TITLE PAGE

Protocol Title: A Phase Ib Trial to Evaluate the Efficacy and Safety of Bintrafusp Alfa Monotherapy in Metastatic or Locally Advanced/Unresectable Urothelial Cancer with Disease Progression or Recurrence Following Treatment with a Platinum Agent

Protocol Number: 213152/Amendment 02

Compound Number or Name:	GSK4045154 bintrafusp alfa (M7824)

Brief Title: A Phase Ib trial to evaluate the efficacy and safety of bintrafusp alfa monotherapy in metastatic or locally advanced urothelial cancer

Study Phase: Phase Ib

Sponsor Name and Legal Registered Address:

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Manufacturer: Merck KGaA

Regulatory Agency Identifying Number(s):

IND	145828
EudraCT	2020-000416-29

Medical Monitor Name and Contact Information can be found in the Study Reference Manual.

Sponsor Signatory:

Rachael M. Easton, MD, PhD
Medical Director, Oncology Clinical Development

Approval Date: 03 Mar 2022

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 2	03 Mar 2022	*TMF-14396625*
Amendment 1	28 May 2020	*2019N411039_01*
Original Protocol	30 Jan 2020	*2019N411039_00*

Amendment 02: 03 Mar 2022

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

Overall Rationale for the Amendment:

Based on the lack of efficacy of bintrafusp alfa in clinical studies in other tumor types, and improved efficacy of other therapies for urothelial cancer, the study sponsor has decided to cease enrollment into the study. In line with the sponsor's decision, this protocol has been amended to provide updated instructions for continued study conduct.

A summary of significant changes from Amendment 1 is provided in the table below together with a brief rationale for the changes:

Section # and Name	Description of Change	Brief Rationale
Full document		Editorial changes have been made throughout document to increase clarity/consistency, adjust abbreviation usage, align with current template requirements, and correct minor typographical errors.

Section # and Name	Description of Change	Brief Rationale
Section 1 Protocol Summary	Text has been added providing an overview of the decision to stop enrollment and the corresponding impacts on study conduct and data collection.	Addition has been made to reflect the overall rationale for Amendment 02. Specifically, based on the lack of efficacy of bintrafusp alfa in clinical studies in other tumor types and improved efficacy of other therapies for urothelial cancer, the study sponsor has decided to cease enrollment into the study. In line with the sponsor's decision, this protocol has been amended to provide updated instructions for continued study conduct.
Section 1.1 Synopsis Section 3 Objectives and Endpoints	Several secondary objectives and endpoints have been updated and [redacted]	Enrollment into the study has been discontinued; study objectives and endpoints have been updated to reflect change in study scope.
Section 1.1 Synopsis Section 1.3 Schedule of Activities Sections 3 Objectives and Endpoints Section 8.3 Evaluation of Anti-Cancer Activity Section 9.6 Independent Radiology Committee	Text has been modified to reflect that an [redacted] will not be utilized for the evaluation of antitumor activity.	Modifications have been made to reflect the sponsor's decision to cease enrollment into the study and the corresponding update of study objectives and study conduct.
Section 1.1 Synopsis Section 1.3 Schedule of Activities	Details have been added regarding data collection to be conducted following the data cut-off (DCO) date.	Addition was made to provide instruction regarding data collection following the DCO date.
Section 1.1 Synopsis Section 4.1 Overall Design Section 4.6 Number of Participants Section 9.2 Sample Size Determination	The sample size has been revised from 40 to 25 participants who will receive bintrafusp alfa.	Modification has been made based on the sponsor's decision to cease enrollment.
Section 1.3 Schedule of Activities	Text indicating that '(unless noted in assessment "Notes")' was added regarding timing of" D1 assessments.	Modification was made for clarity.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities Section 6.1 Study Intervention(s) Administered	Text has been added specifying that study intervention administration duration can be continued for up to 2 years from the time of a confirmed complete response (CR).	Modification was made for consistency with the treatment duration limit presented throughout the rest of the protocol.
Section 1.3 Schedule of Activities CCI [redacted]	Samples for bintrafusp alfa CCI analysis will no longer be collected.	In light of the discontinuation of enrollment, removal of these samples will reduce the burden for ongoing participants.
Section 1.3 Schedule of Activities CCI [redacted]	CCI [redacted]	In light of the discontinuation of enrollment, removal of these samples will reduce the burden for ongoing participants.
Section 1.3 Schedule of Activities CCI [redacted]		In light of the discontinuation of enrollment, removal of these samples will reduce the burden for ongoing participants.
Section 1.3 Schedule of Activities CCI [redacted]	Samples for assessment of bintrafusp CCI [redacted] will no longer be collected.	In light of the discontinuation of enrollment, removal of these samples will reduce the burden for ongoing participants.
Section 2.2.5 Risk Assessment	Text has been added regarding planned hematology surveillance.	Modification was made to correct an inadvertent omission from previous versions of the protocol.
Section 2.2.7 Overall Benefit-Risk Assessment	Text has been added regarding the continuous evaluation of the benefit-risk profile for bintrafusp alfa.	Modification was made to reflect the emerging data from other studies in the consideration of the benefit-risk assessment.

Section # and Name	Description of Change	Brief Rationale
Section 4 Study Design	Text has been added regarding the sponsor's decision to cease enrollment into the study.	Addition was made to reflect the discontinuation of enrollment for this study.
Section 4.1 Overall Design	Text regarding the secondary objectives of the study has been modified.	Modifications were made to correspond to changes in the objectives and endpoints sections of the protocol.
Section 4.1 Overall Design	Text has been added regarding data collection and participant follow-up after the DCO date.	Addition was made to provide instruction regarding data collection and study conduct following the DCO date.
Section 4.4, Archival Tumor Biopsy PD-L1 Status Section 5.1 Inclusion Criteria (Criterion #10) Section 8.11.2 Tumor Tissue	Language regarding prospective and/or retrospective assessment of PD-L1 status has been removed from the protocol.	Text has been updated in line with ceasing enrollment into the study and the update of study conduct.
Section 4.7 Oversight Section 4.7.1 Independent Radiology (Review) Committee (IRC)	Sections have been removed.	Sections were deleted to reflect the sponsor's decision to cease enrollment into the study and the corresponding updates to study objectives and study conduct.
Section 4.7 End of Study Definition (formerly Section 4.8)	The end of study (EOS) definition has been revised to be the last participant's last visit.	Modification was made to reflect the discontinuation of study enrollment.
Section 5.2 Exclusion Criteria (Exclusion Criterion #24)	The duration of 5 half-lives has been updated from 30 days to 35 days.	Modification was made for alignment with the Investigator's Brochure.
Section 6.7 Dose Modification	Text has been added to allow for dose modifications in response to bleeding events.	Addition was made to reflect new language regarding bleeding events in Section 6.8.5.1.
Section 6.8.5.1 Bleeding Events	Language regarding appropriate follow-up for bleeding events has been updated with additional detail.	Language has been updated to be consistent with the Investigator's Brochure.

Section # and Name	Description of Change	Brief Rationale
Section 6.9 Intervention After the End of the Study	Text has been added 1) relating to the potential for study participants to roll over to a continuation study has been deleted, and 2) specifying that participants with continued benefit from study intervention will have access to study intervention until EOS.	Modifications were made to reflect the discontinuation of enrollment into the study and the corresponding updates to study conduct.
Section 6.10 Continued Access to Study Intervention after Data Cut-off (new section)	Text has been added to describe the availability of study intervention after the DCO date.	Modifications were made to reflect the discontinuation of enrollment into the study and the corresponding updates to study conduct.
Section 7.1 Discontinuation of Study Intervention	Text has been added regarding management of participants who discontinue study intervention after the DCO date.	Addition was made to provide instruction regarding study visits and data collection following the DCO date.
Section 7.2 Participant Discontinuation/Withdrawal from the Study	Text has been added specifying that the maximum duration of study treatment is 2 years from first dose or from the time of confirmed CR.	Modification was made for consistency with the treatment duration limit presented throughout the rest of the protocol.
Section 7.2 Participant Discontinuation/Withdrawal from the Study	Text regarding continuation of survival follow-up until 67% of randomized participants have died or withdrawn consent (to a maximum of 3 years) has been deleted.	Modification was made to reflect the change the EOS definition (Section 4.7).
Section 7.4 Participant and Study Completion	Text regarding the definition of a participant's completion of the study has been modified.	The definition of participant completion has been revised to reflect the definition applicable to participants receiving study intervention at the time of Amendment 02.

Section # and Name	Description of Change	Brief Rationale
Section 8.2 Follow-up Assessments	Text has been added to describe the implementation of the DCO date, clinical study database lock, clinical management of participants, and pharmacovigilance procedures to be conducted after the DCO date.	Addition was made to provide instruction regarding data collection following the DCO date and to ensure the necessary sponsor oversight of participants who continue to receive study intervention after the DCO date.
Section 8.3 Evaluation of Anti-Cancer Activity [redacted]	All references to immune-related RECIST (irRECIST) and all of Section 8.3.1.2 have been deleted.	irRECIST has been removed from the study endpoints; corresponding text relating to these evaluation criteria have therefore been deleted.
Section 8.4.1 Physical Examinations	Assessment of infusion site reactions has been moved from Screening (ie, complete physical examination) to the subsequent visits (ie, brief physical examinations).	Modification was made to correction an error in previous version (ie, monitoring of infusion site reactions is not relevant for the Screening period) and to align with the SoA.
Section 8.5.2 Collection of Safety Information After Data Cut-off (new section)	A new section has been added regarding the collection of safety information after the DCO date.	Addition was made to provide instruction regarding data collection following the DCO date and to ensure the necessary sponsor oversight of participants who continue to receive study intervention after the DCO date.
Section 8.5.3 Method of Detecting AEs and SAEs	Text has been added to specify that detection of AEs and SAEs also applied to those events occurring after the DCO date.	Addition was made to ensure appropriate AE and SAE collection from participants who continue to receive study intervention after the DCO date.
Section 8.6 Participant Specific Dose Adjustments Criteria	Text has been added to highlight the exceptions for which dose reductions of study intervention are allowed, as detailed in Section 6.8.	Addition was made for consistency with modifications made in Section 6.7 and Section 6.8.5.1.

Section # and Name	Description of Change	Brief Rationale
Section 9 Statistical Considerations	Text has been added regarding plans for abbreviated reporting of study data and the removal of the previously planned interim analysis.	Modification has been made based on the sponsor's decision to cease enrollment.
Section 9.1 Statistical Hypothesis Section 9.4 Statistical Analyses Section 9.4.2 Primary Endpoint	Instances referring to the final analysis or the EOS analysis have been changed to refer to the primary analysis.	These modifications were made to more accurately describe the analysis of the primary endpoint.
Section 9.4.3 Secondary Endpoints CCI [redacted]	Content has been modified to reflect 1) the deletion of the analysis regarding CCI [redacted]	Modifications were made to correspond to changes made to study objectives and endpoints.
Section 10.3.5 Reporting of SAEs to GSK	Text regarding the reporting of SAEs and AEs leading to discontinuation has been updated.	Modification was made to provide instructions regarding the safety reporting requirements for participants receiving study intervention after the DCO date.
Section 10.4.2 Contraceptive Guidance	A statement has been added that the protocol's contraceptive guidance will also apply to participants who continue to receive study intervention after the DCO date.	Addition was made for clarity.
Section 10.4.3 Collection of Pregnancy Information	A statement has been added that collection of pregnancy information requirements will also apply to participants who continue to receive study intervention after the DCO date.	Addition was made for clarity.
Section 11 References	References no longer cited in the protocol have been deleted.	Modifications were made to correspond to deletions made to text in the body of the protocol.

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1. PROTOCOL SUMMARY

The study sponsor has decided to cease enrollment based on a rapidly evolving treatment landscape in urothelial carcinoma, in addition to recent data showing lack of efficacy of bintrafusp alfa in studies in other tumor types.

In line with the sponsor's decision, this protocol has been amended to provide updated instructions for study conduct.

At the time of writing this protocol amendment, 25 participants have been treated with bintrafusp alfa, and no new safety signals were identified.

In summary, participants still on treatment at the time of the final data cut-off (DCO) date and who the study investigator in agreement with the GSK medical monitor considers are deriving benefit from bintrafusp alfa and do not meet any protocol-defined treatment discontinuation criteria may continue to receive study intervention per the protocol-defined time period after the DCO date, as follows:

- Participants who decide to continue with study intervention are re-consented.
- Participants will be managed in accordance with the local institutional standard of care.
- Serious Adverse Events (SAEs), adverse events (AEs) leading to treatment/study discontinuation, overdoses, and pregnancies will be reported through a paper-based pharmacovigilance (PV) process (see Study Reference Manual) and captured in asset PV database.

A DCO date will be specified that represents the end of data collection for the planned final analysis described in the Reporting and Analysis Plan (RAP). The DCO date will be communicated to the study sites in a letter. Once the final DCO for this study has been reached, no new data will be entered into the clinical study database and the database will be locked for final analysis. At the time of final DCO, participants in follow-up will no longer be followed for survival and will be considered to have completed the study. Although the clinical study database(s) will be closed at the time of the final DCO date, the study remains open until all participants discontinue study treatment and the end of study (EOS) is reached. The EOS is defined as the date of the last visit of the last participant in the study.

The reporting of this study will focus on the primary and secondary objectives only.

