticulocyte count and MCV

Evaluation of infectious cause including screening for viral EBV, CMV, and HHV6

Evaluation for nutritional causes of macrocytosis (B12 and folate)

Pancreatic enzymes

Evaluation for diarrheal causes, shiga toxin, and *Escherichia coli* 0157 Direct antibody test (Coombs test), haptoglobin, LDH, and other etiologies of anemia Evaluation for common drugs causing hemolysis (tacrolimus, cyclosporine, and sirolimus) Evaluation for neurologic changes (alteration in consciousness, concurrent confusion, seizures, pyramidal syndrome, and extrapyramidal syndrome with hypertonia).[33]	
Grading	**Management**
G1 to 2: Evidence of RBC destruction (schistocytosis) without clinical consequences of anemia, and thrombocytopenia Grade II	Continue ICPi with close clinical follow-up and laboratory evaluation. Supportive care.
G3: Laboratory findings with clinical consequences (e.g. renal insufficiency and petechiae) G4: Life-threatening consequences, (e.g., CNS thrombosis or embolism or renal failure)	▪ Permanently discontinue ICPi. ▪ Hematology consult. ▪ Begin therapy with eculizumab (anti-C5 antibody)[a] 900 mg weekly x 4 doses, 1,200 mg Week 5, then 1,200 mg every 2 weeks. ▪ Red blood transfusion according to existing guidelines.
8.4 Aplastic Anemia	
Workup and evaluation History and physical examination (close attention to medications, exposure to radiation, toxins, and recent viral infections) CBC, smear, and reticulocyte count Viral studies including CMV, HHV6, EBV, and parvovirus Nutritional assessments including B12, folate, iron, copper, ceruloplasmin, and vitamin D Serum LDH and renal function Evaluation for infectious causes. Identify marrow hypo/aplasia BM biopsy and BM 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 participant for transfusions and notify blood bank that all transfusions need to be irradiated and filtered	
Grading	**Management**
G1: mild: > 0.5 PMNs x 10^9 /L hypocellular marrow, with marrow cellularity < 25%, Peripheral platelet count > 20,000, reticulocyte count > 20,000	▪ Hold ICPi, provide growth factor support, and close clinical follow-up and laboratory evaluation. ▪ Supportive transfusions as per local guidelines.
G2: moderate: Hypocellular marrow < 25% and two of the following ANC < 500, peripheral platelet < 20,000 and reticulocyte < 20,000	▪ Hold ICPi and provide growth factor support and close clinical laboratory evaluations daily. ▪ Hematology consult. ▪ Administer horse ATG plus cyclosporine. ▪ Supportive transfusions as per local guidelines. All blood products should be irradiated and filtered. ▪ HLA typing and evaluation for bone marrow transplantation if participant is a candidate.
G3 to 4: severe: ANC < 200, platelet count < 20,000, reticulocyte count of < 20,000, plus hypocellular marrow < 25%.	▪ As per G2. ▪ Hold ICPi and monitor weekly for improvement. If not resolved, discontinue treatment until AE has reverted to G1.

	▪ If no response, repeat immunosuppression with rabbit ATG plus cyclosporine, and cyclophosphamide. ▪ For refractory participants, consider eltrombopag plus supportive care.
8.5. Lymphopenia	
Workup and evaluation History (special attention to nutritional status and for lymphocyte depleting therapy such as fludarabine, ATG, steroids, cytotoxic CTX, and radiation exposure, as well as history of AD and family history of AD) Physical examination with special attention to spleen size CBC with differential, peripheral smear, and reticulocyte count CXR for evaluation of presence of thymoma Bacterial cultures and evaluation for infection (fungal, bacterial, and viral – specifically CMV or HIV)	
Grading	**Management**
All grades	No specific action is required for lymphopenia G1 to G3 and ICPi therapy should be continued. For G4 (< 250 PB lymphocyte count), continue ICPi therapy and initiate *Mycobacterium avium* complex prophylaxis and *Pneumocystis jirovecii* prophylaxis, CMV screening. HIV or hepatitis screening if not already done. May consider EBV testing if evidence of lymphadenopathy or hepatitis, fevers, and hemolysis occur c/w lymphoproliferative disease occurs.
8.6. ITP	
Workup and evaluation History and physical examination (special attention for history of viral illness and lymphocyte depleting therapy such as fludarabine, ATG, steroids, and cytotoxic therapy) FH of autoimmunity or personal history of AD CBC, peripheral blood smear, and reticulocyte count Bone marrow evaluation only if abnormalities in the above testing results and further investigation is necessary for a diagnosis Participants with newly diagnosed ITP should undergo testing for HIV, HCV, HBV, and *H. pylori* Direct antigen test should be checked to rule out concurrent Evans' syndrome Nutritional evaluation BM evaluation if other cell lines affected and concern for aplastic anemia	
Grading	**Management**
G1: Platelet count 75 to < 100/ µL	Continue ICPi with close clinical follow-up and laboratory evaluation.
G2: Platelet count 50 to < 75/µL	▪ Hold ICPi but monitor for improvement. If not resolved, interrupt treatment until AE has reverted to G1. ▪ Administer prednisone 1 mg/kg per day (dosage range, 0.5 to 2 mg/kg per day) orally for 4 weeks followed by taper over 4 to 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 25 to < 50/µL	▪ As per G2.

G4: Platelet count < 25/μL	▪ Hematology consult. ▪ Consider as alternative to prednisone or dexamethasone 40 mg daily for 4 days. ▪ If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. ▪ If previous treatment with corticosteroids and/or IVIG has been unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more potent immunosuppression. (*From American Society of Hematology guideline on ITP[34]—consult for further details*)

8.7. Acquired Hemophilia A

Workup and evaluation

Hematology consult

Full blood count to assess platelet number, fibrinogen, PT, PTT, and INR. The typical finding in participants with acquired hemophilia A is a prolonged aPTT 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% to 40% of normal factor activity in blood; 0.05 to 0.4 IU/mL of whole blood	▪ Hold ICPi and discuss resumption with participant only after taking into account the risks and benefits. ▪ Administer 0.5 to 1 mg/kg/d prednisone. ▪ Transfusion support as required. ▪ Treatment of bleeding disorders with hematology consult.
G2: Moderate: 1%- to 5% of normal factor activity in blood; 0.01 to 0.05 IU/mL of whole blood	▪ Hold ICPi and discuss resumption with participant only after taking into account the risks and benefits. ▪ Administration of factor replacement (choice based on BU of titer). ▪ Administer 1 mg/kg/d prednisone ± rituximab (dose 375 mg/m^2 weekly x 4 weeks) and/or cyclophosphamide (dose 1 to 2 mg/kg/d). Choice of rituximab versus cyclophosphamide is participant 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. ▪ Transfusion support as required for bleeding.

G3 to 4: Severe: < 1% of normal factor activity in blood; < 0.01 IU/mL of whole blood	▪ Permanently discontinue ICPi. ▪ Admit participant. ▪ Administration of factor replacement; choice based on BU level of inhibitor. ▪ Bypassing agents may be used (Factor VII FEIBA). Caution should be taken in elderly participants and those with CAD. ▪ Prednisone corticosteroids 1 to 2 mg/kg/d (oral or IV depending on symptoms) ± rituximab (dose 375 mg/m^2 weekly x 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 or immunoadsorption.
Additional considerations Acquired hemophilia A requires special 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.[35]	

Abbreviations: AD = autoimmune disease; AE = adverse event; ANC = antineutrophil cytoplasmic antibodies; ATG = antithymocyte globulin; BM = bone marrow; BU = Bethesda units; CAD = coronary artery disease; CMV = cytomegalovirus; CT = computed tomography; CTX = chemotherapy; CXR = chest X-ray; DIC = disseminated intravascular coagulation; EBV = Epstein-Barr virus; FH = family history; GPI = glycosylphosphatidylinositol; HBV = hepatitis B virus; HCV = hepatitis C virus; HHV6 = human herpesvirus 6; HUS = hemolytic uremic syndrome; ICPi = immune checkpoint inhibitor; INR = international normalized ratio; ITP = immune thrombocytopenia; IV = intravenous; IVIG = intravenous immune globulin; LDH = lactate dehydrogenase; LLN = lower limit of normal; MDS = myelodysplastic syndromes; MMA = methylmalonic acid; MMF = mycophenolate mofetil; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; PEX = plasma exchange; PMN = polymorphonuclear cell; PNH = paroxysmal nocturnal hemoglobinuria; PT = prothrombin time; PTT = partial thromboplastin time; SAE = serious adverse event; TTP = thrombotic thrombocytopenic purpura.

[a] Participants should be immunized with a meningococcal vaccine at least 2 weeks before administering the first dose of eculizumab, unless the risks of delaying eculizumab therapy outweigh the risks of developing a meningococcal infection.

9.0. Recommendations for Identification, Evaluation, and Management of Cardiovascular Toxicities

Cardiovascular toxicities from ICPis can include myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure, vasculitis, and venous thromboembolism. The median time to onset of cardiovascular toxicities is 6 weeks but can range from 2 to 54 weeks.[3] Presenting symptoms could include progressive fatigue, myalgia or weakness, palpitations, chest pain, presyncope or syncope, shortness of breath, and peripheral edema. Severe cases can present with cardiogenic shock or sudden death. Symptoms can often be masked by or coincident with other irAEs (e.g. myositis, pneumonitis, and hypothyroidism) or pulmonary symptoms related to malignancy or comorbid conditions. The presenting symptoms related to immune therapy-induced vasculitis and VTE while variable may include pain, extremity swelling, increased skin vein visibility or purpuric rash, erythema, and cyanosis accompanied by unexplained fever, dyspnea, pleuritic pain, cough, wheezing, or hemoptysis.

Refer to Table A 9 for a complete set of recommendations, definition of grades, and additional considerations for cardiovascular toxicities.

Table A 9 Cardiovascular Toxicities

Cardiovascular Toxicities	
9.1. Myocarditis, Pericarditis, Arrhythmias, Impaired Ventricular Function with Heart Failure, and Vasculitis	
Workup and evaluation ECG Troponin, and CPK to rule out concurrent myositis, especially in participants treated with combination immune therapies. Alternative reasons for elevation should be ruled out. If elevated, troponin should be serially monitored. With elevated troponin, be aware of the potential for triple M irAEs – myositis, myasthenia, and myocarditis – and refer to subspecialties. BNP Echocardiogram Chest X-ray Additional testing to be guided by cardiology and may include: Stress test Cardiac catheterization Cardiac MRI	
Grading	**Management**
G1: Abnormal cardiac biomarker testing without symptoms and with no ECG abnormalities	▪ All grades warrant workup and intervention, given the potential for cardiac compromise. ▪ Hold ICPi for G1 elevated troponin[a] and recheck troponin 6 hours later. May consider resuming once normalized or if believed not to be related to ICPi. ▪ Hold ICPi and discontinue for G ≥ 2. ▪ For participants with G ≥ 2, early (ie, within 24 hours) initiation of high-dose corticosteroids (1 to 2 mg/kg/d of prednisone, oral or IV depending on symptoms) should be considered as it is likely to be beneficial without adverse effects. ▪ Admit participant for cardiology consultation. ▪ Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology. ▪ Immediate transfer to a coronary care unit should be considered for participants with elevated troponin or conduction abnormalities. ▪ For new conduction delay, consider a pacemaker. ▪ In participants 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.[36] Consider abatacept (costimulatory molecule blockade) or alemtuzumab (CD52 blockade) as additional immunosuppression in life-threatening cases.[37, 38]
G2: Abnormal cardiac biomarker testing with mild symptoms or new ECG abnormalities without conduction delay	
G3: Abnormal cardiac biomarker testing with either moderate symptoms or new conduction delay	
G4: Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions	

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 (ie, > 5 mg/kg) in participants with moderate-severe heart failure.[39, 40]

9.2 Venous Thromboembolism

Workup and evaluation

Evaluation of signs and symptoms of PE or DVT may include:

- Clinical prediction rule to stratify participants with suspected VTE
- Venous ultrasound for suspected DVT
- CTPA for suspected PE
- Can also consider D-dimer for low-risk participants based on risk stratification by clinical prediction rule for DVT/PE when CT or Doppler not available or appropriate
- V/Q scan is also an option when CTPA is not appropriate
- Consider other testing, including ECG, chest radiography, BNP and troponin levels, and ABG

Grading	Management
G1: Venous thrombosis (e.g. superficial thrombosis)	▪ Continue ICPi. ▪ Warm compress. ▪ Clinical surveillance.
G2: Venous thrombosis (e.g. uncomplicated deep vein thrombosis), medical intervention indicated	▪ Continue ICPi. ▪ Management according to CHEST, ACC, and/or AHA guidelines and consider consult from cardiology or other relevant specialties. ▪ LMWH, VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial anticoagulation treatment. For long-term anticoagulation, LMWH, edoxaban, rivaroxaban, or apixaban for at least 6 months are preferred over VKAs because of improved efficacy. [41,42] ▪ IV heparin is an acceptable alternative for initial use and oral anticoagulants are acceptable for the long term.
G3: Venous thrombosis (e.g. uncomplicated PE), urgent medical intervention indicated	▪ Hold ICPi and may reintroduce after risk and benefit are considered. ▪ Follow G2 anticoagulation recommendations.
G4: Life-threatening consequences; hemodynamic or neurologic instability; organ damage; loss of extremity(ies)	▪ Hold ICPi and may reintroduce after risk and benefit are considered. ▪ Admit participant and management according to CHEST, ACC, and/or AHA guidelines and with guidance from cardiology. ▪ Respiratory and hemodynamic support. ▪ Follow G2 anticoagulation recommendations with further clinical management as indicated based on symptoms.