1.1. Synopsis

Protocol Title: A Phase Ib Trial to Evaluate the Efficacy and Safety of Bintrafusp Alfa Monotherapy in Metastatic or Locally Advanced/Unresectable Urothelial Cancer with Disease Progression or Recurrence Following Treatment with a Platinum Agent

Short Title: A Phase Ib single-arm clinical trial of bintrafusp alfa monotherapy in metastatic or locally advanced/unresectable urothelial cancer

Background and Rationale:

Worldwide 549,393 new cases of bladder cancer are diagnosed each year. Urothelial cancer is the most common histological type of bladder cancer, accounting for 90% of diagnoses in the United States (US) and Europe. In addition to the bladder, urothelial cancers can also be diagnosed in the urethra, ureters, and renal pelvis. Approximately 25% of urothelial cancer patients, at diagnosis, will have disease that invades the detrusor muscle (muscle-invasive bladder cancer; MIBC) or is metastatic. Cisplatin-containing chemotherapy remains the first-line standard-of-care for those patients able to tolerate it, but most patients will eventually progress. Given the success of checkpoint inhibitor therapy in patients with urothelial cancers, numerous immunomodulatory combinations are under development to counteract resistance to single agent anti-programmed death-1/programmed death-ligand 1 (anti-PD-1/PD-L1) agent; such resistance can be multifactorial and may be related to immunosuppressive signal in the tumor stroma/microenvironment.

While bintrafusp alfa is a bifunctional fusion protein designed to target 2 negative regulatory pathways of immunosuppression in the tumor microenvironment: the cell intrinsic pathway mediated by a tumor cell-immune cell interaction, in which PD-L1 plays a major role, and the cell extrinsic pathway mediated by immunosuppressive cytokines, of which transforming growth factor-β (TGF-β) is a prominent member. The anti-PD-L1 moiety of bintrafusp alfa is identical to the monoclonal antibody (mAb) avelumab (Bavencio), except for 3 amino acid substitutions in the heavy chain constant regions that result in a different human immunoglobulin (Ig) G1 allotype, and 1 amino acid substitution in the heavy chain for antibody fusion protein stability. Avelumab is approved in the US for the treatment of platinum-experienced, locally advanced or metastatic urothelial cancers that have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. TGF-β functions predominantly as an autocrine and a paracrine factor in the local tumor microenvironment, and the TGF-βRII component of bintrafusp alfa functions as a TGF-β neutralizing “trap.” Therefore, a novel design such as bintrafusp alfa, which blocks both the cell intrinsic PD-L1/PD-1 interaction and the immunosuppressive TGF-β, could be more effective than agents that target only a single pathway.

Bintrafusp alfa has been administered to approximately 700 participants in Phase I development (EMR200647-001 and EMR200647-0008) and is currently in Phase II and III development for multiple indications. Bintrafusp alfa has a favorable safety profile with known risks consistent with the bifunctional mechanism of action. In Phase I, bintrafusp alfa has shown encouraging efficacy outcomes, in particular, for participants with non-small cell lung cancer (NSCLC) and biliary tract cancer (BTC). The Phase I studies of bintrafusp alfa did not include participants with urothelial cancers.

Bintrafusp alfa is well-suited for therapeutic evaluation in urothelial cancer due to its ability to interfere with both PD-1/L1 and TGF-β pathways. Preclinical experiments demonstrate that bintrafusp alfa strongly enhances antitumor activity and prolongs survival in mouse tumor models above the effect of either the anti-PD-1/L1 antibody or the TGF-β Trap control alone (at the same molarity as bintrafusp alfa). Therefore, we

hypothesize that it is more efficacious than currently approved checkpoint inhibitors. This trial provides the first evaluation of bintrafusp alfa in participants with urothelial cancer that has progressed following platinum therapy.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• Evaluate the antitumor activity per RECIST 1.1.in participants with metastatic or locally advanced/unresectable urothelial cancer treated with bintrafusp alfa.	• Confirmed Overall Response per RECIST 1.1 assessed by investigator.
Secondary	
• Evaluate the safety and tolerability of bintrafusp alfa in participants with urothelial cancer.	• Frequency and severity of AEs using NCI-CTCAE v5.

CCI

[redacted]

Objectives	Endpoints
CCI [redacted]	[redacted]

CCI [redacted] CCI [redacted] CCI [redacted]

NCI-CTCAE v5 = National Cancer Institute-Common Terminology Criteria for Adverse Events, version 5; CCI [redacted] CCI [redacted] ORR = overall response rate; CCI [redacted]
PD = progressive disease; CCI [redacted] CCI [redacted] PR = partial response;
RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1 CCI [redacted]; SD = stable disease; TGF-β = transforming growth factor beta.

Overall Design:

This is a Phase Ib open label, single arm study of bintrafusp alfa in participants with metastatic or locally advanced/unresectable urothelial cancer with disease progression or recurrence following treatment with a platinum agent.

Bintrafusp alfa will be administered intravenously (IV) at a dose of 1200 mg once every 2 weeks (Q2W) until confirmed disease progression, death, unacceptable toxicity, study withdrawal, for up to 24 months after a confirmed complete response (CR).

Number of Participants:

Approximately 25 participants will be treated in this study.

Intervention Groups and Duration:

The study comprises three periods: screening, treatment, and follow-up. The total duration of study participation begins with the signing of the informed consent form (ICF) through the final protocol-defined follow-up assessment for survival.

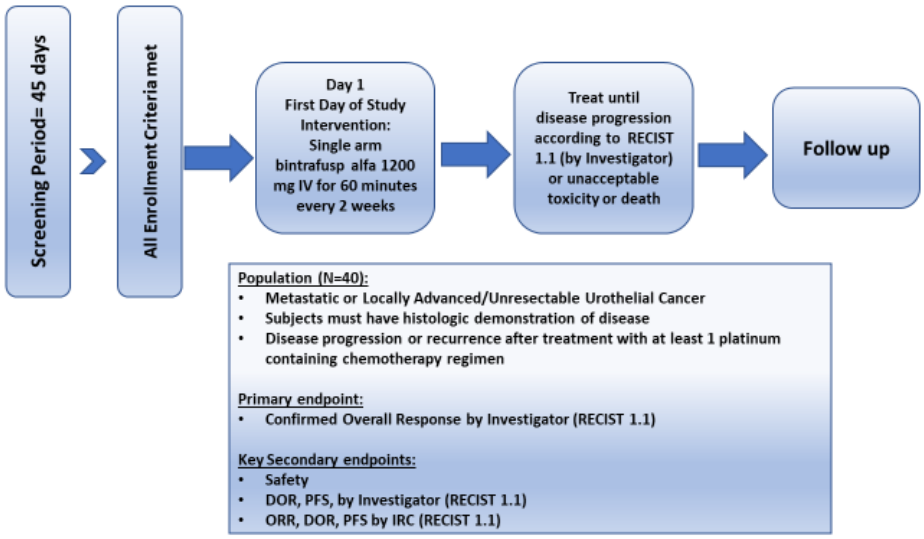
- During the 45-day Screening period, participants will be evaluated for study eligibility per protocol as defined in the Inclusion/Exclusion criteria. Eligible participants must have confirmed diagnosis of metastatic or locally advanced/unresectable urothelial cancer with disease progression or recurrence following treatment with a platinum agent.
- During the Treatment Period, safety and disease assessments will be performed regularly according to the Schedule of Activities (SoA). Treatment will continue until disease progression as determined by RECIST 1.1, death, unacceptable toxicity, sponsor decision to terminate the study, or other protocol-defined criteria are met, for up to 2 years or up to 2 years from confirmed complete response. Note: participants receiving treatment may continue past PD if the participant's ECOG PS has remained at least stable, and if in the opinion of the investigator and in consultation with the GSK medical monitor, the participant will benefit from continued treatment.
- For participants who discontinue study intervention for reasons other than or in the absence of PD, disease evaluation will continue to be performed until confirmed PD (documented), death, start of a new anti-cancer therapy, or withdrawal of consent. After the DCO date, it is expected that disease evaluation will be performed per institutional practice, but these data will not be collected by the sponsor.
- After study treatment is permanently discontinued, participants will be followed for survival and subsequent anti-cancer therapy once every 12 weeks (Q12W) for a maximum of 3 years from the date of enrollment. At DCO, survival and subsequent anti-cancer therapy in participants in follow-up will no longer be collected by the sponsor and participants will be considered to have exited the study.
- After study treatment is permanently discontinued, all SAEs, nonserious treatment-related AEs, and AEs of interest will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up. Related AE of all other AEs will be followed until the last follow up visit. At the

DCO, participants still receiving study intervention will be followed as outlined in Section 8.2.

Participants who permanently discontinue study treatment will enter the follow-up period of the study and undergo the assessments as described in the SoA until the DCO date.

1.2. Study Schema

Figure 1 Study Schema



1.3. Schedule of Activities

- Study participants who continue to receive study intervention after the DCO date (see Section 6.10) will be monitored and receive follow-up care in accordance with standard local clinical practice. Assessments will revert to the standard of care at a participant's study site and only SAEs, AEs leading to treatment/study discontinuation, overdoses, and pregnancies will be reported directly to the sponsor via paper forms (see Section 8.5.2).
- The SoA is presented in Table 1.

Table 1 Schedule of Activities

	Screening	Intervention (treatment) Period									Safety Follow-up		Long Term Follow-up	Notes
Assessment and Procedures	**45 Day- to first dose**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Until PD**	**EOT**	**28 Days (±5 Days) After Last Treatment**	**12 Weeks (± 2 Weeks) After Last Treatment**	**Every 12 Weeks (± 2 Weeks)**	**D1: All assessments must be performed on day indicated (unless noted in assessment "Notes"). Day 15 through PD: Visits can be performed ±3 days. EOT: On day of or within 7 days of decision to discontinue. Follow up: Visits can be performed ±2 Weeks.**
		W1	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**						
		D1	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**						
Informed consent	X													ICF can be signed up to 45 days before start of intervention.
Inclusion and exclusion criteria	X	X												Confirmation of all eligibility is required prior to dosing on W1D1. See SRM for more details
Demography	X													Sec Section 8.
Full physical examination (PE) including height	X	X	X	X	X	X	X	X	Q2W	X	X			Complete PE at Screening; Brief PEs should be performed at subsequent clinical visits and should include infusion site reaction assessments. Refer to Section 8.4.1. Height is required at screening only.
Weight	X	X	X	X	X	X	X	X	Q2W					Weight is required at every treatment visit.
Medical history (includes substance usage, CCI [redacted] CCI [redacted] within 60 days.	X													Substances: alcohol and tobacco use, CCI [redacted] CCI [redacted] within 60 days prior to study intervention.
Disease Characteristics	X													Refer to Section 8.1
Prior anti-cancer drug/radiotherapy/ procedures	X													

	Screening	Intervention (treatment) Period									Safety Follow-up		Long Term Follow-up	Notes
Assessment and Procedures	**45 Day- to first dose**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Until PD**	**EOT**	**28 Days (±5 Days) After Last Treatment**	**12 Weeks (± 2 Weeks) After Last Treatment**	**Every 12 Weeks (± 2 Weeks)**	**D1: All assessments must be performed on day indicated (unless noted in assessment "Notes"). Day 15 through PD: Visits can be performed ±3 days. EOT: On day of or within 7 days of decision to discontinue. Follow up: Visits can be performed ±2 Weeks.**
		W1	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**						
		D1	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**						
Serum or Urine Pregnancy Test (WOCBP only)	X			X		X		X	Q4W		X			Serum pregnancy test only required 24 hours prior to first dose. Monthly urine/serum (preference) pregnancy testing will be performed as consistent with local standards however if a urine test is positive or borderline, or in the event of a missed menstrual period or suspicion of pregnancy, a serum β-hCG test will be required.
HIV	X													HIV testing is not required, only known status will be collected at baseline.
TST, QuantiFERON-TB-Gold, or T-SPOT	X													Performed if positive history of tuberculosis exposure.
Safety Assessments														
Skin Assessment	X				X			X	Q6W	X	X			Refer to Section 8.4.1.
12-lead ECG	X	As clinically indicated												
ECHO	X													MUGA is acceptable if ECHO is not available; for each participant the same modality must be used for all subsequent evaluations.
Vital signs	X	X	X	X	X	X	X	X	Q2W	X	X			Vital signs will be measured after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, pulse rate and oxygen saturation (measured by pulse oximetry). Blood pressure should be taken in the same position throughout the study and captured in the eCRF.
ECOG	X	X	X	X	X	X	X	X	Q2W	X	X			ECOG PS 0 or 1 is required at W1D1. Review Predose.

	Screening	Intervention (treatment) Period									Safety Follow-up		Long Term Follow-up	Notes
Assessment and Procedures	**45 Day- to first dose**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Until PD**	**EOT**	**28 Days (±5 Days) After Last Treatment**	**12 Weeks (± 2 Weeks) After Last Treatment**	**Every 12 Weeks (± 2 Weeks)**	**D1: All assessments must be performed on day indicated (unless noted in assessment "Notes"). Day 15 through PD: Visits can be performed ±3 days. EOT: On day of or within 7 days of decision to discontinue. Follow up: Visits can be performed ±2 Weeks.**
		W1	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**						
		D1	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**						
Hematology and hemostaseology	X	X	X	X	X	X	X	X	Q4W	X	X			Details on blood tests under this category is listed in Table 6. At visits where blood tests are required, results should be reviewed prior to dosing. Hematology should be repeated if not performed within 24 hours of D1.
Clinical chemistry	X	X	X	X	X	X		X	Q4W	X	X			Clinical chemistries are listed in Table 6. At visits where blood tests are required, results should be reviewed prior to dosing. Chemistry should be repeated if not performed within 24 hours of D1.
Free T_4 and TSH	X				X			X	Q6W		X			See Appendix 2
Urinalysis	X	As clinically indicated												See Appendix 2
AE review	See notes										X	X	X	Start at Consent. See Section 8.5.1. The 12-week Safety Follow-up and Long-term Follow-up may be conducted via telephone calls or patient chart reviews as necessary unless there is medical necessity requiring a clinical visit. All nonserious related AEs and AEs of interest will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3) All other AEs will be followed until the last follow up visit.

	Screening	Intervention (treatment) Period									Safety Follow-up		Long Term Follow-up	Notes
Assessment and Procedures	**45 Day- to first dose**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Until PD**	**EOT**	**28 Days (±5 Days) After Last Treatment**	**12 Weeks (± 2 Weeks) After Last Treatment**	**Every 12 Weeks (± 2 Weeks)**	**D1: All assessments must be performed on day indicated (unless noted in assessment "Notes"). Day 15 through PD: Visits can be performed ±3 days. EOT: On day of or within 7 days of decision to discontinue. Follow up: Visits can be performed ±2 Weeks.**
		W1	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**						
		D1	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**						
SAE review	See notes										X	X	X	Start at Consent. For ongoing SAEs see Section 8.5.1. The 12-week Safety Follow-up and Long-term Follow-up may be conducted via telephone calls or patient chart reviews as necessary unless there is medical necessity requiring a clinical visit. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).
Concomitant medication review	X	X	ongoing						X	X	X	X	X	
Study Intervention and Pretreatment														
Bintrafusp alfa administration		X	X	X	X	X	X	X	Q2W					Bintrafusp alfa is administered as a 1200 mg IV infusion over 1 hour (-10 minutes/+20 minutes; ie, over 50 to 80 minutes) Q2W for up to 2 years (or up to 2 years from confirmed CR). See Section 6.1 for information.

	Screening	Intervention (treatment) Period									Safety Follow-up		Long Term Follow-up	Notes
Assessment and Procedures	**45 Day- to first dose**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Until PD**	**EOT**	**28 Days (±5 Days) After Last Treatment**	**12 Weeks (± 2 Weeks) After Last Treatment**	**Every 12 Weeks (± 2 Weeks)**	**D1: All assessments must be performed on day indicated (unless noted in assessment "Notes").** **Day 15 through PD: Visits can be performed ±3 days.** **EOT: On day of or within 7 days of decision to discontinue.** **Follow up: Visits can be performed ±2 Weeks.**
		W1	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**						
		D1	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**						
Response Assessments														
Tumor evaluation/ staging (CT Scan/MRI/ other established methods)	X					X			Q8W up to 6 months., then Q12W	X	X			CT scan with contrast of the chest, abdomen, and pelvis is required. Screening scans for lesion assessments are required within 28 days of first dose. See Section 8.3 for additional information Q8W for the first 6 months (mos.) and Q12W thereafter, and at the final study visit. Schedule should not be affected by dose interruptions/delays. Confirmation of CR and/or PR should be performed at the next scheduled assessment but no sooner than 4 weeks. Before stopping the treatment, progressive disease should be confirmed by imaging at least 4 weeks after progression. See Section 7.1.1. If discontinued intervention without documented progression, then continue imaging Q8W for the first 6 months followed by Q12W until documented PD, or the start of any new anti-cancer therapy. A bone scan should be done as clinically indicated at screening and beyond. TA brain CT/MRI scan should be performed as clinically indicated

	Screening	Intervention (treatment) Period									Safety Follow-up		Long Term Follow-up	Notes
Assessment and Procedures	**45 Day- to first dose**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Until PD**	**EOT**	**28 Days (±5 Days) After Last Treatment**	**12 Weeks (± 2 Weeks) After Last Treatment**	**Every 12 Weeks (± 2 Weeks)**	**D1: All assessments must be performed on day indicated (unless noted in assessment "Notes").** **Day 15 through PD: Visits can be performed ±3 days.** **EOT: On day of or within 7 days of decision to discontinue.** **Follow up: Visits can be performed ±2 Weeks.**
		W1	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**						
		D1	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**						
CCI														CCI
CCI														
Follow-up														
Follow up telephone call												X	X	Survival status. Participants who permanently discontinue study treatment due to disease progression (refer to Section 7.2), will be followed for survival and new anti-cancer therapy (including radiotherapy) Q12W until death or withdrawal of consent. After the DCO date, participants ongoing in the study will be followed according to Section 8.2.
Subsequent anti-cancer therapy (any line)											X	X	X	After DCO, subsequent anti-cancer therapy will not be collected.

Abbreviations: AE = adverse event; CBC = complete blood count; CCI ;CR = complete response; CT = computed tomography; D = day; DCO = data cut-off; CCI ECHO = echocardiogram; ECG = electrocardiogram; eCRF = electronic case report form; EOT = end-of-treatment; HBV = hepatitis B virus; β-hCG = beta human chorionic gonadotropin; HCV = hepatitis C virus ICF = informed consent form; IV = intravenous; MRI = magnetic resonance imaging; MUGA= Multigated Acquisition Scan; CCI PD = disease progression; PE = physical examination; CCI PR = partial response; Q2W = every 2 weeks; Q4W = every 4 weeks; Q6W = every 6 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; CCI SAE = serious adverse event; SRM = Study reference manual; TSH = thyroid-stimulating hormone, V = visit; W = week; WOCBP = women of child bearing potential.

- The timing and number of planned study assessments, including but not limited to safety, CCI [redacted] assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of CCI [redacted] to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging CCI [redacted] data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

2. INTRODUCTION

Bintrafusp alfa (MSB0011359C) is a first-in-class bifunctional fusion protein that combines an anti-programmed cell death-ligand 1 (PD-L1) receptor monoclonal antibody (mAb) and transforming growth factor beta (TGF-β) receptor II as a TGF-β neutralizing 'trap' into a single molecule. Bintrafusp alfa is designed to neutralize the clinically validated PD-L1 target as well as the novel TGF-β target. The approach is supported by preclinical data showing that bintrafusp alfa enhances antitumor activity and prolongs survival in mouse tumor models above the effect of either the anti-PD-L1 mAb or the TGF-β Trap control alone (at the same molarity as bintrafusp alfa). The purpose of this study is to evaluate bintrafusp alfa in participants with metastatic or locally advanced urothelial cancer.

This trial provides the first evaluation of bintrafusp alfa in participants with urothelial cancer that has progressed following platinum therapy.

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

2.1. Study Rationale

The bifunctional activity of bintrafusp alfa is well-suited for evaluation in urothelial cancer. Anti-programmed cell death 1/ligand 1 (PD-1/L1) receptor antibodies are approved for the treatment of locally advanced and metastatic urothelial cancers. However, TGF-β pathways are implicated in blunting the activity of these antibodies in this setting. See Section 2.2.2 for additional details. Bintrafusp alfa interferes with both PD-1/L1 and TGF-β pathways, and therefore, has the potential to be more active than currently approved checkpoint modulators.

2.2. Background

2.2.1. Urothelial Cancer

Worldwide 549,393 new cases of bladder cancer are diagnosed each year [Bray, 2018] Urothelial cancer is the most common histological type of bladder cancer, accounting for 90% of diagnoses in the United States (US) and Europe. In addition to the bladder, urothelial cancers can be diagnosed in the urethra, ureters, and renal pelvis. Approximately 25% of urothelial cancer patients, at diagnosis, will have disease that invades the detrusor muscle (muscle-invasive bladder cancer; MIBC) or is metastatic.

Patients with MIBC and metastatic disease are typically treated with surgery, radiation, and/or chemotherapy as determined by the stage of disease. Prognosis declines with more advanced disease [Sanli, 2017]. Gemcitabine plus cisplatin (GC) and methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) are common chemotherapy regimens with median OS outcomes of 13.8 and 14.8 months, respectively, for previously untreated patients with locally advanced (T4b, N2, N3) or metastatic (M1) disease [Von der Maase, 2000]. Fifty percent of patients may be unsuitable for cisplatin-containing therapy based on Eastern Cooperative Oncology Group performance status (ECOG PS), hearing loss,

neuropathy, or renal or cardiac function [Balar, 2017]. These patients sometimes receive carboplatin and gemcitabine, with median OS of only 9.3 months [De Santis, 2012]. Cisplatin-containing chemotherapy remains the first-line standard-of-care for those patients able to tolerate it, but most patients will eventually progress.

The development of immune checkpoint inhibitors has changed the treatment landscape and is improving the outlook for patients that have progressed after or are ineligible for cisplatin-based therapy. Since 2016, 5 antibodies blocking PD-1 or PD-L1 (i.e., pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab) have received approval for the treatment of urothelial cancer, in the US, European Union (EU), and other countries. Approved indications, depending upon the specific checkpoint inhibitor, include patients that have received or are not eligible for cisplatin-based chemotherapy. Overall response rates have ranged from 14% to 21% for patients that have received cisplatin to 23% to 29% for untreated patients ineligible for cisplatin. In single-arm trials, supporting accelerated/conditional approval, 12-month survival outcomes for participants that received anti-PD-1/L1 checkpoint modulators after cisplatin-based chemotherapy have ranged from 39% to 54%. In KEYNOTE-045 [Bellmunt, 2017], a randomized trial of pembrolizumab versus chemotherapy in participants that had received prior cisplatin therapy, supporting standard approval, the median overall survival (OS) was 10.4 months versus 7.3 months, respectively, and the OS hazard ratio (HR) was 0.7. Given the success of checkpoint inhibitor therapy in patients with urothelial cancers, numerous immunomodulatory combinations are under development to counteract resistance to single agent anti-PD-1/PD-L1 agents; such resistance can be multifactorial and may be related to immunosuppressive signal in the tumor stroma/microenvironment.

2.2.2. Role of TGF-β in Urothelial Cancer Pathogenesis and Clinical Outcome

Although anti-PD-1/L1 antibodies can achieve remarkable antitumor effects in patients with urothelial cancers, the magnitude of the clinical benefit may be limited by other factors in the tumor microenvironment, such as TGF-β. The IMvigor210 study was a Phase II trial evaluating atezolizumab after platinum-based chemotherapy [Mariathasan, 2018]. Assessments of pre-treatment tumor samples using RNA sequencing transcriptome analysis revealed a TGF-β signature that predicted lower response rates and diminished OS following treatment with atezolizumab. Nonclinical models suggested that TGF-β restricts the infiltration of tumors by T-cells, an effect reversed by coadministration of anti-PD-L1 and anti-TGF-β antibodies. Similarly, an exploratory RNA sequencing analysis of tumor samples from KEYNOTE-052 [Goudie, 2011; Grivas, 2019] a study of pembrolizumab monotherapy in participants with cisplatin-ineligible cancer, identified a stromal/TGF-β/EMT signature that predicted a less favorable efficacy outcome. Collectively, these data suggest that outcomes of patients with urothelial cancer could be influenced by TGF-β pathways independent of PD-1/L1.

2.2.3. CCI [redacted]

Bintrafusp alfa is bifunctional fusion protein designed to target 2 negative regulatory pathways of immunosuppression in the tumor microenvironment: the cell intrinsic pathway mediated by a tumor cell-immune cell interaction, in which PD-L1 plays a major

role, and the cell extrinsic pathway mediated by immunosuppressive cytokines, of which TGF-β is a prominent member. The anti-PD-L1 moiety of bintrafusp alfa is identical to the mAb avelumab (Bavencio), except for 3 amino acid substitutions in the heavy chain constant regions that result in a different human immunoglobulin (Ig) G1 allotype, and 1 amino acid substitution in the heavy chain for antibody fusion protein stability. Avelumab is approved in the US for the treatment of platinum-experienced, locally advanced or metastatic urothelial cancer that have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. TGF-β functions predominantly as an autocrine and a paracrine factor in the local tumor microenvironment, and the TGF-βRII component of bintrafusp alfa functions as a TGF-β neutralizing "trap." Therefore, a novel design such as bintrafusp alfa, which blocks both the cell intrinsic PD-L1/1 interaction and the immunosuppressive TGF-β, could be more effective than agents that target only a single pathway.

Bintrafusp alfa was shown to have full biological activity in vitro including the ability to block PD-L1 and neutralize TGF-β simultaneously. Experiments demonstrated that bintrafusp alfa strongly enhances antitumor activity and prolongs survival in mouse tumor models above the effect of either the anti-PD-1/L1 antibody or the TGF-β Trap control alone (at the same molarity as bintrafusp alfa). Details are discussed in the current IB.

2.2.4. Clinical Experience with Bintrafusp Alfa

Bintrafusp alfa has been administered to approximately 700 participants in Phase I development (EMR200647-001 and MS200647-0008) and is currently in Phase II and III development for multiple indications. Bintrafusp alfa has a favorable safety profile with known risks consistent with the bifunctional mechanism of action. In Phase I, bintrafusp alfa has shown encouraging efficacy outcomes, in particular, for participants with non-small cell lung cancer (NSCLC) and biliary tract cancer (BTC). The Phase I studies of bintrafusp alfa did not include participants with urothelial cancers. Details are discussed in the current IB.