Additional considerations

VTE prophylaxis in high-risk outpatients with cancer (Khorana score of 2 or higher before starting a new systemic regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH, provided there are no significant risk factors for bleeding and no drug interactions, as per ASCO VTE guideline.[41]

Although it may be impossible to determine the etiology of thromboembolic disease in participants 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 Grade 4 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 while on immunotherapy and consideration be given to continuing for an additional 6 months following completion of immunotherapy.[41]

Abbreviations: ABG = arterial blood gas; ACC = American College of Cardiology; AHA = American Heart Association; BNP = brain natriuretic peptide; CHEST = American College of Chest Physicians; CPK = creatine phosphokinase; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; CTPA = computed tomography pulmonary angiography; DVT = deep vein thrombosis; ICPi = immune checkpoint inhibitor; irAE = immune-related adverse event; IV = intravenous; LMWH, low-molecular-weight heparin; MRI = magnetic resonance imaging; PE = pulmonary embolism; US = ultrasound; VKA = vitamin K agonist; VTE = venous thromboembolism.

[a] According to CTCAE v5.0, G1 elevated troponin is defined as levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer.

10.0. Recommendations for Identification, Evaluation, and Management of Ocular Toxicities

Immune-related ocular toxicities include uveitis, iritis, and episcleritis. The median onset is 5 weeks but can range from 1 to 72 weeks.[43] Presenting symptoms related to immune therapy-induced ocular toxicities may include blurred vision, change in color vision, photophobia, distortion, scotomas, visual field changes, double vision, tenderness, pain with eye movement, eyelid swelling, proptosis, redness, and/or dryness.

Refer to Table A 10 for a complete set of recommendations, definition of grades, and additional considerations for ocular toxicities.

Table A 10 Ocular Toxicities

Ocular Toxicities
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
Slitlamp examination
Eye pressure
Need to rule out myasthenia gravis
Prior conditions
Exclude participants with history of active uveitis
History of recurrent uveitis requiring systemic immunosuppression or continuous local therapy
Additional considerations:
Clinicians should be aware that ocular irAEs commonly accompany other organ irAEs, and there should be a high level of clinical suspicion, as symptoms may not always be associated with severity. Participants with all grades of ocular symptoms should be referred to ophthalmology.

10.1. Uveitis or Iritis	
Workup and evaluation: As per 10.0 Ophthalmology consult should be universal for the symptoms described in 10.0.	
Grading	**Management**
G1: Anterior uveitis with trace cells	▪ Continue ICPi. ▪ Prompt referral to ophthalmology (usually within 1 week). ▪ Artificial tears.
G2: Anterior uveitis with 1+ or 2+ cells	▪ Hold ICPi temporarily until after ophthalmology consult. ▪ Urgent ophthalmology referral. ▪ Topical corticosteroids (e.g. 1% prednisolone acetate suspension), cycloplegic agents (e.g. atropine), and systemic corticosteroids.[44] ▪ May resume ICPi treatment once off systemic steroids if participant has only ocular irAE, once corticosteroids are reduced to ≤ 10 mg prednisone equivalent. Continued topical or ocular steroids are permitted when resuming therapy to manage and minimize local toxicity. ▪ Retreat after return to G ≤ 1.
G3: Anterior uveitis with 3+ or greater cells; intermediate posterior or pan-uveitis	▪ Permanently discontinue ICPi. ▪ Urgent ophthalmology referral. ▪ Systemic corticosteroids and intravitreal or periocular/ or topical corticosteroids. ▪ Methotrexate may be used in participants who respond poorly to systemic corticosteroids or those with severe sight-threatening inflammation.[44]
G4: Best-corrected visual acuity of 20/200 or worse in the affected eye	▪ Permanently discontinue ICPi. ▪ Emergent ophthalmology referral. ▪ Systemic corticosteroids – prednisone 1 to 2 mg/kg/d or methylprednisolone 0.8 to 1.6 mg/kg/d and intravitreal or periocular or topical corticosteroids per ophthalmologist opinion.
Additional considerations: Consider use of infliximab, other TNFα blockers, or IVIG in cases that are severe and refractory to standard treatment.[45, 46]	

10.2. Episcleritis	
Workup and evaluation: As per 10.0	
Grading	**Management**
G1: Asymptomatic	▪ Continue ICPi. ▪ Prompt ophthalmology referral (usually within 1 week). ▪ Artificial tears.
G2: vision 20/40 or better	▪ Hold ICPi therapy temporarily until after ophthalmology consult. ▪ Urgent ophthalmology referral. ▪ Topical corticosteroids (e.g. 1% prednisolone acetate suspension), cycloplegic agents (e.g. atropine), and systemic corticosteroids.[44]

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 TNFα blockers in cases that are severe and refractory to standard treatment.[45, 46]	

Abbreviations: ICPi = immune checkpoint inhibitor; irAE = immune-related adverse event; IVIG = intravenous immune globulin; TNF = tumor necrosis factor.

Appendix 6 Clinical Laboratory Tests

The protocol-required clinical laboratory assessments are in the following table:

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td>Hematology</td><td colspan="2">Platelet count

Hemoglobin
Hematocrit

<u>Red Blood Cell Count</u>
• Reticulocyte
• Erythrocytes</td><td><u>Mean corpuscular volume (MCV)</u>

Mean corpuscular hemoglobin (MCH)</td><td><u>White Blood Cell Count with Differential</u>:
• Neutrophils
• Lymphocytes
• Monocytes
• Eosinophils
• Basophils
• Absolute neutrophil count
• Absolute lymphocyte count</td></tr>
<tr><td rowspan="3">Biochemistry</td><td>Blood Urea Nitrogen/total urea[1]</td><td>Potassium[1]</td><td>Aspartate aminotransferase[1]</td><td>Total bilirubin[1]</td></tr>
<tr><td>Creatinine[1]</td><td>Sodium[1]</td><td>Alanine aminotransferase[1]</td><td>Protein</td></tr>
<tr><td>Glucose[1]</td><td>Calcium[1]</td><td>Alkaline phosphatase[1]</td><td>Albumin</td></tr>
<tr><td></td><td>Amylase[1]</td><td>Lipase[1]</td><td>Gamma-glutamyl-transferase</td><td>C-reactive protein</td></tr>
<tr><td></td><td>Cholesterol</td><td>Phosphorus/Phosphates[1]</td><td>Lactate dehydrogenase</td><td>Creatine kinase[1]</td></tr>
<tr><td></td><td>Triglyceride</td><td>Magnesium[1]</td><td>Chloride[1]</td><td></td></tr>
<tr><td>Thyroid function (TSH and FT4 [or total T4]) and ACTH</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Coagulation</td><td>aPTT</td><td>Prothrombin time/INR</td><td></td><td></td></tr>
<tr><td colspan="5">Notes:
[1] Core chemistry: not applicable after protocol version 5.0 is approved and implemented</td></tr>
<tr><td>Routine Urinalysis</td><td colspan="4">• Specific gravity.
• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes by dipstick.
• Microscopic examination (if blood or protein is abnormal).
• A full urinalysis (dipstick plus microscopic evaluation) is required at Screening and at the EOT Visit, and a basic urinalysis (dipstick only) at each visit indicated prior to administration of study intervention. If the basic urinalysis is abnormal, then a full urinalysis should be performed.</td></tr>
<tr><td>Other Screening Tests</td><td colspan="4">• Serum or urine hCG pregnancy test (as needed for WOCBP), FSH if applicable.
• HBsAg, HBsAb, and HBcAb. The HCV screening test assesses the presence or absence of antibodies to HCV.
• All study-required laboratory assessments will be performed by local laboratories.</td></tr>
</table>

HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antigen antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.

Appendix 7 Pharmacogenetics

Use/Analysis of DNA

Genetic variation may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact study intervention absorption, distribution, metabolism, and excretion; mechanism of action of the study intervention; disease etiology; and/or molecular subtype of the disease being treated.

- CCI [redacted]. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- In addition, DNA samples will be used for research related to (e.g., study intervention, mechanism of action, indication, related diseases). They may also be used to develop tests or assays, including diagnostic tests related to (e.g., study intervention mechanism of action, indication, related diseases). Pharmacogenetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The results of pharmacogenetic analyses may be reported in the CSR or in a separate study summary.
- Details on processes for collection and shipment of these samples can be found in the Central Laboratory Manual. The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- Retention time and possible analysis of DNA sample after the study ends are specified in the respective ICF.

Appendix 8 Further Information to Sample Size Determination

The following tables describe the information gained from the JAVELIN Bladder 100 study for the control arm and assumptions for different scenarios considered to evaluate the planned sample size.

The time to progression is modelled by piecewise (i.e. over time intervals) constant hazards. For ease of illustration, the hazard within each interval is transformed to a median time to PD in months (-ln(0.5)/hazard).