2.2.5. Risk Assessment

Table 2 Benefit/Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Intervention Product: Bintrafusp alfa		
irAEs	Immune-related AEs have occurred, in Phase I and ongoing studies, at a frequency and severity similar to other checkpoint inhibitors.	• Eligibility criteria exclude participants with history of autoimmune disease. • irAE management guidelines are provided in Appendix 9.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Infusion-related reactions	Infusion-related reactions have been of mild to moderate severity in Phase I and ongoing studies.	• Eligibility criteria exclude participants with history of severe hypersensitivity reactions to monoclonal antibodies or any ingredient used in the study treatment formulation. • Participants who experience infusion related reactions may be premedicated with an antihistamine and with paracetamol (acetaminophen) (for example, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to each dose of bintrafusp alfa. Steroids as premedication are not permitted. • Infusion reaction management guidelines are provided in Section 6.8.3.
Dermatologic adverse events (attributable to TGF-β-inhibition)	Dermatologic AEs attributed to TGF-β-inhibition (including hyperkeratosis, KA, and cSCC) were observed in ~11% of participants in Phase I and ongoing studies. These lesions were previously observed in individuals with genetic mutations in the TGF-β receptor (ie, Ferguson-Smith Syndrome), and participants treated with the TGF-β-targeting agent, fresolimumab. (Goudie, 2011; Morris, 2014)	• AE surveillance instructions are provided in Appendix 9. • Skin AE management guidelines are provided in Section 6.8.2. KA and cSCC were managed in Phase I with simple excision and did not require any participant to discontinue treatment.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Anemia	Anemia is considered a potential risk based on toxicological findings with bintrafusp alfa in cynomolgus monkeys indicating a decrease in Hgb, RBC, and hematocrit which was fully reversible or showed a substantial trend toward recovery.	• Eligibility criteria include minimum hemoglobin requirements. • AE and CBC surveillance instructions are provided in Section 6.8.4. • Hematology surveillance, see SoA, Section 1.3, Table 1.
Mucosal bleeding	Mucosal bleeding is considered a potential risk based on clinical observations of epistaxis, hemoptysis, gingival bleeding, or hematuria of mild to moderate severity in Phase I studies EMR200647-001 and MS200647-0008.	• Eligibility criteria include minimum platelet and coagulation requirements. • AE surveillance instructions are provided in Appendix 9 In general, these reactions resolve without discontinuation of treatment.
Bleeding Events	Bleeding events are a potential risk.	• Eligibility criteria include an exclusion for bleeding diathesis or recent major bleeding. • AE surveillance/dose modification instructions are provided in Section 6.8.5.1.
Alterations of wound healing or repair of tissue damage	Alterations in wound healing or repair of tissue damage is considered a potential risk because TGF-β pathways have been implicated in repair of skin and other tissue injuries.	• AE surveillance instructions are provided in Appendix 9.
Embryofetal toxicities	Embryo-fetal toxicities are a known risk of the PD-1/ PD-L1 targeting class.	• Eligibility criteria include contraception requirements.

Abbreviations: KA=keratoacanthoma; cSCC= cutaneous squamous-cell carcinoma

2.2.6. Benefit Assessment

The anti-PD-L1 moiety of bintrafusp alfa is identical to the anti-PD-L1 monoclonal antibody avelumab (Bavencio), except for 3 amino acid substitutions in the heavy chain constant regions that result in a different human immunoglobulin (Ig) G1 allotype, and 1 amino acid substitution in the heavy chain for antibody fusion protein stability. Avelumab has been approved for the treatment of platinum-experienced, locally advanced or metastatic urothelial carcinoma in the USA based on a response rate of

16.1% and a 12-month OS of 54.3%. Bintrafusp alfa is a bifunctional biologic that combines anti-PD-L1 activity with transforming growth factor beta (TGF-β) receptor II as a TGF-β neutralizing 'trap' into a single molecule. Preclinical models have shown bintrafusp alfa that bintrafusp alfa enhances antitumor activity and prolongs survival in mouse tumor models above the effect of either the anti-PD-L1 mAb or the TGF-β Trap control alone. In Phase I, bintrafusp alfa has shown encouraging efficacy outcomes in selected indications.

Bintrafusp alfa is well-suited for therapeutic evaluation in urothelial cancer due to its ability to interfere with both PD-1/L1 and TGF-β pathways. Preclinical experiments demonstrate that bintrafusp alfa strongly enhances antitumor activity and prolongs survival in mouse tumor models above the effect of either the anti-PD-1/L1 antibody or the TGF-β Trap control alone (at the same molarity as bintrafusp alfa). Therefore, we hypothesize that it is more efficacious than currently approved checkpoint inhibitors.

2.2.7. Overall Benefit-Risk Assessment

Anti-PD-1/PD-L1 antibodies are standard therapies in patients that have progressed after platinum-based chemotherapy. Bintrafusp alfa includes anti-PD-L1 function as well as an anti-TGF-β Trap function. Given the manageable safety profile of bintrafusp alfa in ongoing studies and the evidence for activity in Phase I, the benefit-risk assessment for this study remains favorable. The benefit-risk for bintrafusp alfa will be continuously evaluated based on emerging data from the current and other studies of the study intervention.

Additional information about the known and expected benefits and risks and reasonably expected AEs of bintrafusp alfa are found in Section 2.2.5 and Section 2.2.6, and the current version of the IB. See Section 2.2.5 and Section 6.8 for special precautions and management of AEs, respectively.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• Evaluate the antitumor activity per RECIST 1.1.in participants with metastatic or locally advanced/unresectable urothelial cancer treated with bintrafusp alfa.	• Confirmed Overall Response per RECIST 1.1 assessed by investigator.
Secondary	
• Evaluate the safety and tolerability of bintrafusp alfa in participants with urothelial cancer.	• Frequency and severity of AEs using NCI-CTCAE v5.

CCI

[redacted]

Objectives	Endpoints
CCI [redacted]	

CCI [redacted] CCI [redacted] CCI [redacted]

NCI-CTCAE v5 = National Cancer Institute-Common Terminology Criteria for Adverse Events, version 5; CCI [redacted] CCI [redacted] ORR = overall response rate; CCI [redacted] PD = progressive disease; CCI [redacted] CCI [redacted] PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; CCI [redacted] SD = stable disease; TGF-β = transforming growth factor beta.

4. STUDY DESIGN

Based on the lack of efficacy of bintrafusp alfa in clinical studies in other tumor types, and a rapidly evolving treatment landscape for urothelial cancer, the study sponsor has decided to cease enrollment into the study. In line with the sponsor's decision, this protocol has been amended to provide updated instructions for continued study conduct.

4.1. Overall Design

This is a Phase Ib open-label, global, multicenter, single-arm trial of bintrafusp alfa administered to participants with metastatic or locally advanced/unresectable urothelial cancer with disease progression or recurrence following treatment with a platinum agent.

The primary study objective is to evaluate the objective response rate (ORR) per RECIST v1.1. Secondary objectives include evaluation of safety and tolerability of bintrafusp alfa.

Participants who permanently discontinue study treatment will enter the follow-up period of the study and undergo the assessments as indicated in Section 8.

Approximately 25 participants will be treated in this study.

The study includes:

- 45-day screening period
- Treatment with bintrafusp alfa 1200 mg as an IV infusion Q2W until disease progression as determined by the investigator using RECIST v1.1 [Eisenhauer, 2009] death, unacceptable toxicity, study withdrawal, or up to 2 years (see Section 7).
- Participants who have experienced a confirmed complete response (CR) can continue treatment for a maximum of 24 months after confirmation of response (at the discretion of the investigator). If the investigator believes that a participant with confirmed CR may benefit from treatment beyond 24 months, it may be permissible to continue treatment after discussion with the GSK medical monitor.
- Participants with SD or PR should continue treatment up to a period of 24 months from first dose until disease progression, or any other discontinuation criterion is met.
- Safety Follow-up: will continue until 12 weeks after the last dose of bintrafusp alfa. The 12-week Safety Follow-up can be conducted via telephone calls or patient chart reviews unless there is medical necessity requiring a clinical visit.
- Long-term Follow-up: should be performed every 12 weeks after the Safety Follow-up according to the Schedule of Activities (SoA; see Table 1). Long-term Follow-up should be performed by chart reviews or telephone calls.
- Once the DCO date for the final analysis for this study has been reached, the clinical study database will be closed to new data and any participants that continue to receive study intervention at this time will be followed as described in Section 8.2.

Biopsies prior to study treatment are required, as described in eligibility criteria (Section 5.1). CCI [redacted] CCI [redacted]

The overall study design is shown in the Study Schema [Figure 1]. A detailed SoA is located in Table 1.

4.2. Scientific Rationale for Study Design

The bifunctional activity of bintrafusp alfa is well-suited for evaluation in urothelial cancer. Anti-PD-1/PD-L1 antibodies are approved for the treatment of locally advanced and metastatic urothelial cancers. However, Transforming Growth Factor β (TGF-β) pathways are implicated in blunting the activity of these antibodies in urothelial cancers. Bintrafusp alfa interferes with both PD-1/PD-L1 and TGF-β pathways, and therefore, has the potential to be more active than currently approved checkpoint modulators.

4.3. Justification for Dose

The recommended Phase II dose (RP2D) for bintrafusp alfa is 1200 mg CCI [redacted] as an IV infusion Q2W. The selection of RP2D is based on the available clinical data from the Phase I Studies EMR200647-001 and MS200647-0008, including safety/tolerability, PK, and pharmacodynamics (PD L1 target occupancy in peripheral blood mononuclear cell and TGF-β plasma concentrations), as well as efficacy in second-line NSCLC cohorts from the EMR200647-001 study. The selection of RP2D is also supported by population pharmacokinetic (PopPK) and exposure response modeling and simulation. The dose is being investigated in ongoing Phase II/III studies of bintrafusp alfa.

Refer to the IB for detailed data and analyses supporting the RP2D.

4.4. Archival Tumor Biopsy: PD-L1 Status

Archival tissue will be submitted to a central laboratory to confirm expression of PD-L1 at the time of screening. (The most recently collected archival tumor tissue is requested). Analyses will be performed retrospectively, using the SP263 PD-L1 assay.

4.5. Fresh Tumor Biopsy

Baseline tumor biopsy (during 45-day screening period) is required for enrollment into this study (See Section 8.11.2) (See Section 5.1, Inclusion Criterion #5). A limited number of participants (maximum 10) that are unsuitable for biopsy (e.g., unacceptable risk, tumor characteristics are likely to yield inadequate specimens, etc.) may be considered for enrollment following discussion with the sponsor.

Biopsies on treatment and at disease progression are optional.

4.6. Number of Participants

Approximately 25 participants will be treated in this study. Participants who discontinue will not be replaced. See Section 9.3 for definitions of the populations for analyses.

Pending evidence for favorable benefit:risk as compared to standard therapies, the trial may be expanded, following amendment.

4.7. End of Study Definition

A participant has completed the study if he or she has completed all study parts, including the last visit or the last scheduled procedure shown in Table 1.

The end of the study (EOS) is defined as when the last participant's last visit has been reached. Note that any serious adverse events (SAEs) ongoing at the EOS will be followed as outlined in Section 8.5.2.

The sponsor will initiate final study reporting following the DCO date.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. Can give signed informed consent/assent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
2. At least eighteen (18) years of age at the time of signing the informed consent.
3. Histologically confirmed locally advanced or metastatic or locally advanced/unresectable urothelial carcinoma (including renal pelvis, ureter, urinary bladder, urethra). Mixed histologies are acceptable provided transitional cell carcinoma is the predominant histology.
   a) Measurable disease per RECIST v1.1 criteria.
   b) Experienced disease progression or recurrence either (1) following platinum-containing chemotherapy for metastatic or locally advanced/unresectable urothelial cancer or (2) within 12 months from completion of neo-adjuvant or adjuvant platinum-containing chemotherapy for localized muscle-invasive urothelial cancer.
4. Able to provide, a tumor tissue sample collected during screening and prior to administration of bintrafusp alfa (see Study Reference Manual [SRM] for details). See Section 4.5
5. Able to provide an archival tumor sample (preferably from the most recent biopsy). Archival material is formalin fixed tumor tissue sample from a biopsy of a tumor lesion. See SRM and Section 8.11.2 for further details on tumor tissue requirements.
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1. See Appendix 10.
7. Adequate organ system functions as defined by the laboratory assessments listed in Appendix 2.

System	Laboratory Values
Hematologic[a]	
ANC	≥1.5 x 10^9/L
Hemoglobin	≥9 g/dL
Platelets	≥100 x 10^9/L
INR or PT[b]	≤1.5 x ULN
Hepatic	
Albumin	≥2.5 g/dL
ALT and AST	≤2.5 x ULN or ≤5 x ULN for participants with documented liver metastases
Total bilirubin	Bilirubin ≤1.5 x ULN (isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
Renal	
Calculated CrCl[c]	≥30 mL/min
Cardiac	
Ejection Fraction[d]	≥50%

Abbreviations: ANC = Absolute neutrophil count; ALT = alanine aminotransferase; CrCl = creatinine clearance; ECHO=echocardiogram; eGFR=estimated glomerular filtration rate; MUGA= multigated acquisition scan; ULN = upper limit of normal; WNL = within normal limits

a. Participants may be transfused or receive growth factor treatment to meet minimum hematologic values up to 10 days prior to determining eligibility.
b. Participants receiving anticoagulant therapy exempt.
c. Estimated CrCl/eGFR is required to be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or Cockcroft-Gault formula; either formula is acceptable and must be consistently used for each participant throughout the study. Alternatively, investigators may use 24-hour urine to determine CrCl (refer to Appendix 11).
d. MUGA is acceptable if ECHO is not available; for each participant the same modality must be used for all subsequent evaluations.

8. Life expectancy of at least 12 weeks.

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

- Not a woman of childbearing potential (WOCBP) as defined in Appendix 4.

OR

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

OR

        - Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay.

- During the intervention period
- After the study intervention period (i.e., after the last dose of study intervention is administered) for at least 2 months.

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

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

Additional requirements for pregnancy testing during and after study intervention are in Appendix 2.

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.

Male participants:

- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
- Male participants are eligible to participate if they agree to the following from the time of first dose of study until 125 days after the last dose of study treatment to allow for clearance of any altered sperm:
  - Refrain from donating sperm.

  PLUS, either:

  - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on long term and persistent basis) and agree to remain abstinent.

  OR

  - Must agree to use contraception/barrier as detailed below.
- Agree to use a male condom and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Section 10.4.2 when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

5.2. Exclusion Criteria

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

Medical Conditions

1. Active brain and/or leptomeningeal disease that is symptomatic or requires therapeutic intervention. Participants with asymptomatic CNS metastases who are

clinically stable as demonstrated by serial brain images and have no requirement for corticosteroids for at least 14 days prior to enrollment are eligible.

2. History of malignancy other than urothelial cancer within the last 3 years except for localized tumors that have been treated with curative intent or have not required therapy in the past 2 years. (e.g., resected non-melanoma skin cancer, etc.).
3. No more than 2 lines of systemic therapy for the treatment of metastatic disease. If the most recent therapy was not a platinum-based regimen, the participant must have progressed on or after that therapy.
4. Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice.

   NOTE: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) is acceptable if participant otherwise meets entry criteria.
5. Current pneumonitis or history of non-infectious pneumonitis that required systemic immunosuppressive treatment.
6. Active autoimmune disease that required systemic immunosuppressive treatment within the past 2 years.
7. Received prior allogeneic/autologous bone marrow or solid organ transplant.
8. Receiving systemic corticosteroids (>10 mg daily oral prednisone or equivalent) or other immunosuppressive agent within 7 days prior to study treatment. Inhaled or topical steroids are permitted.

   Note:
   a) Physiologic doses of corticosteroids for treatment of endocrinopathies or steroids with minimal systemic absorption, including (e.g., topical, inhaled, intra-articular, ophthalmic, intranasal); corticosteroids may be continued if the participant is on a stable dose
   b) Steroids as premedication for hypersensitivity reactions (e.g., computed tomography [CT] scan premedication) are permitted.

9. Known severe hypersensitivity reactions to monoclonal antibodies or any ingredient used in the study treatment formulation (Grade ≥3 according to National Cancer Institute-Common Terminology Criteria for Adverse Events, version 5 [NCI-CTCAE v5]).
10. Active infection requiring systemic therapy.
11. Received any live vaccine within 30 days prior first dose of intervention.
12. Known history of positive test for human immunodeficiency virus (HIV) with the exception of participants with CD4+ T-cell (CD4+) counts ≥350 cells/μL and no history of AIDS-defining opportunistic infections.
13. Active hepatitis B virus (HBV) (HBV surface antigen-positive).
14. Active hepatitis C virus (HCV) infection, or positive HCV antibody, with the exception of participants that (1) have HCV viral load below the limits of

quantitation and (2) completed curative antiviral therapy or are receiving and compliant with antiviral therapy

15. History or evidence of cardiac abnormalities within the 6 months prior to first dose of intervention which include:

    a. Serious, uncontrolled cardiac arrhythmia or clinically significant electrocardiogram abnormalities including second degree (Type II) or third-degree atrioventricular block or QTcF interval >450 msec (or QTcF >480 msec for participants with bundle branch block).

    b. Cardiomyopathy, myocardial infarction, acute coronary syndromes (including unstable angina pectoris), coronary angioplasty, stenting or bypass grafting

    c. Congestive heart failure (Class II, III, or IV) as defined by the New York Heart Association functional classification system

    d. Symptomatic pericarditis

16. Participants with history of bleeding diathesis or recent major bleeding events considered by the investigator as high risk for investigational drug treatment are also excluded.
17. Any other serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.

Prior/Concomitant Therapy

18. Received prior systemic anti-cancer therapy within 2 weeks prior to study treatment.
19. Received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
20. Received prior therapy targeting TGF-β (e.g., Galunistertib, etc.).
21. Received radiation therapy (or other non-systemic disease therapy) within 2 weeks prior to study treatment.
22. Undergone major surgery within 4 weeks prior to administration of study treatment.
23. Residual toxicities attributed to prior anti-cancer therapy that are clinically significant or unmanaged and > Grade 1 or previous baseline other than neuropathy (≤ Grade 2), alopecia, and fatigue.
24. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 35 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

25. Exposure to more than 2 investigational anti-cancer medicinal products within 12 months prior to the first dosing day.

Other Exclusions

26. Is known to abuse alcohol or drugs.
27. Has any psychiatric condition that would prohibit the understanding or rendering of informed consent or consistent participation in study procedures?
28. Has legal incapacity or limited legal capacity.

5.3. Lifestyle Considerations

No lifestyle restrictions are planned for this study; however, male participants with partners of childbearing potential and women of childbearing potential must utilize appropriate contraception as described in Appendix 4.

5.3.1. Meals and Dietary Restrictions

Not applicable.

5.3.2. Alcohol and Tobacco Use

Alcohol and tobacco use will be collected in the eCRF. See Table 1.

5.3.3. Activity

Participants will provide one or more biopsies during the study and are expected to limit activity according to institutional protocols relevant to the biopsy site.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any SAEs.

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

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Bintrafusp alfa is administered as a 1200 mg IV infusion over 1 hour (-10 minutes/ +20 minutes; i.e., over 50 to 80 minutes) Q2W for up to 2 years from first dose or 2 years from the time of confirmed CR.

Intervention Name	**Bintrafusp alfa**
CCI [redacted]	
Dosage Form	Solution for infusion
Unit Dose Strength(s)/Dose Level	10 mg/mL in single-use glass vials.
Route of Administration	Intravenous infusion
Dosing Instructions	1200 mg over 1 hour (-10 minutes/+20 minutes; ie, over 50 to 80 minutes) once every 2 weeks. See Section 6.8.3 for special precautions and management of adverse events.
Supplier Information	Bintrafusp alfa will be supplied by the sponsor and packaged, labelled, and distributed for clinical studies by a suitable service provider and finally released by a Sponsor qualified person according to Good Manufacturing Practices.
Packaging and Labeling	Bintrafusp alfa is formulated as a 10 mg/mL solution and is supplied by the sponsor in USP/Ph Eur type I vials filled to allow an extractable volume of 60 mL (600 mg/60 mL) and closed with rubber stoppers in serum format complying with USP and Ph Eur with an aluminum crimp seal closure. Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

6.2. Preparation/Handling/Storage/Accountability

Further guidance and information for the preparation, handling, and storage of study intervention(s) are provided in the Pharmacy Manual.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. Further guidance and information for final disposition of unused study treatment are provided in SPM.

3. 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).
4. Further guidance and information for the final disposition of unused study intervention are provided in the SRM and Pharmacy Manual.

- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and generation of aerosols and mists. In case of unintentional occupational exposure notify the monitor, medical monitor, and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

Precaution will be taken to avoid direct contact with the study intervention. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, medical monitor and/or GSK study contact.

6.3. Measures to Minimize Bias: Randomization and Blinding

This study is a single arm, non-blinded or randomized trial.

6.4. Storage

Bintrafusp alfa drug product should be stored in a refrigerator (2°C to 8°C) until use. Bintrafusp alfa must not be frozen and should be stored in the original packaging.

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

6.5. Treatment Compliance

Study treatments will be intravenously administered to participants at the site. Administration will be documented in the source documents and reported in the eCRF.

6.6. Concomitant Medications and Non-Drug Therapies

Participants should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate. Participants will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the study (Final Study Visit). Any concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the electronic case report form (eCRF). The minimum requirement is that drug name, dose and the dates of administration are to be recorded. Additionally, a complete list of all prior anti-cancer therapies will be recorded in the eCRF.

Palliative radiotherapy may be administered to non-target lesions during the study following discussion with the medical monitor. The indication, dose and dates of administration are to be recorded in the eCRF.

Questions regarding concomitant medications should be directed to the GSK medical monitor for clarification.

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

6.6.1. Prohibited Medicines

Anti-cancer therapy other than bintrafusp alfa (e.g., chemotherapy, radiotherapy, immunotherapy, investigational, etc.) is prohibited except as noted in Section 6.6.

Systemic immunosuppressive drugs are prohibited except as required for the short-term treatment of allergic reactions or immune-related AEs.

Live vaccines should not be administered.

6.7. Dose Modification

Bintrafusp alfa will be administered according to Table 1. Dose modifications are not permitted with the exception of the allowance for bleeding events noted in Section 6.8.5. Dose interruptions are allowed as described Table 3. If there is a dose delay, efficacy assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays.

6.8. Management of Adverse Events of Interest

Adverse events of interest are serious or nonserious AEs specific to the known mechanism of action of the study intervention that are of clinical interest requiring ongoing monitoring.

6.8.1. Immune-related Adverse Events

Immune-related AEs are specific to immunotherapies and vary by organ system. Immune-related AEs are important identified risks for bintrafusp alfa.

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

- Grade 1: study treatment should be continued with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities.
- Grade 2: study treatment may be suspended for most Grade 2 toxicities, with consideration of resuming when symptoms revert to Grade 1 or less. Corticosteroids may be administered (initial dose of 0.5 to 1 mg/kg/d of prednisone or equivalent).

- Grade 3: study treatment is generally suspended and the high-dose corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisolone 1 to 2 mg/kg/d) treatment should be initiated. Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy.
- Grade 4: in general, permanent discontinuation of study treatment is recommended, with the exception of endocrinopathies that have been controlled by hormone replacement.

Detailed recommendations for irAE management of specific organ systems as per published guidelines are provided in Appendix 9 . These recommendations are in accordance with ASCO Clinical Practice Guidelines in collaboration with NCCN guidelines (Brahmer, 2018).

6.8.2. Potential TGF-β Mediated Dermatologic Adverse Events

Management guidelines for potential TGF-β-mediated dermatologic AEs:

- Discontinuation or interruption of study treatment is generally not required. Continuation of treatment should be evaluated by the investigator.
- Emollients may continue to be used. Diagnostic and treatment plan should be developed in collaboration between investigator and dermatologist. In general, treatment of TGF-β-mediated dermatologic lesions such as hyperkeratosis, KA and cSCC should be based on local guidelines/standard of care. Lesion evaluation should include excision biopsy of one representative lesion to confirm diagnosis.
- Treatment and follow-up for KA and cSCC will depend on number and localization of lesions.
    - For single lesions: Full excision may be recommended.
    - For multiple lesions or location not suitable for full excision other treatment options may be offered by the dermatologist, such as Mohs surgery, cryotherapy, or other standard treatment options depending on the pathology. Use of retinoids if recommended by dermatologist, may be considered after discussion with medical monitor.
- Close clinical follow-up for re-evaluation, resolution, or potential recurrence should be implemented. Spontaneous resolution of KA lesions without surgical intervention has been observed, typically occurring within weeks after discontinuing bintrafusp alfa.

The number and localization of lesions, diagnosis (including histopathological diagnosis), treatment, and outcome should be appropriately documented in the eCRF. Consult with study medical monitor as needed for management of TGF-β-mediated dermatologic lesions.

6.8.3. Infusion-related Reactions Including Immediate Hypersensitivity

Infusion-related reactions (IRRs) including immediate hypersensitivity are important identified risks for bintrafusp alfa.

Infusion reactions may vary in manifestation and timing, and signs and symptoms usually develop during or shortly after drug infusion which generally resolves completely within 24 hours of completion of infusion.

Further information regarding mitigation of IRRs are detailed in Table 2.

As a routine precaution, for the first 2 infusions, all participants enrolled in this study must be observed for 2 hours post end of infusion, in an area with resuscitation equipment and emergency agents.

At all times during bintrafusp alfa study treatment, immediate emergency treatment of an IRR or a severe hypersensitivity reaction according to institutional standards must be assured. To treat possible hypersensitivity reactions like anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.

Table 3 Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE v5 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.
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.	• Stop bintrafusp alfa infusion. Increased monitoring of vital signs as medically indicated as participants are deemed medically stable by attending investigator. If symptoms resolve quickly or decreased to Grade 1, resume infusion at 50% of original rate with close monitoring of any worsening otherwise dosing held until resolution of symptoms with mandated premedication for the next schedule. If worsens to Grade 3 or 4, follow treatment modification guidelines accordingly.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (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 bintrafusp alfa infusion immediately and disconnect infusion tubing from the participant with additional appropriate medical measures and close monitoring until deemed medically stable by attending investigator. Hospitalization may be indicated. • Participants will be permanently withdrawn immediately from bintrafusp alfa treatment and must not receive any further bintrafusp alfa treatment

IV = intravenous; NCI-CTCAE v5= National Cancer Institute-Common Terminology Criteria for Adverse Events, version 5; NSAIDs = nonsteroidal anti-inflammatory drugs.
For Grade 3 or 4 infusion-related reactions, bintrafusp alfa discontinuation is mandated.
For all types and grades of infusion reactions, details about drug physical constitution, method of preparation and infusion must be recorded.

In the event of a Grade 2 IRR that does not improve or worsens after implementation of the dose modifications indicated in Table 3 (including reducing the infusion rate by 50%), the investigator may consider treatment with corticosteroids and the infusion should be stopped for that day. At the next infusion, the investigator may consider the addition of H2 blocker antihistamines (for example, famotidine or ranitidine), in addition

to premedication, for select participants. However, prophylactic steroids are NOT permitted. At next dose, if the participant has a second IRR Grade ≥2 on the slower infusion rate, with the addition of further medication to premedication, the infusion should be stopped, and the participant removed from treatment.

If a severe hypersensitivity reaction occurs, the participant must be treated according to the best available medical practice. Management of hypersensitivity may include:

1. Epinephrine injection and IV dexamethasone
2. Cardiac, blood pressure, heart rate, and oxygen saturation monitoring
3. Intensive care unit transfer if required.

Participants should be instructed to report any delayed reactions to the investigator.

6.8.4. Treatment-related Anemia

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

General guidance for anemia management and evaluation:

1. Participants must enter the study with hemoglobin values at least 9 g/dL; routine blood test parameters are specified in Appendix 2.
2. Transfusion should be performed at the discretion of the investigator.
3. Relevant hematologic testing for treatment-related anemias should be done prior to blood transfusion, if clinically feasible. Guidance for evaluation of suspected treatment-related anemias is provided in Table 4.
4. Discuss further management with medical monitor for clinically significant treatment-related anemias.

Guidance for evaluation of suspected treatment-related anemias is provided in Table 4.