Table 22 PFS Information and Assumptions

	Control	Opt. Scenario	Pos. Scen. 1	Pos. Scen. 2	No-eff. Scen. 3
Proportion in Population: minimal risk / no ACT after PD / ACT after PD	0.16 / 0.21 / 0.63	0.20 / 0.20 / 0.60	0.20 / 0.20 / 0.60	0.20 / 0.20 / 0.60	0.16 / 0.21 / 0.63
Med. Time to PD: Day 50 to 110	2.0 months	4.5 months	4.0 months	3.0 months	2.2 months
Med. Time to PD: Day 110 to 170	5.1 months	6.6 months	6.1 months	7.1 months	5.2 months
Med. Time to PD: > Day 170	9.8 months	11.3 months	10.8 months	11.8 months	9.9 months
Med. OS Time without PD	80.7 months	82.2 months	81.7 months	82.7 months	80.8 months

Table 23 Progression-free Survival Function of Control Arm (Based on Multi-state Model)

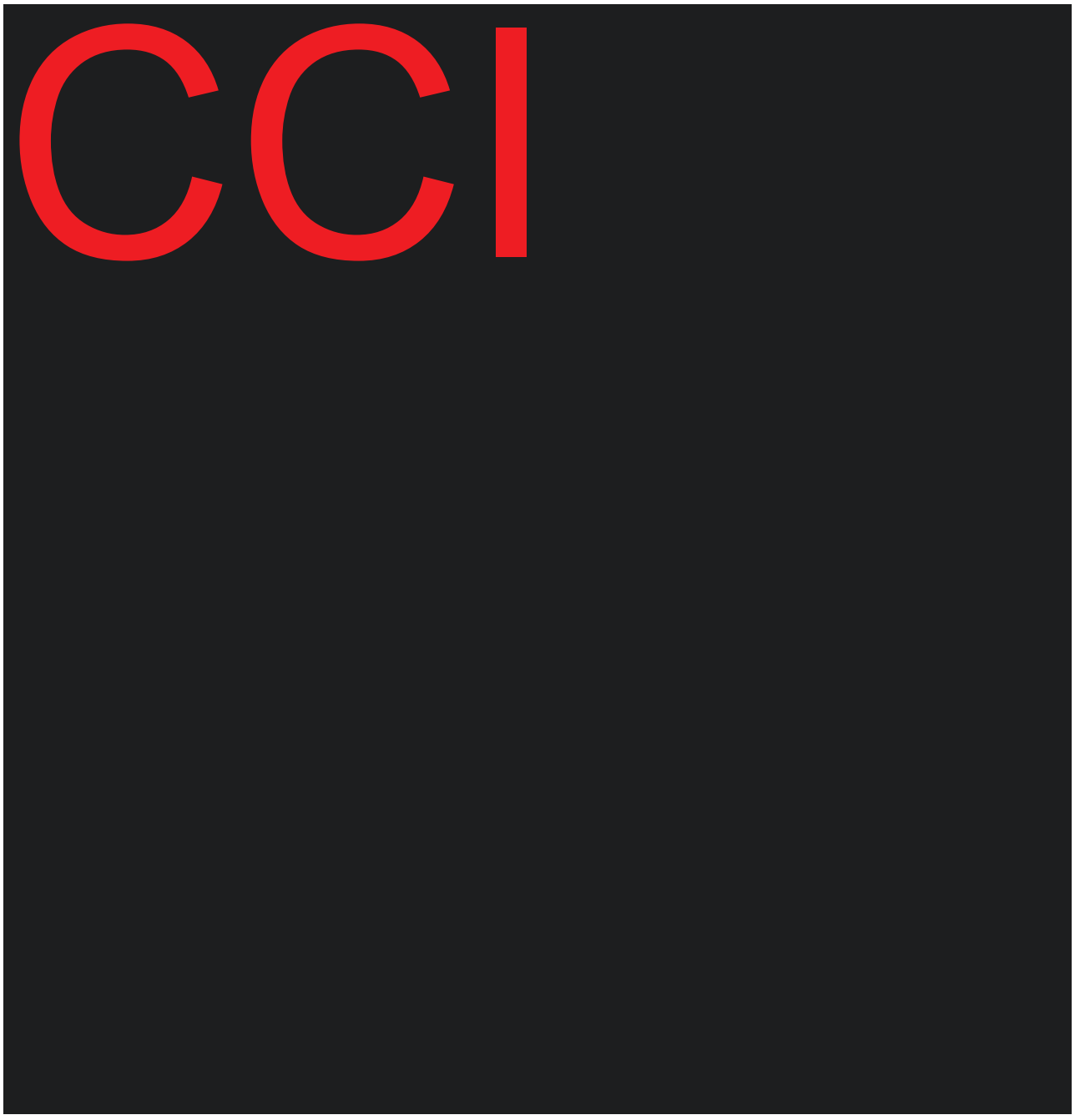
3 Months	6 Months	9 Months	12 Months	15 Months	75% Quantile	Median	25% Quantile
0.680	0.460	0.395	0.342	0.300	2.628	4.961	19.844

Table 24 OS Information and Assumptions

OS	Control	OS Scenario based on Pos. PFS Scenario 1
Med. Time from PD to Death and no ACT: < 500 days	7.7 months	8.7 months
Med. Time from PD to Death and ACT: < 500 days	12.1 months	13.1 months
Med. Time from PD to Death: > 500 days	6.0 months	7.0 months

Table 25 Overall Survival Function of Control Arm (Based on Multi-state Model)

6 Months	12 Months	18 Months	24 Months	30 Months	75% Quantile	Median
0.888	0.718	0.580	0.440	0.403	10.776	21.290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Appendix 10 Country-specific Requirements

Applicable for EU/EEA:

This clinical trial is conducted in compliance with the protocol, with Regulation [EU] No 536/2014 and with the principles of good clinical practice.

When cases meet the SUSAR criteria for submission to Eudravigilance database, they will be submitted via gateway, according to distribution rules set up in the Sponsor's safety database.

Appendix 11 Protocol Amendment History

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

Version 4.1, 10 March 2025

Section # and Name	Description of Change	Brief Rationale
8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting	Added SUSARs to list of terms defined in Appendix 4	To direct Investigators to SUSAR definition
8.3.3 Regulatory Reporting Requirements for Serious Adverse Events	Added reporting requirements for SUSARs	To be in accordance with Clinical Trial Directive/EU CTR
Appendix 2 Study Governance, Regulatory and Ethical Considerations	Added a clarification that protocol will be conducted in compliance with Regulation [EU] No 536/2014	To be in accordance with Clinical Trial Directive/EU CTR
Appendix 4	Added SUSAR definition	To be in accordance with Clinical Trial Directive/EU CTR
Appendix 10 Country-specific Requirements	Added Appendix 10 to describe submission of SUSAR to Eudravigilance database	To be in accordance with Clinical Trial Directive/EU CTR

Version 4.0, 25 September 2024

The SoAs for Version 4.0 are also presented below the summary of changes enacted with Version 4.0. Note: The Version 4 SoAs presented in this appendix are not valid for the current Version 5.0.

Section # and Name	Description of Change	Brief Rationale
Title Page	Changed the EudraCT number (2021-003669-36) to the EUCT number (2023-510139-12-00)	Due to EU CTR transition
Synopsis and Section 3 Objectives and Endpoints	For the secondary objective of Duration of Response, a criterion was added that participants must have an objective response according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, as assessed by the Investigator, with the first-line platinum-containing chemotherapy	For clarification
Synopsis (Study Intervention Groups and Duration) and Section 4.1 Overall design	Added statement that “permitted visit windows are detailed in the schedule of activities”.	For clarity and added information for Investigators

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities Table 2	Intervention Period – deleted "Until acceptable toxicity"	For consistency with other tables and because there are other reasons participants may discontinue study intervention
1.3 Schedule of Activities Table 4	Added "30-day" to the SFU and to Sampling notes column to distinguish from 90-day follow-up	For clarity
1.3 Schedule of Activities Table 4	Deleted asterisk from Sacituzumab Govitecan PK indicating EOI sample at Cycle 2 Day 8 (Week 5) and added back asterisk for Cycle 2 Day 1 (Week 4)	To correct error from Version 3.0
1.3 Schedule of Activities Table 4	Corrected note to indicate EOI sample at Day 22 (Cycle 2 Day 1)	To correct error from Version 3.0
1.3 Schedule of Activities Table 5	Added "30-day" to the FU and to Sampling notes column to distinguish from 90-day follow-up	For clarity
1.3 Schedule of Activities Table 5	Deleted asterisks from Group C Avelumab and M6223 PK indicating EOI sample at Cycle 3 Day 1 (Week 5) and added asterisks for Cycle 2 Day 1 (Week 3)	To correct error from Version 3.0
1.3 Schedule of Activities Table 6	Added "30 and 90-day" to the EOT/SFU column and to Sampling notes	For clarity
2.3.1 Risk Assessment – Table 7 Risk Assessment Table	Added risk for patients with pre-existing autoimmune disease, that the risk of immune-mediated adverse reactions following immune-checkpoint inhibitor therapy may be increased	Updated information from observational studies
6.3.2 Blinding Blinding Method	Updated to state that the study team will be fully unblinded at the interim analysis	The Sponsor has reevaluated the potential impact of bias introduced by fully unblinding against the value of getting unblinded information early to be able to plan future clinical development.
6.5.1 Avelumab Immune-related Adverse Events	Added sclerosing cholangitis, arthritis, polymyalgia rheumatica and Sjogren's syndrome to list of important identified risks; immune-related myocarditis and pancreatitis were moved and placed under the umbrella term of "other immune-related events"	Updated according to latest avelumab Investigator's Brochure
6.5.2 Sacituzumab Govitecan	Added statement that granulocyte colony-stimulating factor should be administered as clinically indicated when absolute neutrophile count is below 1500/mm^3 on Day 1 of any cycle or neutrophil count below is 1000/mm^3 on Day 8 of any cycle until resolved to ≤ Grade 1 and that in the case of Grade 4 neutropenia, both drugs should be interrupted and resumed once the participant has recovered	Additional information for Investigators
9.2 Sample Size Determination	Updated text regarding trigger for the interim and final analyses	For greater clarity

Section # and Name	Description of Change	Brief Rationale
9.4.4 Sequence of Analyses Table 24 Sequence of Analysis	Changed timing of analysis from number of events "per treatment-control comparison" to "in each of the treatment-control comparisons"	The initial protocol was designed with the expectation of adding additional investigation and control groups over the study's duration to be able to control the number of events needed to achieve a specific probability of success for each treatment-control comparison and analyze intervention and control groups in batches; however, given that all investigational treatment groups are now compared against the same control group, and in the absence of a planned futility analysis to prematurely stop the trial, there is no longer a need to independently control the number of events. The desired probability of success for each treatment-control comparison is deemed met upon the completion of the last comparison reaching the necessary number of events.
9.4.4 Sequence of Analyses Table 24 Sequence of Analysis	Deleted notes	with changes to the table, notes are no longer needed
Appendix 5 Table A 4 Endocrine Toxicities	4.3. Pituitary – Hypophysitis* - added note to permanently discontinue avelumab therapy for recurrent Grade ≥ 3 hypophysitis	To be in alignment with latest avelumab Investigator's Brochure

Table 1 Group B Schedule of Activities (not applicable for current Protocol Version 5.0)

Assessments and Procedures Group B: Avelumab + Sacituzumab Govitecan	Screening	Intervention Period			End of Treatment/Follow up After Last Dose				Notes
		Avelumab + sacituzumab govitecan			EOT	Safety FU		Long-Term FU	
		Sacituzumab govitecan Days 1 and 8 of each 3-week cycle		Avelumab Q2W	7 days	30 days	90 days	Every 12 weeks	
		Week 1, 4, 7, 10, 13, 16, 19, 22…	Week 2, 5, 8, 11, 14, 17, 20, 23…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Window	**Within 28 days prior to randomization.**	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of avelumab the minimum interval in between doses can be no less than 10 days. In case of SG, if treatment delays are greater than 2 days, the next treatment date should be calculated based on the actual treatment day or Day 8 should be skipped. Day 8 administration of SG must be no less than 7 days after Day 1.
Informed Consent	X								
Inclusion and Exclusion Criteria	X								Recheck clinical status before randomization.
Demography	X								
Physical Examination	X	X		X (see Notes)	X	X			Full PE at Screening and EOT. At all other visits should be a brief PE (i.e. a signs and symptom-orientated physical examination) that includes, at a minimum, assessments of those symptoms that are tailored to the participant's symptoms. If the Screening PE was performed within 3 days prior to Day 1, it does not have to be repeated at Visit 1. Every 3 weeks (Day 1 of each SG 3-week cycle) or every 2 weeks (Day 1 of every avelumab dosing) if SG is discontinued before avelumab.

Assessments and Procedures Group B: Avelumab + Sacituzumab Govitecan	Screening	Intervention Period			End of Treatment/Follow up After Last Dose				Notes
		Avelumab + sacituzumab govitecan			EOT	Safety FU		Long-Term FU	
		Sacituzumab govitecan Days 1 and 8 of each 3-week cycle		Avelumab Q2W	7 days	30 days	90 days	Every 12 weeks	
		Week 1, 4, 7, 10, 13, 16, 19, 22…	Week 2, 5, 8, 11, 14, 17, 20, 23…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Window	**Within 28 days prior to randomization.**	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of avelumab the minimum interval in between doses can be no less than 10 days. In case of SG, if treatment delays are greater than 2 days, the next treatment date should be calculated based on the actual treatment day or Day 8 should be skipped. Day 8 administration of SG must be no less than 7 days after Day 1.
Vital Signs	X	X	X	X	X	X			Includes height (collect at Screening only), respiratory rate, temperature, weight, blood pressure, and pulse rate, which should be taken before other study procedures (e.g., blood draws study drug premedication) with the participant in the seated position after the participant has been sitting quietly for at least 5 minutes.
ECOG Performance Status	X	X		X (see Notes)	X	X			Every 3 weeks (Day 1 of each SG 3-week cycle) or every 2 weeks (Day 1 of every avelumab dosing) if SG is discontinued before avelumab.
Medical and Oncological Conditions	X								To include tobacco use. See Section 8 for oncological history details.
Serum/Urine Pregnancy Test (WOCBP only)	X			X (see Notes)	X	X			Every 4 weeks (every other avelumab dosing if SG is discontinued before avelumab).
Hepatitis B and C screening	X								Hepatitis B surface antigen, hepatitis B surface antigen antibody, hepatitis B core antibody, hepatitis C virus antibody (See Appendix 6).