Table 4 Evaluation Guidance of Suspected Treatment-related Anemia Adverse Events

Baseline anemia evaluation (prior to transfusion, if feasible)	
Hb and CBC with differential (eg, MCV, RDW, ANC, hematocrit, reticulocytes counts) Peripheral blood smear for cell morphological assessment Complete metabolic panel including liver panel-LFTs, bilirubin, LDH, renal function, and serum folate, B12 values and other chemistries Coagulation factors (PT, PTT, INR) Urinalysis including culture Iron panel (TIBC, ferritin, iron) TSH/hormonal panel Fecal-occult blood testing Erythropoietin Haptoglobin	
Further recommendation based on suspected etiology (in addition to Baseline anemia testing)	
Unknown etiology, suspect possible hemolysis	Coombs test, fibrinogen, d-dimer Consider hematology consultation. Consider blood transfusion at clinical discretion.
Unknown etiology, suspect possible bleeding	Consider blood transfusion at clinical discretion. Consider surgical/interventional radiology consultation. Consider imaging, as clinically indicated (eg, FAST scan, CT scan, MRI, angiography). Consider endoscopy (upper/lower)
Unknown etiology despite above work-up	Hematology consultation Consider bone marrow aspiration/morphologic evaluation

ANC = absolute neutrophil count; CBC = complete blood count; CT = computed tomography; FAST = focused assessment with sonography for trauma; Hb = hemoglobin; INR = international normalized ratio; LDH = lactate dehydrogenase; LFT = liver function test; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; PT =prothrombin time; PTT = partial thromboplastin time; RDW = red cell distribution width; TIBC = total iron-binding capacity; TSH = thyroid-stimulating hormone.

6.8.5. Additional Risks

6.8.5.1. Bleeding Events

Bleeding events are a potential risk for bintrafusp alfa (refer to IB).

For all participants:

For Grade ≥2 tumor bleeding, study treatment must be held until the event recovers to Grade ≤1. If a Grade ≥3 tumor bleeding event has been observed, regardless of causality with the study intervention, upon resumption of the study intervention the bintrafusp alfa dose should be reduced to 600 mg Q2W. Once there is stable resolution and no recurrence of bleeding on the reduced dose, the investigator is encouraged to communicate with the medical monitor regarding a potential dose re-escalation after careful benefit-risk assessment. Treatment should be permanently discontinued if the investigator considers the participant to be at risk for additional severe bleeding. In case of a rapid decrease of hemoglobin (Hgb), see Table A8 (Management of Hematologic irAEs in Patients Treated with ICPis) in Section 10.9.

If a Grade ≥3 non-tumor bleeding event is observed, study treatment must be permanently discontinued unless an alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic event, etc.). In case of alternative explanations for the Grade ≥3 bleeding event, study treatment should be held until the event recovers to Grade ≤1. If a Grade ≥3 bleeding event is observed, regardless of causality with the study intervention, upon resumption of study intervention, the bintrafusp alfa dose should be reduced to 600 mg Q2W. Once a Hgb decrease recovers to Grade ≤1 or there is stable resolution and no recurrence of bleeding on the reduced dose, the investigator is encouraged to communicate with the medical monitor regarding a potential dose re-escalation after careful benefit-risk assessment. The dose of bintrafusp alfa may be re-escalated to full dose (1200 mg Q2W) once Hgb is stabilized without further need for blood transfusion in the subsequent cycles. The timing of re-escalation will be determined on a case-by-case basis. See Section 6.8.4 regarding the stabilization of anemia.

For Grade 4 non-tumor bleeding, treatment must be permanently discontinued if no alternative explanation is identified. In case of rapid decrease of Hgb, such as a decrease greater than 2.0 g/dL across a 2-week period, withhold the subsequent cycles of study intervention until HgB is stabilized and do a thorough assessment of bleeding (for example, upper and lower gastrointestinal [GI] endoscopy, contrast-enhanced CT scan, etc.). If Grade ≥1 bleeding is observed or suspected, withhold the bintrafusp alfa until the bleeding is resolved/controlled and resume the dose of bintrafusp alfa, decreased to 600 mg Q2W. The dose of bintrafusp alfa may be re-escalated to full dose (1200 mg Q2W) once Hgb is stabilized to Grade 1 or baseline without further need for blood transfusion in the subsequent cycles; the investigator is encouraged to communicate with the medical monitor to re-escalate the dose. The timing of re-escalation will be determined on a case-by-case basis. See Section 6.8.4 regarding stabilization of anemia.

6.8.5.2. Alterations in Wound Healing or Repair of Tissue Damage

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

6.8.5.3. Embryofetal Toxicity

Embryo-fetal toxicities are a known risk of the PD-1/L1 targeting class. Animal models link the PD-1/L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Embryo-fetal and reproductive toxicities have also been investigated in animal models for a humanized monoclonal antibody targeting TGF-β1. At doses as high as 30 mg/kg, no maternal reproductive toxicity or embryo-fetal lethality were observed in rabbits (Hilbish, 2016). To mitigate these potential risks, pregnant participants are excluded from the study, and all participants of childbearing/conceiving potential must use highly-effective contraception.

6.9. Intervention After the End of the Study

Study participants that continue to benefit from study intervention beyond the DCO date will continue to have access to study intervention until the EOS as defined in Section 4.7. There is no planned intervention following the EOS.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

Refer to the SoA (Table 1) for follow-up assessments of participants who are to be followed for disease progression and survival after they permanently discontinue from bintrafusp alfa until the DCO date and from the DCO date to the EOS.

6.10. Continued Access to Study Intervention After Data Cut-off

Participants who are considered to be deriving benefit from study intervention by the investigator, with agreement with the GSK medical monitor, and who do not meet any protocol-defined treatment discontinuation criteria may continue to receive study intervention after the DCO date for up to 2 years after their first dose or up to 2 years from time of confirmed CR. Please see the SRM for details regarding drug resupply.

Drug accountability data will also be collected at site visits.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In some instances, it may be necessary for a participant to permanently discontinue study intervention for any of the following reasons:

- A participant may discontinue from the study intervention at any time at his/her own request (i.e., withdrawal of consent), and without giving a reason.
- Occurrence of an exclusion criterion, which is clinically relevant and affects the participant's safety, if discontinuation is considered necessary by the investigator and/or sponsor.
- A participant may be discontinued at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons (See Section 6.8 for TEAEs and AEs of Interest that require treatment discontinuation).
- Confirmed PD per RECIST 1.1, with the exception that participants receiving treatment may continue past PD if the participant's ECOG PS has remained at least stable, and if in the opinion of the investigator, the participant will benefit from continued treatment (See Section 7.1.1).
- Unacceptable toxicity.
- Some TEAEs and AEs of Interest require withdrawal from treatment (Section 6.8).
- Drug must not be given to a known pregnant participant (refer to Appendix 4).
- Use of a prohibited concomitant drug, as defined in Section 6.6.1, where the predefined consequence is withdrawal from the study intervention.

The SoA (Table 1) specifies the data to collect at study intervention discontinuation, 28-day safety follow-up, follow-up, and any additional evaluations that need to be completed.

In case of discontinuation from the study intervention:

- The day of End-of-Treatment will correspond to the day of withdrawal (or within 7 days).

- An attempt should be made to perform all assessments scheduled for the End-of-Treatment visit if possible. If not possible, the most clinically relevant assessments and appropriate eCRFs for the End-of-Treatment visit should be prioritized as feasible.

- Participants will be asked to continue Safety and Survival Follow-up, which includes the collection of data on survival, and subsequent anti-cancer therapy. After completion of the follow-up period or after the End-of-Treatment visit, whichever is applicable, the appropriate eCRF section for Study Termination must be completed.

- If the participant is enrolled into a new study or any new therapy post-withdrawal from study intervention, the Safety Follow-up visit should be scheduled prior to the start of the new treatment irrespective of the 28-day Safety Follow-up period.

- For participants discontinuing from study treatment after the DCO date for final analysis, no study-specific visits or eCRF completion will be required per Section 8.2.

7.1.1. Disease Progression

Disease progression must be assessed by the investigator and documented in the participants CRF. Before stopping the treatment, progressive disease should be confirmed by imaging at least 4 weeks after progression according to RECIST v1.1 unless:

- Study intervention is not tolerated, or

- ECOG PS is declining, or

- The investigator considers an alternative intervention to be in the best interest of the study participant.

The decision to continue treatment beyond confirmed PD should be discussed with the medical monitor and documented in the study records if the investigator believes that the participant would continue to benefit according to Table 1.

Participants who continue beyond progression will be evaluated for further tumor response as per the protocol schedule. Treatment should be discontinued upon documentation of further, unequivocal, disease progression or upon meeting any other criteria for discontinuation.

7.1.2. Liver Chemistry Stopping Criteria

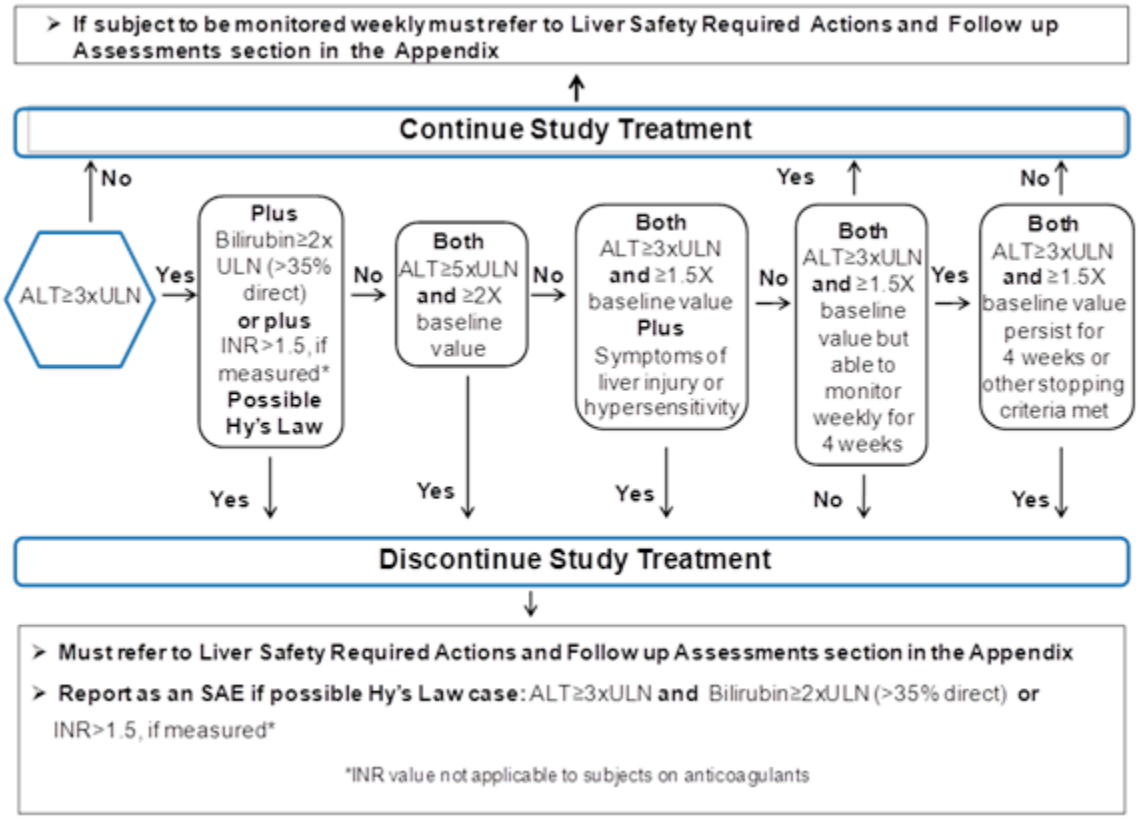
Liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in Appendix 6.

- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.

Figure 2 Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm including Participants <u>WITH</u> documented liver metastases/tumor infiltration at baseline AND entry criteria ALT >2.5x ULN but ≤5x ULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

7.1.2.1. Study Intervention Restart or Rechallenge after liver stopping criteria

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.1.3. QTc Stopping Criteria

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
  - For example, if a participant is eligible for the protocol based on QTcF, then QTcF must be used for discontinuation of this individual participant as well.
  - Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.

- The scheduled QTc evaluations should be based on single ECG readings.
- Withdrawal of participants is to be based on an average QTcF value of triplicate ECGs. If a single ECG demonstrates a prolonged QTcF interval, then obtain 2 more ECGs over a brief period (e.g., 5-10 minutes) and then use the averaged QTcF values of the 3 ECGs to determine whether the participant should be discontinued from the study.
    - If a participant meets either of the following criteria, they must be discontinued from study treatment: QTcF >500 msec OR Change from baseline of QTcF >60 msec.
    - For participants with underlying bundle branch block and baseline QTcF <450 msec, discontinue if QTcF is >500 msec. For participants with baseline QTcF 450-480 msec, discontinue if QTcF is >530 msec.
    - QTcF = QT duration corrected for heart rate by Fridericia's formula. See the SoA (Table 1) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.4. Adverse Drug Reaction Stopping Criteria

Adverse drug reactions are defined in this study as any AEs related to study intervention assessed by the investigator and/or sponsor.

Management guidelines for AEs of Interest (Immune-related AEs, TGF-β-mediated dermatologic AEs, Infusion-related reactions, and treatment-related anemia) as described in Section 6.8 supersede the general guidelines below.

Adverse Drug Reactions (ADRs) requiring discontinuation of study treatment include:

- Any Grade 4 ADRs.
- Persistent Grade 3 non-hematologic ADRs that do not recover to Grade 0 or 1 within 6 weeks after dose of treatment Recurrent Grade 3 ADRs (after recovery to Grade 0 or 1) that last more than 72 hours, with optimal medical management, also require discontinuation.
- Any ADR requiring treatment with corticosteroids beyond 12 weeks at doses greater than 10 mg prednisone (or equivalent) per day.

Exceptions to the criteria for discontinuation:

- Fatigue.
- Isolated laboratory values out of normal range that do not have any clinical correlation.
- Endocrinopathies controlled with hormone replacement therapy.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Keratoacanthomas and/or cSCC (see Section 6.8.2).

7.2. Participant Discontinuation/Withdrawal from the Study

Participants will receive study treatment for a maximum of approximately 2 years (from first dose or from the time of confirmed CR), or until the occurrence of disease progression (See Section 7.1), death or unacceptable toxicity, including meeting stopping criteria for liver chemistry defined in Section 7.1.2. In addition, study treatment may be permanently discontinued for any of the following reasons:

- deviation(s) from the protocol
- request of the participant or proxy (withdrawal of consent by participant or proxy)
- investigator's discretion
- participant is lost to follow-up
- study is closed or terminated.
- 3 consecutive missed doses unless the GSK medical monitor agrees that further treatment may benefit the participant

The primary reason study treatment was permanently discontinued must be documented in the participant's medical records and electronic case report form (eCRF).

All participants who permanently discontinue study treatment without disease progression will be followed for progression according to the protocol schedule until:

a. new anti-cancer therapy is initiated
b. progression
c. death, or
d. study has completed

All participants who permanently discontinue study treatment will be followed Q12W (±2 weeks) for survival and the start of new anti-cancer therapy to a maximum of 3 years, unless otherwise indicated (see Section 8.2). If participants are unable or unwilling to attend clinic visits during follow-up, contact to assess survival may be made via another form of communication (e.g., phone, email, etc.).

If the participant voluntarily discontinues from treatment due to toxicity, 'adverse event (AE)' will be recorded as the primary reason for permanently discontinuation on the electronic case report form (eCRF).

All participants who discontinue from study treatment will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in Table 1.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

7.4. Participant and Study Completion

A participant will be considered to have completed the study if the participant dies or otherwise progresses during the treatment or follow-up period or has been in follow-up for a maximum of 3 years or until the DCO date is reached, whichever is sooner. Document the cause of death in the CRF. A participant will be considered to have withdrawn from the study if the participant has not died or progressed and is lost to follow-up, has withdrawn consent, or at the investigator's discretion is no longer being followed.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in Table 1.

- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in Table 1, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in Table 1.
    - **Note:** Repeat or unscheduled samples may be taken for safety reasons, based on emerging data or for technical issues with the samples.

8.1. Screening Assessments

All screening assessments must be performed within 45 days prior to the first dose unless otherwise specified. Screening scans for lesion assessments are required within 28 days of the first dose. The ICF may be signed within 45 days prior to enrollment; tumor tissue biopsy procedure must be performed during the screening period after participant ICF obtained. An archived tumor sample is mandatory and will be used for PD-L1 testing.

The term 'baseline' refers to the assessment performed during the screening period prior to first dose of study treatment that serves as a comparison or control. For example, the baseline laboratory assessment is the laboratory assessment performed prior to first dose.

Refer to Table 1 for additional details on assessments required at Screening and prior to the start of study intervention.

The following assessments are required during screening:

- Informed Consent
- Demographic parameters such as year of birth and sex will be captured
- Medical history including cardiovascular medical history, tobacco use, prior use of probiotics and antibiotics within (60 of first dose) and other risk factors will be assessed as related to the inclusion/exclusion criteria.
- Complete physical examination.

- Skin assessments are performed at Baseline on all participants (refer to Table 1 and Section 8.4.1). A detailed medical history of genetic or iatrogenic dermatologic conditions, skin type, geographical location, occupational or environmental exposure to radiation or chemicals will be queried.
- Disease characteristics including medical, surgical, and treatment history (best response to prior therapy [radiotherapy and systemic] will be recorded), date of initial diagnosis, primary tumor location, stage at initial diagnosis, histology, and current sites of disease will be taken as part of the disease history/status. In addition, molecular characterization of cancer, including PD-L1 expression by IHC will be recorded. If PD-L1 expression has been previously determined, results and type of assay utilized (e.g., Ventana SP263, Ventana SP142, Dako 28-8, or Dako 22C3) must be recorded in eCRF.
- A brain CT/MRT scan performed as clinically indicated.
- ECOG Performance Status.
- Vital Signs (refer to Section 8.4.3).
- Concomitant medication
  - Recorded starting from screening through post-study treatment follow-up.
  - Record all medications the participant is taking including prescription medications, over-the-counter drugs or preparations, and herbal preparations including any cannabinoids and/or recreational drugs used.
  - At a minimum, the drug name, route of administration, dose, and frequency of dosing, along with start and stop dates must be recorded.
- Electrocardiogram (ECG; refer to Section 8.4.4).
- Echocardiogram at screening. MUGA is acceptable if ECHO is not available; for each participant the same modality must be used for all subsequent evaluations.
- Laboratory assessments (hematology, chemistry, urinalysis T4, TSH, and serum pregnancy as appropriate). (refer to Appendix 2 for requirements).

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- Newly collected tumor tissue sent to central laboratory (refer to the SRM for requirements). Mandatory.
- Archival Tumor sample obtained and will be sent to central lab (refer to the SRM for requirements).
- HBV and HBC testing
- HIV known status.
- TST, QuantiFERON-TB-Gold, or T-SPOT (if positive history of tuberculosis exposure).

Baseline scans for lesion assessments per RECIST v1.1 guideline [Eisenhauer, 2009] are required within 28 days of enrollment and include:

- CT scan with contrast of the chest, abdomen, and pelvis is required.
  - **Note:** Contrast-enhanced computed tomography (CT) of chest/abdomen/pelvis covering the area from the superior extent of the thoracic inlet to the symphysis pubis is the first choice of imaging modality. If a participant cannot receive iodinated contrast, or if regional radiation regulations prevent full CT scan, magnetic resonance imaging (MRI) of the abdomen and pelvis, using gadolinium enhancement (according to local protocol) is permitted, and should be acquired in conjunction with the unenhanced CT of the chest. The same modality, and preferably the same scanner, should be used per participant throughout the study.
- Other areas should be evaluated as indicated by the participant's underlying disease prior to screening.
- Refer to RECIST version 1.1 guidelines for use of FDG-PET/CT [Eisenhauer, 2009].
- Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

8.2. Follow-up Assessments

Participants who permanently discontinue study treatment for any reason, except withdrawal of consent (refer to Section 7.2), will be followed for survival and new anti-cancer therapy (including radiotherapy) Q12W until death or the DCO date, whichever is sooner. A DCO date will be specified that will represent the end of data collection for the planned final analysis described in the Reporting and Analysis Plan (RAP). Refer to the SoA in Table 1 for the follow-up schedule.

Once the final DCO date for this study has been reached, no new data will be entered into the clinical study database and the database will be locked for final analysis. Participants who are considered to be deriving benefit from study intervention in the opinion of the investigator, with agreement from the GSK medical monitor, and do not meet any protocol-defined treatment discontinuation criteria may continue to receive study intervention for a defined period after the DCO date, as follows:

- Participants will be managed in accordance with the local institutional standard of care.
- SAEs, AEs leading to treatment/study discontinuation, overdoses, and pregnancies will be reported through a paper-based pharmacovigilance (PV) process and captured in the asset PV database. Investigators will report all SAEs, overdoses, and pregnancy cases until 35 days (5 half-lives) after receipt of a given participant's last dose of study intervention or start of subsequent anti-cancer therapy. Any SAE will be followed until resolution unless the event is considered by the investigator to be unlikely to resolve, or the participant is lost to follow-up.

Participants in survival follow-up at the time of the final DCO date will be considered to have completed the study.

Although the clinical study database will be closed at the time of the final DCO date, the study will remain open until all participants discontinue study intervention and the EOS definition is reached.

8.3. Evaluation of Anti-Cancer Activity

RECIST version 1.1 guidelines will be used to determine the overall tumor burden at baseline, select target and non-target lesions, and in the disease assessments throughout the duration of the study. The primary measure of response-based efficacy endpoints is according to RECIST v1.1 definition as assessed by the investigator [Eisenhauer, 2009].

- Response assessments will be performed Q8W for the first 6 months and Q12W thereafter, until end of treatment, and at the final study visit (refer to Table 1).
- If bintrafusp alfa is discontinued without documented progression, then continue imaging Q8W for the first 6 months from first dose of bintrafusp alfa followed by Q12W until documented PD, or the start of any new anti-cancer therapy.
- For post-baseline assessments, a window of [±3 days] is permitted to allow for flexible scheduling.

Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays.

If the last radiographic assessment was 6 weeks or more prior to the participant's withdrawal from study treatment and PD has not been documented, a disease assessment should be obtained at the time of withdrawal from study treatment. See Table 1 for the schedule of assessments of anti-cancer activity.

- All the scans performed during screening need to be repeated at subsequent visits for tumor assessment.
- To ensure comparability between the baseline and subsequent assessments, the same method of assessment and the same technique must be used when assessing response.

Refer to the imaging manual for details on imaging/clinical assessment requirements and submission guidelines.

Tumor responses to treatment will be assigned based on the evaluation of the response of target, non-target, and new lesions according to RECIST v1.1.

Treatment decisions will be made by the treating investigator based on RECIST v1.1. Study intervention should continue until disease progression, unacceptable toxicity, or any criterion for withdrawal from the trial or study intervention occurs (see Section 7). Before stopping the treatment, progressive disease should be confirmed by imaging at least 4 weeks after initial progression according to RECIST v1.1.

See Section 7.1 for more information about continued study intervention after disease progression.

The intervention should be stopped immediately if the participant does not tolerate bintrafusp alfa or if therapeutic failure occurs that requires urgent treatment with an additional drug or results in clinically significant progression/deterioration.

8.3.1. Disease Response Assessments

8.3.1.1. RECIST v1.1

RECIST v1.1 guidelines will be used to determine the overall tumor burden at screening, select target and non-target lesions, and in the disease assessments through the duration of the study [Eisenhauer, 2009]. See the SRM for additional information.

- As indicated in RECIST version 1.1 guidelines:
  - Lymph nodes that have a short axis of <10 mm are considered non-pathological and must not be recorded or followed.
  - Pathological lymph nodes with <15 mm but ≥10 mm short axis are considered non-measurable.
  - Pathological lymph nodes with ≥15 mm short axis are considered measurable and can be selected as target lesions; however, lymph nodes should not be selected as target lesions when other suitable target lesions are available.
  - Measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected based on their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases must not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation must not be considered as target lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease) must be identified as non-target and must also be recorded at baseline. Non-target lesions will be grouped by organ. Measurements of these lesions are not required, but the presence or absence of each must be noted throughout follow-up.

Disease assessment modalities may include imaging (e.g., CT scan, MRI, bone scan) and physical examination (as indicated for palpable/superficial lesions).

At each post-baseline assessment, evaluation of the sites of disease (all target and non-target lesions) identified by the baseline scans is required. CT scans with contrast of the chest, abdomen and pelvis, or if contra-indicated (more details will be available in the

SRM/imaging manual), MRI, is required at each post-baseline assessment. To ensure comparability between the baseline and subsequent assessments, the same method of assessment and the same technique will be used when assessing response.

Refer to Table 1 for the frequency of disease assessment. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays.

Participants whose disease responds (either CR or PR) should have a confirmatory disease assessment performed at least 4 weeks after the date of assessment during which the response was demonstrated. More frequent disease assessments may be performed at the discretion of the investigator.

If study treatment is resumed upon disease progression and following consultation with the investigator and GSK medical monitor, imaging scans which indicated progression will serve as the baseline scans. Representative new lesions, if measurable, may be incorporated into the evaluation of disease burden.

The foreseen treatment duration is until disease progression verified by a scan subsequent to the initial documentation of PD, unacceptable toxicity, or any criterion for withdrawal from the trial or study intervention occurs (see Section 7.1.1).

8.4. Safety Assessments

Planned time points for all safety assessments are provided in Table 1.

8.4.1. Physical Examinations

- A complete physical examination performed at Screening will include, at a minimum, assessment of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- A brief physical examination performed at each subsequent visit will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen), and infusion site reaction assessments.
- Skin assessments are performed at Baseline and every 6 weeks for all participants. A detailed medical history of genetic or iatrogenic dermatologic conditions, skin type, geographical location, occupational or environmental exposure to radiation or chemicals will be queried. For participants experiencing a dermatologic-related AE (hyperkeratosis, KA, or cSCC), initial biopsy with pathology report of initial AE is expected. Additional excisional biopsies of suspicious lesions should occur, and management discussed with the medical monitor as indicated. Dermatology consultation is encouraged for diagnosis, outcome and follow-up. Skin biopsy pathology testing is performed locally.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Abnormal findings are to be reassessed at subsequent visits.

8.4.2. ECOG Performance Status

Performance status will be assessed using the ECOG scale at each visit; refer to Appendix 10.

8.4.3. Vital Signs

- Vital signs will be measured after 5 minutes of rest in a semi-recumbent or supine position, and will include temperature, systolic and diastolic blood pressure, pulse rate, and oxygen saturation (measured by pulse oximetry). Blood pressure should be taken in the same position throughout the study and captured in the eCRF.
- Vital signs will be measured more frequently if warranted by clinical condition of the participant.
- Height will be recorded at Screening only.
- Weight will be measured and recorded (in kilograms) at baseline and at every treatment visit.

8.4.4. Electrocardiograms

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

8.4.5. Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to Table 1 for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal and related to study intervention during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- Urine or serum pregnancy test according to local standards. Refer to Table 1, and Table 6.
- All protocol-required laboratory assessments, as defined in Appendix 2 must be conducted in accordance with the laboratory manual and Table 1.

8.5. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention (see Section 7).

8.5.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF at the time points specified in the Table 1. Any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.

All AEs will be collected from the signing of the ICF at the time points specified in Table 1. Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the 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 must promptly notify the sponsor.