Assessments and Procedures Group B: Avelumab + Sacituzumab Govitecan	Screening	Intervention Period			End of Treatment/Follow up After Last Dose				Notes
		Avelumab + sacituzumab govitecan			EOT	Safety FU		Long-Term FU	
		Sacituzumab govitecan Days 1 and 8 of each 3-week cycle		Avelumab Q2W	7 days	30 days	90 days	Every 12 weeks	
		Week 1, 4, 7, 10, 13, 16, 19, 22…	Week 2, 5, 8, 11, 14, 17, 20, 23…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Window	**Within 28 days prior to randomization.**	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of avelumab the minimum interval in between doses can be no less than 10 days. In case of SG, if treatment delays are greater than 2 days, the next treatment date should be calculated based on the actual treatment day or Day 8 should be skipped. Day 8 administration of SG must be no less than 7 days after Day 1.
Clinical Laboratory Tests Full hematology[a] and Coagulation	X	X	X	X (see Notes)	X	X			See Appendix 6. Samples for clinical laboratory tests for all treatment cycles may be drawn up to 72 hours prior of infusion. For Cycle 1 Day 1, results must be reviewed and meet inclusion criteria prior to infusion. [a]Dosing is permitted if absolute neutrophil count is ≥ 1500/mm^3 on Day 1 and ≥ 1000/ mm^3 on Day 8 Day 1 of every avelumab dosing if SG is discontinued before avelumab.
Full serum chemistry	X	X	X	X (see Notes)					Full serum chemistry to be performed at Screening, Cycle 1 Day 1, and Day 1 of every cycle thereafter. If SG is discontinued before avelumab then full serum chemistry should be performed at every 3rd avelumab dosing or if clinically indicated.

Assessments and Procedures Group B: Avelumab + Sacituzumab Govitecan	Screening	Intervention Period			End of Treatment/Follow up After Last Dose				Notes
		Avelumab + sacituzumab govitecan			EOT	Safety FU		Long-Term FU	
		Sacituzumab govitecan Days 1 and 8 of each 3-week cycle		Avelumab Q2W	7 days	30 days	90 days	Every 12 weeks	
		Week 1, 4, 7, 10, 13, 16, 19, 22…	Week 2, 5, 8, 11, 14, 17, 20, 23…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Window	**Within 28 days prior to randomization.**	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of avelumab the minimum interval in between doses can be no less than 10 days. In case of SG, if treatment delays are greater than 2 days, the next treatment date should be calculated based on the actual treatment day or Day 8 should be skipped. Day 8 administration of SG must be no less than 7 days after Day 1.
Core serum chemistry				X (see notes)	X	X	X		If SG is still ongoing, core serum chemistry will be performed prior to avelumab administration if clinically indicated. If SG is discontinued before avelumab, core serum chemistry will be performed at every avelumab administration if no full serum chemistry is performed.
Thyroid Function (TSH and FT4 [or total T4])	X	Every 6 weeks starting Week 7 or earlier if clinically indicated			X				Every 6 weeks at Cycle 3 (Week 7) and Cycle 5 (Week 13), then every 3 avelumab administrations (Week 19, 25, 31…).
ACTH	X								
Urinalysis	X	If clinically indicated			X	X			
12-lead ECG	X	If clinically indicated			X				Electrocardiograms will be recorded after the participant has been in a supine position breathing quietly for at least 5 minutes.
Randomization		X							

Assessments and Procedures Group B: Avelumab + Sacituzumab Govitecan	Screening	Intervention Period			End of Treatment/Follow up After Last Dose				Notes
		Avelumab + sacituzumab govitecan			EOT	Safety FU		Long-Term FU	
		Sacituzumab govitecan Days 1 and 8 of each 3-week cycle		Avelumab Q2W	7 days	30 days	90 days	Every 12 weeks	
		Week 1, 4, 7, 10, 13, 16, 19, 22…	Week 2, 5, 8, 11, 14, 17, 20, 23…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Window	**Within 28 days prior to randomization.**	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of avelumab the minimum interval in between doses can be no less than 10 days. In case of SG, if treatment delays are greater than 2 days, the next treatment date should be calculated based on the actual treatment day or Day 8 should be skipped. Day 8 administration of SG must be no less than 7 days after Day 1.
Avelumab				X					Avelumab Q2W until unacceptable toxicity. When infusions of sacituzumab govitecan and avelumab occur on the same days, treatment administration will start with avelumab and then the combination agent.
Sacituzumab govitecan		X	X						Sacituzumab govitecan: Day 1 and 8 of 21-day treatment cycles until unacceptable toxicity. When infusions of sacituzumab govitecan and avelumab occur on the same days, treatment administration will start with avelumab and then sacituzumab govitecan.
AE & SAE Review	X	⇐==========⇒			X	X	X		
Concomitant Medication Review	X	⇐==========⇒			X	X			

Assessments and Procedures Group B: Avelumab + Sacituzumab Govitecan	Screening	Intervention Period			End of Treatment/Follow up After Last Dose				Notes
		Avelumab + sacituzumab govitecan			EOT	Safety FU		Long-Term FU	
		Sacituzumab govitecan Days 1 and 8 of each 3-week cycle		Avelumab Q2W	7 days	30 days	90 days	Every 12 weeks	
		Week 1, 4, 7, 10, 13, 16, 19, 22…	Week 2, 5, 8, 11, 14, 17, 20, 23…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Window	**Within 28 days prior to randomization.**	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of avelumab the minimum interval in between doses can be no less than 10 days. In case of SG, if treatment delays are greater than 2 days, the next treatment date should be calculated based on the actual treatment day or Day 8 should be skipped. Day 8 administration of SG must be no less than 7 days after Day 1.
Tumor Assessments	X	X: (see Notes)							After Screening, the visit window for tumor assessments will be ± 5 days. Tumor assessments will be Q8W for the 1st year after randomization and Q12W thereafter. CT/MRI scans will be collected until PD is assessed by the Investigator according to RECIST v1.1 regardless of initiation of subsequent anticancer therapy. Confirmatory imaging of PD required at least 4 weeks from initial assessment. See Section 8.1.
Subsequent anticancer therapy					X	X	X	X	
Survival Assessment						X	X	X	90-day and long-term follow up may be telephone visits.
PK and Biomarkers	See Notes								See Table 4

Assessments and Procedures Group B: Avelumab + Sacituzumab Govitecan	Screening	Intervention Period			End of Treatment/Follow up After Last Dose				Notes
		Avelumab + sacituzumab govitecan			EOT	Safety FU		Long-Term FU	
		Sacituzumab govitecan Days 1 and 8 of each 3-week cycle		Avelumab Q2W	7 days	30 days	90 days	Every 12 weeks	
		Week 1, 4, 7, 10, 13, 16, 19, 22…	Week 2, 5, 8, 11, 14, 17, 20, 23…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Window	**Within 28 days prior to randomization.**	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of avelumab the minimum interval in between doses can be no less than 10 days. In case of SG, if treatment delays are greater than 2 days, the next treatment date should be calculated based on the actual treatment day or Day 8 should be skipped. Day 8 administration of SG must be no less than 7 days after Day 1.
PRO				X	X				NCCN FACT FBISI-18, CCI [redacted] to be completed prior to infusion. See Section 8.9. ePROs will line up with avelumab infusions Q2W until a patient reached radiological PD. If the patient continues with treatment post-PD, they will then get the ePRO Q4W (i.e. every other avelumab infusion).

ACTH = adrenocorticotropic hormone; AE = adverse event; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ePRO = electronic patient reported outcome; CCI [redacted]; FT4 = free thyroxine; FU = follow up; MRI = magnetic resonance imaging; NCCN FACT FBISI-18 = NCCN/FACT bladder symptom index; PD = progressive disease; PE = physical examination; PK = pharmacokinetics; PRO = patient reported outcomes; Q2W = every 2 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; random = randomization; RECIST v1.1= Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = serious adverse event; SG = sacituzumab govitecan; TSH = thyroid-stimulating hormone; CCI [redacted]; WOCBP = women of childbearing potential.

Table 2 Group A and C Schedule of Activities (not applicable for current Protocol Version 5.0)

Assessments and Procedures Group A: Avelumab Group C: Avelumab + M6223	Screening	Intervention Period	End of Treatment / Follow up After Last Dose				Notes
		Q2W	EOT	Safety FU		Long-Term FU	
		Weeks 1, 3, …	7 days	30 days	90 days	Every 12 weeks	
Visit Window	**Within 28 days prior to random.**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of treatment delays greater than 2 days, the next treatment date should be calculated based on the actual treatment day. Participants should not be dosed before 10 days from the last dose.
Informed Consent	X						
Inclusion and Exclusion Criteria	X						Recheck clinical status before randomization.
Demography	X						
Physical Examination	X	X	X	X			Full PE at Screening and EOT. At all other visits should be a brief PE (i.e. a signs and symptom-orientated physical examination) that includes, at a minimum, assessments of those symptoms that are tailored to the participant's symptoms. If the Screening PE was performed within 3 days prior to Day 1, it does not have to be repeated at Visit 1.
Vital Signs	X	X	X	X			Includes height (collect at Screening only), respiratory rate, temperature, weight, blood pressure and pulse rate, which should be taken before other study procedures (e.g., blood draws study drug premedication) with the participant in the seated position after the participant has been sitting quietly for at least 5 minutes.
ECOG Performance Status	X	Every 4 weeks	X	X			Every 4 weeks (every other avelumab dosing).
Medical and Oncological Conditions	X						To include tobacco use. See Section 8 for oncological history details.