8.5.2. Collection of Safety Information After Data Cut-off

After the DCO for the final analysis, in alignment with Section 6.10, participants still deriving benefit will continue to receive bintrafusp alfa. For these participants, GSK will continue to collect safety information, including SAEs, AEs leading to treatment/study discontinuation, overdoses, and pregnancy cases via paper forms (refer to the SRM) that will be submitted directly to GSK per defined time frames as follows:

- SAEs, AEs leading to treatment/study discontinuation, overdoses, and pregnancy cases will be reported until 35 days (5 half-lives) after last dose or the start of subsequent anti-cancer therapy, whichever comes first.
- An SAE will be followed until resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

Reporting of these events (SAEs, AEs leading to discontinuation of study intervention, overdoses, and pregnancies) will continue to be in accordance with the protocol. The sponsor retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the time of the DCO date for the final analyses, if judged necessary.

8.5.3. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports, including after DCO date, are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.5.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AEs of interest (as defined in Section 6.8) will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.5.5. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.6. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 2 months after the last dose of bintrafusp alfa.

- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.5.7. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 and all deaths, whether they are considered SAEs, must be recorded in the CRF within one week of occurrence.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.5.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as an SAE.

Death due to disease under study is to be recorded on the death eCRF form.

However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the participant, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design/procedures and the disease progression, then this must be reported as an SAE.

NOTE: If either of the following conditions apply, then the event must be recorded and reported as a SAE (instead of a disease-related event):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or
- The investigator considers that there is a reasonable possibility that the event was related to treatment with study treatment(s).

8.6. Participant Specific Dose Adjustments Criteria

Dose reductions for bintrafusp alfa are not permitted while participant is being treated on-study, except as described in Section 6.8. Dosing may be held in the event of an AE that is deemed related to treatment. If 3 or more consecutive doses are held, the investigator must discuss the case with the GSK medical monitor to confirm that further treatment with bintrafusp alfa may benefit the participant.

8.7. Treatment of Overdose

For this study, any dose of bintrafusp alfa greater than 2 times more (ie, >2400 mg) than the planned dose administered within a 24-hour time period will be considered an overdose. This is based on dose-escalation study data in which participants safely received up to 30 mg/kg bintrafusp alfa Q2W (including with doses >2400 mg) with no observed maximum tolerated doses (refer to the IB). Safety at significantly higher doses has not been clinically evaluated.

In case of overdose with clinical correlation, symptomatic treatment must be used; there are no known antidotes for the compound.

In event of overdose, infusion should be discontinued, and participants should be observed closely for any signs of toxicity. Supportive treatment should be provided if clinically indicated. If an AE occurs resulting from overdose, it should follow SAE reporting criteria as indicated in Appendix 3.

If an incidence of overdose occurs meeting the protocol-defined definition without any association of symptoms or laboratory abnormalities, then it must be transmitted by the same process specified for SAE reporting in Appendix 3, section on Reporting Serious Adverse Events, using the terminology "accidental or intentional overdose" without adverse effects.

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CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

[redacted]

8.11.2. Tumor Tissue

Study participants are required, as described in eligibility criteria, to provide a fresh tumor biopsy and an archival tumor tissue sample.

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[redacted]

Archival tissue will be submitted to a central laboratory for expression of PD-L1 at the time of screening. Analyses will be performed retrospectively. Other biomarkers may be evaluated as determined by additional research and data. Details for sample collection, storage, and shipment will be provided in the SRM.

8.11.3. Stool Collection for Microbiome Analysis

Stool specimens offer accessible means of evaluating the gut microbial community. Association of the stool microbiome composition with physiological and medical conditions and response to treatments has been reported for numerous indications. The relationship between antibiotic/probiotic use prior to treatment and antitumor activity may also be evaluated. Refer to Table 1 for the schedule.

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[redacted]

CCI

[redacted]

CCI

[redacted]

8.13. Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

As of Protocol Amendment 02, the interim analysis described herein will no longer be conducted.

The final analysis will include all data collected through the DCO date. An abbreviated reporting (to include only the primary and secondary endpoints in Section 3) of the data will be performed and additional details will be described in the RAP.

9.1. Statistical Hypotheses

The primary endpoint of the study is the objective response according to RECIST 1.1, based on the tumor assessment results from investigator.

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9.2. Sample Size Determination

A total of 25 participants will receive bintrafusp alfa.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Screened	All participants who sign the ICF.
Safety/Treated	All participants who were administered at least 1 infusion of bintrafusp alfa. This is the primary analysis population for reporting efficacy and safety.
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CCI [redacted]

9.4. Statistical Analyses

The RAP for primary analysis reporting will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.4.1. General Considerations

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

9.4.2. Primary Endpoint

The primary efficacy endpoint is objective response by the investigator assessment, CCI [redacted]

CCI [redacted]

The primary efficacy endpoint will be analyzed based on the Safety/Treated population unless otherwise specified.

The ORR is defined as the percentage (%) of participants with a PR or CR as assessed by investigator using RECIST 1.1. The corresponding 95% CI for ORR will also be calculated using the Clopper-Pearson (exact) method.

CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

9.4.3. Secondary Endpoints

The secondary endpoints will be analyzed based on the Safety/Treated population unless otherwise specified.

Endpoints	Key Statistical Analysis / Reporting
Frequency and severity of AEs	The number and percent of participants with AEs will be summarized.

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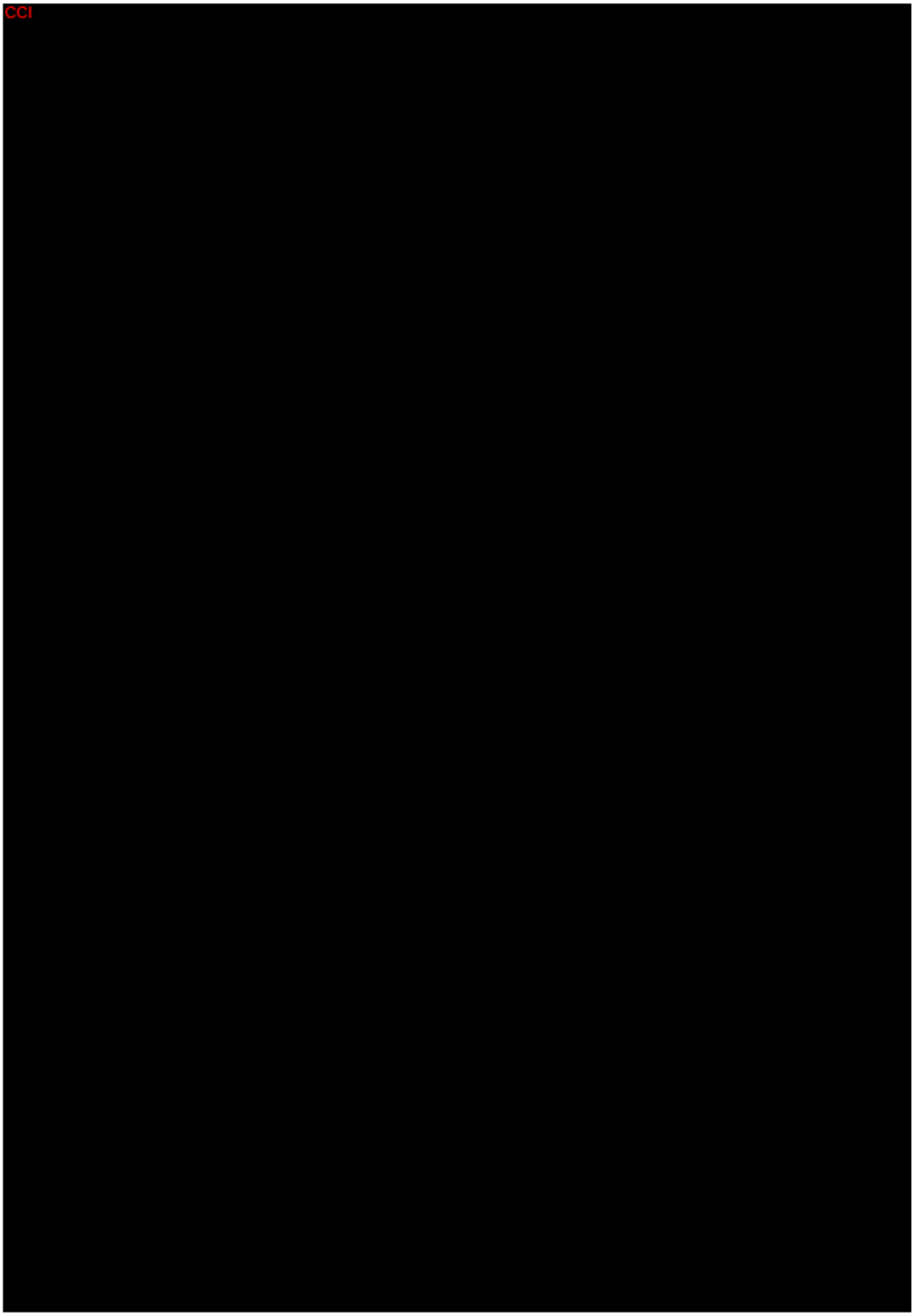
[redacted]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[redacted]

9.4.5. Other Safety Analyses

All safety analyses will be performed on the Safety/Treated population.

Safety endpoints include AEs, AEs of Interest, clinical laboratory assessments, vital signs, physical examination, and ECOG PS.

TEAEs are those events with onset dates occurring during the on-treatment period or if the worsening of an event is during the on-treatment period.

Additional analyses of AEs (e.g., AEs of Interest, Severity, Relationship to Study Intervention) and other Safety Endpoints will be described in more details in the RAP. All safety analyses will be made on the Safety Population.

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CCI

[redacted]

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[redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.4. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding
- A manuscript will be progressed for publication in CCI [redacted] literature if the results provide important scientific or medical knowledge.

10.1.5. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- 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 provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data can be found in the SRM and Monitoring Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- 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 study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.8. Publication Policy

- 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 the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the local laboratory unless otherwise specified.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing.
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention. Refer to Table 1 for the schedule.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure plus an additional 28 days and correspond with the time frame for female participant contraception in Section 5.1, Inclusion Criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 6 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments[1]	**Parameters** **All parameters are performed locally**			
Hematology[5]	• Platelet Count • RBC Count • Hemoglobin • Hematocrit • %Reticulocytes • Absolute lymphocyte count • Absolute neutrophil count	• RBC Indices: • MCV • MCHC • RDW • aPTT • Prothrombin time • aINR	<u>WBC count with Differential</u>: • Neutrophils (ANC) • Lymphocytes • Monocytes • Eosinophils • Basophils	
Clinical Chemistry Panel[5]	• Blood Urea Nitrogen/total urea • Creatinine • Glucose • Lipase • C-reactive protein	• Potassium • Sodium • Calcium • Chloride • Amylase	• Aspartate Aminotransferase[2] (AST) • Alanine Aminotransferase (ALT)[2] • Alkaline phosphatase[2] • Albumin[2]	• Bilirubin (total indirect/direct[2]) • Total Protein[2] • GGT[2]
Routine Urinalysis[3]	• Specific gravity, physical appearance, color • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, by dipstick • Microscopic examination (if blood or protein is abnormal)			
Thyroid Panel	• Free T_4, TSH			

Laboratory Assessments[1]	**Parameters** **All parameters are performed locally**
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[4] • Hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody. • TST, QuantiFERON-TB-Gold, or T-SPOT (if positive history of tuberculosis exposure)[6] The results of each test must be entered into the CRF.

NOTES : ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CRP = C reactive protein; GGT = gamma-glutamyltransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; RDW = red cell distribution width; T4 = free thyroxine; TSH = thyroid-stimulating hormone; TST = tuberculin skin test; WBC = white blood cell.

1. Performed as indicated in Section 1.3 (Schedule of Activities).
2. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.2 and Section 10.6. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
3. Routine urinalysis performed at Screening and as clinically indicated thereafter.
4. Local urine or serum pregnancy testing, as required by local regulation or IRB/IEC.
5. Chemistry and Hematology should be repeated if not performed within 24 hours of Day 1.
6. Performed at Screening if positive history. Discuss with medical monitor if another test not listed is standard of care for your institution.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether considered related to the study intervention. • NOTE: 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 a study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- 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.

10.3.2. Definition of SAE

If an event is not an AE per 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:
Results in death
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 AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent or significant 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.

Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should 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 should usually be considered 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.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to record the CV in the CRF within one week of occurrence for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

10.3.4. Recording and Follow-Up of AE and 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, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- 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.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

  Other measures to evaluate AE and SAE may be utilized (e.g., NCI-CTCAE v5).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- 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 **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an 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 AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK 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 GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.

- Contacts for SAE reporting can be found in SRM.

SAE and AEs Leading to Study Discontinuation Reporting to GSK via Paper CRF

- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and email to OAX37649@gsk.com or fax to +44 (0) 208 754 7822. Site will enter the SAE or AE data into the electronic system as soon as it becomes available unless paper SAEs and AEs leading to study discontinuation (where indicated) are being collected after DCO (below).
- The paper SAE/AE data collection tool will also be utilized for SAE and AE (where indicated) reporting after the DCO for final analysis, at which time no entry into the eCRF will be required, as the clinical database will be closed.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SRM.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

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

Women in the following categories are not considered WOCBP

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

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

10.4.2. Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 5.1.
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 7 when having penile-vaginal intercourse with a woman of childbearing potential
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and for at least 120 days after the last dose of study treatment.

Female participants

Table 7 Highly Effective Contraceptive Methods

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
Sexual abstinence • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual 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.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

Note: This contraceptive guidance will also apply to participants who continue to receive study intervention after the DCO date.

10.4.3. Collection of Pregnancy Information

Male participants with partners who become pregnant

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