Assessments and Procedures Group A: Avelumab Group C: Avelumab + M6223	Screening	Intervention Period	End of Treatment / Follow up After Last Dose				Notes
		Q2W	EOT	Safety FU		Long-Term FU	
		Weeks 1, 3, …	7 days	30 days	90 days	Every 12 weeks	
Visit Window	**Within 28 days prior to random.**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of treatment delays greater than 2 days, the next treatment date should be calculated based on the actual treatment day. Participants should not be dosed before 10 days from the last dose.
Serum/Urine Pregnancy Test (WOCBP only)	X	Every 4 weeks	X	X			Every 4 weeks (every other avelumab dosing).
Hepatitis B and C screening	X						Hepatitis B surface antigen, hepatitis B surface antigen antibody, hepatitis B core antibody, hepatitis C virus antibody (Refer to Appendix 6).
Clinical Laboratory Tests Full hematology and coagulation	X	X	X	X			Full hematology and coagulation test as detailed in Appendix 6. Samples for clinical laboratory tests for all treatment cycles may be drawn up to 72 hours prior of infusion. For Cycle 1 Day 1, results must be reviewed and meet inclusion criteria prior to infusion.
Full serum chemistry	X	X (See notes)					Full serum chemistry at Screening and every visit for first 2 cycles and every 6 weeks thereafter.
Core serum chemistry		X (See notes)	X	X	X		Core serum chemistry will be performed on day 1 of every avelumab and/or M6223 administration, if no full serum chemistry is performed.
Thyroid Function (TSH and FT4 [or total T4])	X	Every 6 weeks or earlier if clinically indicated	X				Every 6 weeks starting at Week 7 (or earlier if clinically indicated), then 13, 19…
ACTH	X						
Urinalysis	X	If clinically indicated	X	X			

Assessments and Procedures Group A: Avelumab Group C: Avelumab + M6223	Screening	Intervention Period	End of Treatment / Follow up After Last Dose				Notes
		Q2W	EOT	Safety FU		Long-Term FU	
		Weeks 1, 3, …	7 days	30 days	90 days	Every 12 weeks	
Visit Window	**Within 28 days prior to random.**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of treatment delays greater than 2 days, the next treatment date should be calculated based on the actual treatment day. Participants should not be dosed before 10 days from the last dose.
12-lead ECG	X	If clinically indicated	X				Electrocardiograms will be recorded after the participant has been in a supine position breathing quietly for at least 5 minutes.
Randomization		X					
Avelumab		X					Group A: avelumab monotherapy. Group C: avelumab + M6223. When infusions of M6223 and avelumab occur on the same days, treatment administration will start with avelumab and then the combination agent.
M6223		X					
AE & SAE Review	X	⇐==========⇒	X	X	X		
Concomitant Medication Review	X	⇐==========⇒	X	X			
Tumor Assessments	X	X: see Notes					After Screening, the visit window for tumor assessments will be ± 5 days. Tumor assessments will be Q8W for the first year after randomization and Q12W thereafter. CT/MRI scans will be collected until PD is assessed by the Investigator according to RECIST v1.1. regardless of initiation of subsequent anticancer therapy. Confirmatory imaging of PD required at least 4 weeks from initial assessment. See Section 8.1.
Subsequent anticancer therapy			X	X	X	X	

Assessments and Procedures Group A: Avelumab Group C: Avelumab + M6223	Screening	Intervention Period	End of Treatment / Follow up After Last Dose				Notes
		Q2W	EOT	Safety FU		Long-Term FU	
		Weeks 1, 3, …	7 days	30 days	90 days	Every 12 weeks	
Visit Window	**Within 28 days prior to random.**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of treatment delays greater than 2 days, the next treatment date should be calculated based on the actual treatment day. Participants should not be dosed before 10 days from the last dose.
Survival Assessment				X	X	X	90-day and long-term follow up may be telephone visits.
PK and Biomarkers	See Notes						See Table 5.
PRO		X	X				NCCN FACT FBISI-18, CCI [redacted], CCI [redacted] to be completed prior to infusion. See Section 8.9. ePROs will line up with avelumab infusions Q2W until a patient reached radiological PD. If the patient continues with treatment post-PD, they will then get the ePRO Q4W (i.e. every other avelumab infusion).

ACTH = adrenocorticotropic hormone; AE = adverse event; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ePRO = electronic patient reported outcome; CCI [redacted]; FT4 = free thyroxine; MRI = magnetic resonance imaging; NCCN FACT FBISI-18 = NCCN/FACT bladder symptom index; PD = progressive disease; PE = physical examination; Q2W = every 2 weeks; Q8W = every 8 weeks, Q12W = every 12 weeks; RECIST v1.1= Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Table 3 Group D Schedule of Activities (not applicable for current Protocol Version 5.0)

Assessments and Procedures Group D: Avelumab + NKTR-255	Screening (within 28 days prior to random.)	Intervention Period		End of Treatment/Follow-up After Last Dose				Notes
		Avelumab + NKTR-255 PD		EOT	Safety FU		Long-Term FU	
		NKTR-255 Q4W	Avelumab Q2W	7 days (± 7 days)	30 days (± 7 days)	90 days (± 7 days)	Every 12 weeks	
		Week 1, 5,9,13,17,21…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Windows	**Within 28 days prior to randomization**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of treatment delays greater than 2 days, the next treatment date should be calculated based on the actual treatment day. In the case of avelumab, participants should not be dosed before 10 days from the last dose.
Informed Consent	X							
Inclusion and Exclusion Criteria	X							Recheck clinical status before randomization.
Demography	X							
Physical Examination	X	X	X (see Notes)	X	X			Full PE at Screening and EOT. At all other visits should be a brief PE (i.e. a signs and symptom-orientated physical examination) that includes, at a minimum, assessments of those symptoms that are tailored to the participant's symptoms. If the Screening PE was performed within 3 days prior to Day 1, it does not have to be repeated at Visit 1.
Vital Signs	X	X	X	X	X			Includes height (collect at Screening only), respiratory rate, temperature, weight, blood pressure, and pulse rate, which should be taken before other study procedures (e.g., blood draws study drug premedication) with the participant in the seated position after the participant has been sitting quietly for at least 5 minutes.

Assessments and Procedures Group D: Avelumab + NKTR-255	Screening (within 28 days prior to random.)	Intervention Period		End of Treatment/Follow-up After Last Dose				Notes
		Avelumab + NKTR-255 PD		EOT	Safety FU		Long-Term FU	
		NKTR-255 Q4W	Avelumab Q2W	7 days (± 7 days)	30 days (± 7 days)	90 days (± 7 days)	Every 12 weeks	
		Week 1, 5,9,13,17,21…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Windows	**Within 28 days prior to randomization**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of treatment delays greater than 2 days, the next treatment date should be calculated based on the actual treatment day. In the case of avelumab, participants should not be dosed before 10 days from the last dose.
ECOG Performance Status	X	X	X (see Notes)	X	X			Every 2 weeks
Medical/Oncological condition	X							To include tobacco use. See Section 8 for oncological history details.
Serum/Urine Pregnancy Test (WOCBP only)	X	X	X (see Notes)	X	X			Every 4-week cycle of avelumab + NKTR-255
Hepatitis B and C screening	X							Hepatitis B surface antigen, hepatitis B surface antigen antibody, hepatitis B core antibody, hepatitis C virus antibody (Refer to Appendix 6).
Clinical Laboratory Tests Full hematology and Coagulation	X	X	X	X	X			See Appendix 6. Samples for clinical laboratory tests for all treatment cycles may be drawn up to 72 hours prior of infusion. For Cycle 1 Day 1, results must be reviewed and meet inclusion criteria prior to infusion.

Assessments and Procedures Group D: Avelumab + NKTR-255	Screening (within 28 days prior to random.)	Intervention Period		End of Treatment/Follow-up After Last Dose				Notes
		Avelumab + NKTR-255 PD		EOT	Safety FU		Long-Term FU	
		NKTR-255 Q4W	Avelumab Q2W	7 days (± 7 days)	30 days (± 7 days)	90 days (± 7 days)	Every 12 weeks	
		Week 1, 5,9,13,17,21…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Windows	**Within 28 days prior to randomization**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of treatment delays greater than 2 days, the next treatment date should be calculated based on the actual treatment day. In the case of avelumab, participants should not be dosed before 10 days from the last dose.
Full serum chemistry	X	X	X					Full serum chemistry to be performed at Screening. Day 1 of every 3rd avelumab dosing (every 6 weeks) if NKTR-255 is discontinued before avelumab.
Core serum chemistry			X (See notes)	X	X	X	-	Core serum chemistry will be performed on day 1 of every avelumab administration if no full serum chemistry is performed.
Thyroid Function (TSH and FT4 [or total T4])	X	Every 6 weeks starting Week 7 or earlier if clinically indicated		X				Every 6 weeks starting at Week 7 (or earlier if clinically indicated), then on Week 13, Week 19…
ACTH	X							
Urinalysis	X	If clinically indicated		X	X			
12-lead ECG	X	X		X				Electrocardiograms will be recorded after the participant has been in a supine position breathing quietly for at least 5 minutes. ECG will be collected at predose of NKTR-255. Additional ECG(s) will be collected at the end of infusion on C1D1 (Week 1), C2D1 (Week 5), and C3D1 (Week 9). End-of-infusion ECGs should be collected within 30 minutes of the end of infusion.

Assessments and Procedures Group D: Avelumab + NKTR-255	Screening (within 28 days prior to random.)	Intervention Period		End of Treatment/Follow-up After Last Dose				Notes
		Avelumab + NKTR-255 PD		EOT	Safety FU		Long-Term FU	
		NKTR-255 Q4W	Avelumab Q2W	7 days (± 7 days)	30 days (± 7 days)	90 days (± 7 days)	Every 12 weeks	
		Week 1, 5,9,13,17,21…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Windows	**Within 28 days prior to randomization**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of treatment delays greater than 2 days, the next treatment date should be calculated based on the actual treatment day. In the case of avelumab, participants should not be dosed before 10 days from the last dose.
Randomization		X						
Avelumab			X					Avelumab Q2W until unacceptable toxicity for all the cohorts.
NKTR-255		X						NKTR-255 Day 1 Q4W treatment cycles until unacceptable toxicity. Cohort D infuse NKTR-255 first with a 3-hour period before infusing avelumab. If no IRR occurs for the first 2 cycles, the sites can shorten the in-between infusion period to 1 hour.
AE & SAE Review	X	⇐==========⇒		X	X	X		
Concomitant Medication Review	X	⇐==========⇒		X	X			
Tumor Assessments	X	X (see Notes)						After Screening, the visit window for tumor assessments will be ± 5 days. Tumor assessments will be Q8W for the 1st year after randomization and Q12W thereafter. CT/MRI scans will be collected until PD is assessed by the Investigator according to RECIST v1.1 regardless of initiation of subsequent anticancer therapy. Confirmatory imaging of PD required at least 4 weeks from initial assessment. See Section 8.1.

Assessments and Procedures Group D: Avelumab + NKTR-255	Screening (within 28 days prior to random.)	Intervention Period		End of Treatment/Follow-up After Last Dose				Notes
		Avelumab + NKTR-255 PD		EOT	Safety FU		Long-Term FU	
		NKTR-255 Q4W	Avelumab Q2W	7 days (± 7 days)	30 days (± 7 days)	90 days (± 7 days)	Every 12 weeks	
		Week 1, 5,9,13,17,21…	Week 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23…					
Visit Windows	**Within 28 days prior to randomization**	**± 2 days**	**± 2 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	In case of treatment delays greater than 2 days, the next treatment date should be calculated based on the actual treatment day. In the case of avelumab, participants should not be dosed before 10 days from the last dose.
Subsequent anticancer therapy				X	X	X	X	
Survival Assessment					X	X	X	90-day and long-term follow-up may be telephone visits.
PK and Biomarkers	See Notes				X	X		On 30 days and 90 days safety FU, only PK and immunogenicity will be assessed. See Table 6.
PRO			X	X				NCCN FACT FBISI-18, CCI [redacted] to be completed prior to infusion. ePROs will line up with avelumab infusions Q2W until a patient reached radiological PD. If the patient continues with treatment post-PD, they will then get the ePRO Q4W (i.e. every other avelumab infusion).

ACTH = adrenocorticotropic hormone; AE = adverse event; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ePRO = electronic patient reported outcome; CCI [redacted]; FT4 = free thyroxine; FU = follow-up; MRI = magnetic resonance imaging; NCCN FACT FBISI-18 = NCCN/FACT bladder symptom index; PD = progressive disease; PE = physical examination; PK = pharmacokinetics; PRO = patient reported outcomes; Q2W = every 2 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; random = randomization; RECIST v1.1= Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = serious adverse event; SG = sacituzumab govitecan; CCI [redacted] 1A1; WOCBP = women of childbearing potential.

Table 4 Group B Bioanalytical and Biomarkers Schedule of Assessments (not applicable for current Protocol Version 5.0)

Assessments & Procedures Group B: Avelumab + Sacituzumab Govitecan	Screening	Intervention Period (Weeks) Q3W								EOT/ 30-day SFU	Notes
	within 28 days prior to randomi-zation	Cycle 1 Day 1 (Week 1)	Cycle 1 Day 8 (Week 2)	Cycle 1 Day 15 (Week 3)	Cycle 2 Day 1 (Week 4)	Cycle 2 Day 8 (Week 5)	Cycle 3 Day 1 (Week 7)	≥ Week 13 and ≤ Week 25 Day 1	> Week 25 and ≤ Week 109 Day 1	7 days (± 7 days) after last dose and 30-day SFU	
Avelumab PK[a]		X*		X		X*	X	Every 6 weeks	Every 12 weeks	X	• Predosing PK samples: within 2 hours prior to IV infusion on Day 1 (C1D1), 15 (C1D15), 29 (C2D8), 43 (C3D1), and then every 6-week intervals up to and including Week 25, then every 12 weeks, up to Week 109, and EOT, and SFU. • Post infusion samples will be collected at the EOI on Days 1 (C1D1) and 29 (C2D8). * PK samples will be collected both prior to infusion (within 2 hours) and also at the EOI (within 5 minutes). The exact time of each draw should be recorded. Blood samples should be collected prior to CT scan if scheduled on the same day.
Immunogenicity for avelumab		X		X			X	Every 6 weeks	Every 12 weeks	X	Immunogenicity samples will be collected within 2 hours prior to infusion on Days 1 (C1D1), 15 (C1D15), 43 (C3D1), and then every 6-week intervals up to and including Week 25, and then every 12 weeks up to Week 109, EOT, and 30-day SFU.

Assessments & Procedures Group B: Avelumab + Sacituzumab Govitecan	Screening	Intervention Period (Weeks) Q3W								EOT/ 30-day SFU	Notes
	within 28 days prior to randomi-zation	Cycle 1 Day 1 (Week 1)	Cycle 1 Day 8 (Week 2)	Cycle 1 Day 15 (Week 3)	Cycle 2 Day 1 (Week 4)	Cycle 2 Day 8 (Week 5)	Cycle 3 Day 1 (Week 7)	≥ Week 13 and ≤ Week 25 Day 1	> Week 25 and ≤ Week 109 Day 1	7 days (± 7 days) after last dose and 30-day SFU	
PK for Sacituzumab govitecan (derived from unconjugated SN-38 and total SN-38)[a]		X*	X		X*	X	X	Days 1 and 8 every other cycle (every 6 weeks)	Days 1 and 8 every 4th cycle (every 12 weeks)	X	• Predosing PK samples will be collected at the following time points (within 2 hours prior to IV infusion) on Days 1 (C1D1), 8 (C1D8), 22 (C2D1), 29 (C2D8), 43 (C3D1), and then Days 1 and 8 every other cycle (6-week intervals) up to and including Week 25, then Days 1 and 8 of every 4th cycle (12 weeks) up to Week 109, EOT, and SFU. • Post infusion samples will be collected at the EOI on Days 1 (C1D1) and 22 (C2D1). *PK samples will be collected both prior to infusion (within 2 hours) and also at the EOI (within 5 minutes). The exact time of each draw should be recorded. Blood samples should be collected prior to CT scan if scheduled on the same day.
Immunogenicity for Sacituzumab govitecan		X			X		X	Every 6 weeks	Every 12 weeks	X	Immunogenicity samples will be collected within 2 hours prior to infusion on Days 1 (C1D1), 22 (C2D1), 43 (C3D1), and then every 6-week intervals up to and including Week 25, then, and then every 12 weeks up to Week 109, EOT, and 30-day SFU.

	Screening	Intervention Period (Weeks) Q3W								EOT/ 30-day SFU	Notes
Assessments & Procedures Group B: Avelumab + Sacituzumab Govitecan	within 28 days prior to randomi-zation	Cycle 1 Day 1 (Week 1)	Cycle 1 Day 8 (Week 2)	Cycle 1 Day 15 (Week 3)	Cycle 2 Day 1 (Week 4)	Cycle 2 Day 8 (Week 5)	Cycle 3 Day 1 (Week 7)	≥ Week 13 and ≤ Week 25 Day 1	> Week 25 and ≤ Week 109 Day 1	7 days (± 7 days) after last dose and 30-day SFU	

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Assessments & Procedures Group B: Avelumab + Sacituzumab Govitecan	Screening within 28 days prior to randomi-zation	Intervention Period (Weeks) Q3W Cycle 1 Day 1 (Week 1)	Cycle 1 Day 8 (Week 2)	Cycle 1 Day 15 (Week 3)	Cycle 2 Day 1 (Week 4)	Cycle 2 Day 8 (Week 5)	Cycle 3 Day 1 (Week 7)	≥ Week 13 and ≤ Week 25 Day 1	> Week 25 and ≤ Week 109 Day 1	EOT/ 30-day SFU 7 days (± 7 days) after last dose and 30-day SFU	Notes
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C1D1 = Cycle 1 Day 1; C1D15 = Cycle 1 Day 15; C2D8 = Cycle 2 Day 8; C3D1 = Cycle 3 Day 1; CT = computed tomography; CCI ; CCI ; EOI = end of infusion; EOT = end of treatment; CCI ; CCI ; IV = intravenous; PD = progressive disease; CCI ; PK = pharmacokinetic; Q2W = every 2 weeks; SFU = safety follow up; SG = sacituzumab govitecan.

a If one study intervention is prematurely discontinued, a PK sample for that study intervention should only be collected at the EOT and SFU visits.

Table 526 Group A and C Bioanalytical and Biomarkers Schedule of Assessments (not applicable for current Protocol Version 5.0)

Assessments & Procedures Group A: Avelumab Group C: Avelumab + M6223	Screening	Intervention Period (Weeks) Q2W											EOT/ 30-day SFU	Notes
	within 28 days prior to randomi-zation	Cycle 1 (Week 1)				Cycle 2 (Week 3)				Cycle 3 (Week 5)	≥ Week 11 and ≤ Week 23	> Week 23 and ≤ Week 107	7 days (± 7 days) after last dose and 30-day SFU	
Day		1	2	3	8	1	2	3	8	1	1	1		
Group A: Avelumab PK		X*				X				X*	Every 6 weeks	Every 12 weeks	X	Group A: PK samples for avelumab will be collected as follows: • Predosing PK samples will be collected within 2 hours prior to IV infusion on Day 1 (C1D1), Day 15 (C2D1), Day 29 (C3D1), then every 6 weeks up to and including Week 23, then every 12 weeks, up to Week 107, EOT, and 30-day SFU. • End of infusion samples will be collected at the EOI (within 5 minutes) on Day 1 (C1D1) and Day 29 (C3D1). *PK samples will be collected both prior to infusion (within 2 hours) and also at the EOI (within 5 minutes). The exact time of each draw should be recorded. Blood samples should be collected prior to CT scan if scheduled on the same day.

Assessments & Procedures Group A: Avelumab Group C: Avelumab + M6223	Screening	Intervention Period (Weeks) Q2W											EOT/ 30-day SFU	Notes
	within 28 days prior to randomi-zation	Cycle 1 (Week 1)				Cycle 2 (Week 3)				Cycle 3 (Week 5)	≥ Week 11 and ≤ Week 23	> Week 23 and ≤ Week 107	7 days (± 7 days) after last dose and 30-day SFU	
Day		1	2	3	8	1	2	3	8	1	1	1		
Group A: Immunogenicity for avelumab		X				X				X	Every 6 weeks	Every 12 weeks	X	For avelumab only: immunogenicity samples will be collected within 2 hours prior to infusion on Day 1 (C1D1), Day 15 (C2D1), Day 29 (C3D1), then every 6 weeks up to and including Week 23, then every 12 weeks, up to and including Week 107, and EOT, and 30-day SFU.
Group C: PK for Avelumab[a]		X*	X		X	X*	X		X	X	Every 6 weeks	Every 12 weeks	X	Group C: PK samples for avelumab and M6223 will be collected as follows: • Predosing PK samples will be collected within 2 hours prior to IV infusion on Day 1 (C1D1), Day 15 (C2D1), and Day 29 (C3D1), and then every 6 weeks up to and including Week 23, then every 12 weeks, up to and including Week 107, EOT, and 40-day SFU. • *PK samples will be collected both prior to infusion (within 2 hours) and also at the EOI (within 5 minutes). • Additional post infusion samples will be collected on Day 2 (C1D2), Day 8 (C1D8), Day 30 (C2D2), Day 36 (C2D8), i.e. 24 hours, 168 hours after the start of infusion in the cycle (within 2 hours).

Assessments & Procedures Group A: Avelumab Group C: Avelumab + M6223	Screening	Intervention Period (Weeks) Q2W											EOT/ 30-day SFU	Notes
	within 28 days prior to randomi-zation	Cycle 1 (Week 1)				Cycle 2 (Week 3)				Cycle 3 (Week 5)	≥ Week 11 and ≤ Week 23	> Week 23 and ≤ Week 107	7 days (± 7 days) after last dose and 30-day SFU	
Day		1	2	3	8	1	2	3	8	1	1	1		
														The exact time of each draw should be recorded. Blood samples should be collected prior to CT scan if scheduled on the same day.
Group C: PK for M6223[a]		X*	X		X	X*	X		X	X	Every 6 weeks	Every 12 weeks	X	*PK samples will be collected both prior to infusion (within 2 hours) and also at the EOI (within 5 minutes).
Group C: Immunogenicity for avelumab		X				X				X	Every 6 weeks	Every 12 weeks	X	For both avelumab & M6223: immunogenicity samples will be collected within 2 hours prior to infusion on Days 1(C1D1), 15 (C2D1), 29 (C3D1), and then every 6 weeks up to and including Week 23, then every 12 weeks, up to Week 107, and EOT, and 30-day SFU.
Group C Immunogenicity for M6223		X				X				X	Every 6 weeks	Every 12 weeks	X	

Assessments & Procedures Group A: Avelumab Group C: Avelumab + M6223	Screening	Intervention Period (Weeks) Q2W											EOT/ 30-day SFU	Notes
	within 28 days prior to randomi-zation	Cycle 1 (Week 1)				Cycle 2 (Week 3)				Cycle 3 (Week 5)	≥ Week 11 and ≤ Week 23	> Week 23 and ≤ Week 107	7 days (± 7 days) after last dose and 30-day SFU	
Day		1	2	3	8	1	2	3	8	1	1	1		

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Assessments & Procedures Group A: Avelumab Group C: Avelumab + M6223	Screening	Intervention Period (Weeks) Q2W											EOT/ 30-day SFU	Notes
	within 28 days prior to randomi-zation	Cycle 1 (Week 1)				Cycle 2 (Week 3)				Cycle 3 (Week 5)	≥ Week 11 and ≤ Week 23	> Week 23 and ≤ Week 107	7 days (± 7 days) after last dose and 30-day SFU	
Day		1	2	3	8	1	2	3	8	1	1	1		
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Immunopheno-typing		X	X		X	X	X		X	X	X (C6D1, Week 11)			Whole blood samples will be collected at C1D1, C1D2, C1D8, C2D1, C2D2, C2D8, C3D1, C6D1.

Assessments & Procedures Group A: Avelumab Group C: Avelumab + M6223	Screening	Intervention Period (Weeks) Q2W											EOT/ 30-day SFU	Notes
	within 28 days prior to randomi-zation	Cycle 1 (Week 1)				Cycle 2 (Week 3)				Cycle 3 (Week 5)	≥ Week 11 and ≤ Week 23	> Week 23 and ≤ Week 107	7 days (± 7 days) after last dose and 30-day SFU	
Day		1	2	3	8	1	2	3	8	1	1	1		
Gene expression (Group C only)		X	X		X	X	X		X	X	Every 6 weeks			Whole blood samples for PD-L1 gene expression analysis will be collected prior to IV infusion (C1D1, C2D1), 24 hours (C1D2, C2D2), and 168 hours (C1D8, C2D8) after the start of infusion in the first and second cycles. Additional predosing samples will be collected prior to infusion on C3D1, and then every 6-week interval up to/including Week 23.
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Abbreviations: C1D1 = Cycle 1 Day 1; C1D15 = Cycle 1 Day 15; C2D8 = Cycle 2 Day 8; C3D1 = Cycle 3 Day 1; CT = computed tomography; CCI ; CCI ; EOI = end of infusion; EOT = end of treatment; CCI ; CCI ; IV = intravenous; PD = progressive disease; CCI ; PK = pharmacokinetic; Q2W = every 2 weeks; SFU = safety follow up.

a If one study intervention is prematurely discontinued, a PK sample for that study intervention should only be collected at the EOT and SFU visits.

Table 6 Group D Bioanalytical and Biomarkers Schedule of Activities (not applicable for current Protocol Version 5.0)

Assessments & Procedures	Screening	Intervention Period (Weeks) Q4W												EOT/SFU	Notes
Group D avelumab + NKTR-255	within 28 days prior to randomi-zation	Cycle 1 (Week 1)					Cycle 2 (Week 5)					Cycle 3 (Week 9)	> Week 9 and ≤ Week 25	> Week 25 and ≤ Week 109	7 days (± 7 days) after last dose and 30 and 90-day SFU	
Day		1	1 4h±1h	2	4	8	1	1 4h±1h	2	4	8	1	1	1		
Immuno-genicity for avelumab		X					X					X	Every 8 weeks	Every 12 weeks	X	Immunogenicity samples will be collected within 2 hours prior to infusion on Day 1 (C1D1), 29 (C2D1), Day 57 (C3D1, Week 9), and then every 8 weeks up to and including Week 25, then every 12 weeks, up to Week 109, and EOT, and 30 and 90-day SFU.
Avelumab PK[a]		X*		X		X	X*		X		X	X*	Every 8 weeks	Every 12 weeks	X	PK samples for avelumab will be collected as follows: • Predosing PK samples will be collected within 2 hours prior to IV infusion on Day 1 (C1D1), Day 29 (C2D1), Day 57 (C3D1, Week 9), and then every 8 weeks up to and including Week 25,

Assessments & Procedures	Screening	Intervention Period (Weeks) Q4W												EOT/SFU	Notes
Group D avelumab + NKTR-255	within 28 days prior to randomi-zation	Cycle 1 (Week 1)					Cycle 2 (Week 5)					Cycle 3 (Week 9)	> Week 9 and ≤ Week 25	> Week 25 and ≤ Week 109	7 days (± 7 days) after last dose and 30 and 90-day SFU	
Day		1	1 4h±1h	2	4	8	1	1 4h±1h	2	4	8	1	1	1		
PK for NKTR-255[a]		X*		X		X	X*		X		X	X*	Every 8 weeks	Every 12 weeks	X	then every 12 weeks, up to and including Week 109, EOT, and 30 and 90-day SFU. • End of infusion samples will be collected within 5 minutes at the EOI on Day 1 (C1D1), Day 29 (C2D1), and Day 57 (C3D1). • Additional post infusion samples will be collected on Day 2 (C1D2), Day 8 (C1D8), Day 30 (C2D2), Day 36 (C2D8), i.e. 24 hours, 168 hours after the start of infusion in the cycle (within 2 hours). *PK samples will be collected both within 2 hours prior to infusion and also at the end of infusion. The exact time of each draw should be recorded. Blood samples should be collected prior to CT scan if scheduled on the same day.

Assessments & Procedures	Screening	Intervention Period (Weeks) Q4W												EOT/SFU	Notes
Group D avelumab + NKTR-255	within 28 days prior to randomi-zation	Cycle 1 (Week 1)					Cycle 2 (Week 5)					Cycle 3 (Week 9)	> Week 9 and ≤ Week 25	> Week 25 and ≤ Week 109	7 days (± 7 days) after last dose and 30 and 90-day SFU	
Day		1	1 4h±1h	2	4	8	1	1 4h±1h	2	4	8	1	1	1		
Immuno-genicity for NKTR-255		X					X					X	Every 8 weeks	Every 12 weeks	X[b]	Immunogenicity samples will be collected within 2 hours prior to infusion on Days 1(C1D1), 29 (C2D1), 57 (C3D1), and then every 8 weeks up to and including Week 25, then every 12 weeks, up to and including Week 109, and EOT, and 30 and 90-day SFU.

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Assessments & Procedures	Screening	Intervention Period (Weeks) Q4W												EOT/SFU	Notes
Group D avelumab + NKTR-255	within 28 days prior to randomi-zation	Cycle 1 (Week 1)					Cycle 2 (Week 5)					Cycle 3 (Week 9)	> Week 9 and ≤ Week 25	> Week 25 and ≤ Week 109	7 days (± 7 days) after last dose and 30 and 90-day SFU	
Day		1	1 4h±1h	2	4	8	1	1 4h±1h	2	4	8	1	1	1		

[redacted]

Assessments & Procedures	Screening	Intervention Period (Weeks) Q4W												EOT/SFU	Notes
Group D avelumab + NKTR-255	within 28 days prior to randomi-zation	Cycle 1 (Week 1)					Cycle 2 (Week 5)					Cycle 3 (Week 9)	> Week 9 and ≤ Week 25	> Week 25 and ≤ Week 109	7 days (± 7 days) after last dose and 30 and 90-day SFU	
Day		1	1 4h±1h	2	4	8	1	1 4h±1h	2	4	8	1	1	1		

[redacted]

Assessments & Procedures Group D avelumab + NKTR-255	Screening	Intervention Period (Weeks) Q4W												EOT/SFU	Notes
	within 28 days prior to randomi-zation	Cycle 1 (Week 1)					Cycle 2 (Week 5)					Cycle 3 (Week 9)	> Week 9 and ≤ Week 25	> Week 25 and ≤ Week 109	7 days (± 7 days) after last dose and 30 and 90-day SFU	
Day		1	1 4h±1h	2	4	8	1	1 4h±1h	2	4	8	1	1	1		
																CCI
Immuno-phenotyping		X			X	X	X			X	X	X	C6D1, Week 21			Whole blood samples will be collected at C1D1, C1D4, C1D8, C2D1, C2D4, C2D8, C3D1, and C6D1
Gene expression		X	X[b]	X		X	X	X[b]	X		X	X	Every 8 weeks			Whole blood samples for PD-L1 gene expression analysis will be collected prior to IV infusion (C1D1, C2D1), 4 hours (C1D1, C2D1) after start of infusion*, 24 hours (C1D2, C2D2), and 168 hours (C1D8, C2D8) after start of infusion in the first and second cycles. Additional predosing samples will be collected prior to infusion on C3D1, and then at every 8-week

Assessments & Procedures	Screening	Intervention Period (Weeks) Q4W												EOT/SFU	Notes
Group D avelumab + NKTR-255	within 28 days prior to randomi-zation	Cycle 1 (Week 1)					Cycle 2 (Week 5)					Cycle 3 (Week 9)	> Week 9 and ≤ Week 25	> Week 25 and ≤ Week 109	7 days (± 7 days) after last dose and 30 and 90-day SFU	
Day		1	1 4h±1h	2	4	8	1	1 4h±1h	2	4	8	1	1	1		
																interval up to/including Week 25. [b]Optional

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C1D1 = Cycle 1 Day 1; C1D15 = Cycle 1 Day 15; C2D8 = Cycle 2 Day 8; C3D1 = Cycle 3 Day 1; CT = computed tomography; CCI
CCI ; EOI = end of infusion; EOT = end of treatment; CCI ; CCI
IV = intravenous; PD = progressive disease; CCI ; PK = pharmacokinetic; Q2W = every 2 weeks; SFU = safety follow-up.

a If one study intervention is prematurely discontinued, PK samples for that study intervention should only be collected at the EOT and SFU visits.

Version 3.0, 20 March 2023

Section # and Name	Description of Change	Brief Rationale
Synopsis Section 3 Objectives and Endpoints	Updated secondary of disease related physical symptoms: changed the estimand strategy for the intercurrent event of treatment discontinuation from a treatment-policy to a hypothetical strategy.	The endpoint will be analyzed assuming that all participants are treated with avelumab combination regimens or avelumab monotherapy until Week 13 ensuring comparability between treatment groups.
Synopsis Section 6.3.2 Blinding	Removed stipulation that the dedicated team reviewing safety data will be “masked to treatment” and added to statement regarding Special consideration to any unexpected/unlabeled toxicities Grade ≥ 3 and SAEs.	Clarification
Synopsis Section 6.3.2 Blinding	Added to statement regarding Special consideration to any unexpected/unlabeled toxicities Grade ≥ 3, SAEs that this would be “regardless of causality and defined adverse events assessed as related to any of the IMPs.”	Clarification that this will pertain to any Grade ≥ 3 and SAEs regardless of causality
1.3 Schedule of Activities Tables 1 to 3 Visit windows	Added to note in case of Avelumab the minimum interval in between doses can be no less than 10 days.	For clarity
1.3 Schedule of Activities Tables 1 to 3 Hepatitis B and C screening	Added note specifying tests	For clarity
1.3 Schedule of Activities Tables 1 to 3 Clinical Laboratory Tests	Added to note that “Samples for clinical laboratory tests for all treatment cycles may be drawn up to 72 hours prior of infusion. For Cycle 1 Day 1, results must be reviewed and meet inclusion criteria prior to infusion.”	For clarity and additional instruction
1.3 Schedule of Activities Tables 1 Clinical Laboratory Tests	Updated note specifying that full chemistry should be performed on Day 1 of each cycle (deleted Day 8) and that of if SG is discontinued before avelumab, then full serum chemistry should be performed at every 3rd avelumab dosing or if clinically indicated.	For clarity, additional instruction, and to decrease participant burden in blood sampling
1.3 Schedule of Activities Tables 1 to 3 Thyroid Function (TSH and FT4 [or total T4])	Added total T4 and added to not that sampling should occur earlier (than stipulated) if clinically indicated	For clarity and additional instruction
1.3 Schedule of Activities Tables 1 to 3 Tumor Assessments	Added to note visit windows After Screening, the visit window for tumor assessments will be ± 5 days.	To provide flexibility

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities Tables 1 to 3 PRO assessments	Added to note that PRO assessments should be completed prior to infusion	Additional instruction to Investigators
1.3 Schedule of Activities Table 3 12-Lead ECGs	Added that end-of-infusion ECGs should be collected within 30 minutes of the end of infusion	Additional instruction to Investigators
1.3 Schedule of Activities Tables 4 to 6	Modified PK note presentation of to present in bullet form	For clarity and consistency across tables
1.3 Schedule of Activities Tables 4 to 6	Stipulated that for PK end-of-infusion blood draw should be within 5 minutes of end of infusion	Additional instruction to Investigators and ensure consistency
1.3 Schedule of Activities Tables 4 to 6	For PK blood draws, stipulated that “The exact time of each draw should be recorded. Blood samples should be collected prior to CT scan if scheduled on the same day.”	Additional instruction to Investigators
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1.3 Schedule of Activities Tables 4 to 6	Added footnote that if 1 study intervention is prematurely discontinued, a PK sample for that study intervention should only be collected at the EOT and SFU visits	Additional information for Investigators
1.3 Schedule of Activities Table 5	Corrected header from > Week 23 and ≤ Week 109 to > Week 23 and ≤ Week 107	For internal consistency with table notes
1.3 Schedule of Activities Table 6	Corrected header from > Week 25 and ≤ Week 113 to > Week 25 and ≤ Week 109	For internal consistency with table notes
Section 2.2.3 Avelumab (background)	Added information on median overall survival time from JAVELIN 100 Bladder study	Additional information for Investigators
Table 7	Deleted/modified some text and referred to IB	To avoid discrepancies between protocol and IB due to continuously updated data in IBs
Table 7 – NKTR-255	Added row for neutropenia and thrombocytopenia	For additional information for Investigators
Sections 4.2.1.1 through 4.2.1.4	Updated safety information, deleted tables of AEs/SAEs, and referred reader to IB	Alignment with IB and avoid discrepancies between protocol and IB due to continuously updated data in IBs
Section 5.1 Inclusion Criteria	Inclusion Criterion 6, change requirement from 15 slides to 10 slides	Required for proper assessment

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	Inclusion Criterion 10c regarding statement that participants may have been transfused, added "during the screening period in order to meet inclusionary criteria provided there is no active bleeding".	Provide clarity to Investigators
Section 5.1 Inclusion Criteria	Inclusion Criterion 12, add statement that "Participants diagnosed and documented with Gilbert's syndrome are eligible for enrollment".	Provide clarity to Investigators
Section 5.2 Exclusion Criteria	Modified text regarding other malignancies to state "Other malignancies should be discussed with the Sponsor." and deleted "possible exceptions" language	To avoid possible "waivers"
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Section 5.2 Exclusion Criteria	Exclusion Criterion 14: Added anti-TIGIT and agents targeting Nectin-4 to list of prior immunotherapies that would exclude participation	Provide clarity to Investigators
Section 5.2 Exclusion Criteria	Exclusion Criterion 15: Updated wording regarding radiation therapy from "major radiation therapy ≤ 2 weeks prior to randomization" to "radiation therapy (aside from palliative therapy) ≤ 2 weeks prior to randomization"	Clarification
Section 5.2 Exclusion Criteria	Exclusion Criterion 17: Added to statement allowing inactivated vaccines that they must have been administered ≥ 2 weeks prior first dose of study treatment. Updated language to state "All SARS-CoV-2 vaccines approved or authorized by local Health Authorities are allowed"	Clarification
6.1 Study Intervention	Updated dose formulation unit dose strength of sacituzumab govitecan from 180 to 200 mg and added note that the dose of 180 mg indicated on the label describes the minimum extractable amount of drug per vial.	Correction/clarification
Section 6.3.2 Blinding	Updated bullet point from: "A rolling review of safety data of participants under treatment will be done in the proposed combinations by a dedicated team composed of safety and medical representatives, who are masked to treatment"	Provide clarity

Section # and Name	Description of Change	Brief Rationale
	to "A rolling review of safety data of participants under treatment will be done in the proposed combinations by a dedicated team composed of safety and medical representatives. To detect and react to occurrence of potential unacceptable toxicities, this review team will have access to participant-level information including the treatment group. Access to any aggregated data analysis by treatment group is not permitted for any study team members during the ongoing study."	
Section 6.5.1 Avelumab	Added statement pertaining to post infusion observation that after the fourth infusion, participants should be monitored according to local standards.	Greater clarity and instructions to Investigators
Section 6.5.1 Avelumab – Table 9 (formerly Table 17)	Added note that if the infusion-related reaction occurs after the infusion, the next infusion must be performed at 50% of previous rate and added footnote to table stipulating that once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions.	Greater clarity and instructions to Investigators
Section 6.5.2 Sacituzumab Govitecan – Table 11 (formerly Table 19)	In the case of severe neutropenia, added to administer G-CSF as soon as clinically indicated	Additional instructions to Investigators
Section 6.5.2 Sacituzumab Govitecan – Table 12 (formerly Table 20)	Added note that if the infusion-related reaction occurs after the infusion, the next infusion must be performed at 50% of original rate of sacituzumab govitecan and 50% of previous rate of avelumab and added footnote to table stipulating that once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions.	Greater clarity and instructions to Investigators
Section 6.5.2 Sacituzumab Govitecan	Added "or according to local standards" to statement regarding participant monitoring after first 8 weeks	For clarity and ensure compliance with local standards
Section 6.5.3 M6223 – Table 13 (formerly Table 21)	Added note that if the infusion-related reaction occurs after the avelumab infusion please consider decreasing the next infusion rate by 50% of previous rate of avelumab and added footnote to table stipulating that once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions.	Greater clarity and instructions to Investigators
Section 6.5.4 NKTR-255	Added text providing information on infusion-related reactions and flu-like symptoms	Greater clarity and instructions to Investigators
Section 6.5.4 NKTR-255	Updated and added information on mitigation and management of cytokine release syndrome and updated table (Table 16, formerly Table 23) on treatment algorithm for management of cytokine release syndrome	For clarity and additional information to Investigators
Section 6.5.4 NKTR-255	Added new text on neutropenia and thrombocytopenia	Greater clarity and instructions to Investigators
Section 6.8.3 Prohibited Medicines	Updated vaccine language to be in alignment with updated Exclusion Criterion 17	For clarity and internal document consistency

Section # and Name	Description of Change	Brief Rationale
Section 6.8.3 Prohibited Medicines	Deleted bisphosphonate or denosumab treatment as prohibited medicines	For consistency with avelumab program
Section 7.1.1 Study Intervention Beyond Progression	Added "radiological" to decision statement concerning decision to continue treatment: The decision to continue treatment beyond confirmed radiological progression should be approved by the Sponsor and documented in the study records.	Clarity
Section 8.2.3 Electrocardiograms	Deleted QTcB from ECG measurements: heart rate, PR, RR, QRS, QT, and ~~QTcB or~~ QTcF.	For clarity and consistency of data collected
8.3.5 Adverse Events of Special Interest and Other Specific Adverse Events	Updated section title (formerly Adverse Events of Special Interest) and added list of AESIs	Greater clarity and instructions to Investigators
8.3.5.2 Immune-related adverse events Appendix 5	Updated reference and guidelines for management and treatment of all categories of immune-related adverse events	Updated information for Investigators with latest guidelines
CCI		
Section 8.4 Pharmacokinetics	Deleted "Confirmed positive antibodies may be further characterized" from third bullet	Stated in Section 8.7 (Immunogenicity Assessments)
Section 8.4 Pharmacokinetics	Deleted "serum" from second bullet point and added reference to Laboratory Manual	NKTR-255 PK samples are in plasma. The lab manual describes the collection of samples correctly
CCI		
Section 9.2 Sample Size Calculation – Table 19 (formerly Table 26)	Updated probability of success for one arm (OA or PA) for OS from 38.7% to 52.3%	Updated/corrected calculation
Section 9.2 Sample Size Calculation – Table 20 (formerly Table 27)	Updated probability of success for one arm (OA or PA) for OS from 42.5% to 53.7%	Updated/corrected calculation
Section 9.4.1 Efficacy analyses	Table 22 Efficacy Estimand Attributes, added: Disease related physical symptoms secondary estimand and method of analysis	For clarity and consistency with other endpoint/estimand sections

Section # and Name	Description of Change	Brief Rationale
Appendix 5 The Recommendations for irAE Management, in Accordance with the American Society of Clinical Oncology Clinical Practice Guidelines (Schneider 2021)	Updated entire section	To be in alignment with the latest irAE management guidelines

Version 2.2, 28 October 2022 (local amendment for France and Italy only)

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall Design	Added statement that for France and Italy, enrollment will not start before the first safety run-in phase has been completed.	Safety precaution

Version 2.1, 20 July 2022 (local amendment for Germany and France only)

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	Deleted incorrect paragraph break in Inclusion Criterion 13: Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay during the study intervention period	Formatting fixed to add clarity.
Section 5.2 Exclusion Criteria	Exclusion Criterion 11: 11. Pregnant female participants; breastfeeding female participants; and female participants of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in the protocol for the duration of the study and for at least ~~30 days~~ **6 months** after the last dose of investigational product. **Male participants who are unwilling or unable to follow the Contraception and Barrier Requirements (see Appendix 3) for the duration of the study and for at least 3 months after the last dose of study intervention.**	Language corrected and clarified.

Version 2.0, 04 February 2022

Section # and Name	Description of Change	Brief Rationale	Version
Section 1.3, Table 3	12-lead ECG Notes: **ECG will be collected at pre dose of NKTR-255. Additional ECG(s) will be collected at the end of infusion on C1D1 (Week 1), C2D1 (Week 5), and C3D1 (Week 9).**	To address FDA feedback.	2.0
Section 1.3, Table 3	PK and Biomarkers Notes: [a]*On 30 days and 90 days safety FU, **only** PK and immunogenicity will be assessed ~~(not necessarily the biomarkers)~~.	Added clarifying language.	2.0
Section 1.3, Table 4	Avelumab PK Notes: ***PK will be taken at both within 2 hours prior to IV infusion and EOI.**	To address FDA feedback.	2.0

[redacted]

Section # and Name	Description of Change	Brief Rationale	Version
Section 1.3, Table 6	Avelumab PK Notes: [b]On SFU visit, only PK and immunogenicity will be assessed ~~(not necessarily the biomarkers)~~.	Language clarified.	2.0
Section 1.3, Table 6	PK for NKTR-255 Notes: [b]On SFU visit, only PK and immunogenicity will be assessed ~~(not necessarily the biomarkers)~~.	Language clarified.	2.0
[redacted]			
Section 1.3, Table 6	Gene expression Notes: Whole blood samples for PD-L1 gene expression analysis will be collected prior to IV infusion ~~at~~ (C1D1, C2D1), **4 hours** (C1D1 ~~at 4hr~~, **C2D1**) after ~~IV~~ **start of** infusion*, **24 hours** (C1D2, **C2D2**), **and 168 hours** (C1D8, **C2D8** ~~C2D1, C2D1 at 4 hr~~) after ~~IV~~ **start of** infusion*, ~~C2D2, C2D8~~, **in the first and second cycles. Additional predosing samples will be collected prior to infusion on** C3D1, and then **at** every 8-week ~~intervals~~ **interval** up to/including Week 25.	To address FDA feedback.	2.0
Section 4.2.1.3 and Table 13	~~Four~~ **Five** patients **(total 6 events)** had Grade ≥ 3 lymphopenia, none had clinical manifestations and all events resolved within 9 days without intervention. "Lymphocyte count decreased" was deleted and included under the preferred term "lymphopenia."	Data were updated.	2.0

Section # and Name	Description of Change	Brief Rationale	Version
CCI			
Section 5.1	The following was added to inclusion criterion 6: **Provision of a tumor biospecimen is required for randomization into the study. The sample must be submitted to the Central Laboratory prior to randomization and deemed acceptable to allow the patient to randomize. Refer to the Central Laboratory Manual for additional specifications.**	To ensure that participants' biopsies collected at Screening are adequate for biomarker analysis to support exploratory endpoints.	2.0
CCI			
Section 8.3.5	In addition to an internal DMC, who will be fully unblinded, safety data will also be evaluated in a rolling fashion **(at least biweekly)** by a dedicated team composed of safety and medical representatives during the safety run-in and throughout the entire trial.	To address FDA feedback.	2.0

Section # and Name	Description of Change	Brief Rationale	Version
Section 8.4	• Whole blood samples ~~of~~ **ranging from** approximately 3.5 **to 4** mL per drug per collection time point (maximum 7**.5** mL per arm per time point) will be collected for detection of avelumab, M6223, Sacituzumab and NKTR-255 in serum.	To address FDA feedback.	2.0
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.	2.0

Appendix 12 Sponsor Signature Page

Study Title:	A Phase II, multicenter, randomized, open-label, parallel-arm, umbrella study of avelumab (MSB0010718C) in combination with other anti-tumor agents as a maintenance treatment in participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with first line platinum-containing chemotherapy
Regulatory Agency Identifying Numbers:	US IND: 156990 EUCT: 2023-510139-12-00
Clinical Study Protocol Version:	31 July 2025/Version 5.0

I approve the design of the clinical study:

_____ _____

Signature Date of Signature

Name, academic degree:	PPD, MD
Function/Title:	PPD
Institution:	PPD
Address:	
General Merck Phone Number:	
General Merck Fax Number:	Not Applicable
E-mail	PPD

Appendix 13 Coordinating Investigator Signature Page

Study Title:	A Phase II, multicenter, randomized, open-label, parallel-arm, umbrella study of avelumab (MSB0010718C) in combination with other anti-tumor agents as a maintenance treatment in participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with first line platinum-containing chemotherapy
Regulatory Agency Identifying Numbers:	US IND: 156990 EUCT: 2023-510139-12-00
Clinical Study Protocol Version:	31 July 2025/Version 5.0
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, ICH GCP (Topic E6) and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

Name, academic degree:	PPD, MD
Function/Title:	Coordinating Investigator
Institution:	John Hopkins University
Address:	4940 Eastern Av, 301 Building, PPD 21224 Baltimore, Maryland United States
Telephone number:	PPD
Fax number:	Not Applicable
E-mail address:	PPD

Appendix 14 Principal Investigator Signature Page

Study Title:	A Phase II, multicenter, randomized, open-label, parallel-arm, umbrella study of avelumab (MSB0010718C) in combination with other anti-tumor agents as a maintenance treatment in participants with locally advanced or metastatic urothelial carcinoma whose disease did not progress with first line platinum-containing chemotherapy
Regulatory Agency Identifying Numbers:	US IND: 156990 EUCT: 2023-510139-12-00
Clinical Study Protocol Version:	31 July 2025/Version 5.0
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, ICH GCP (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: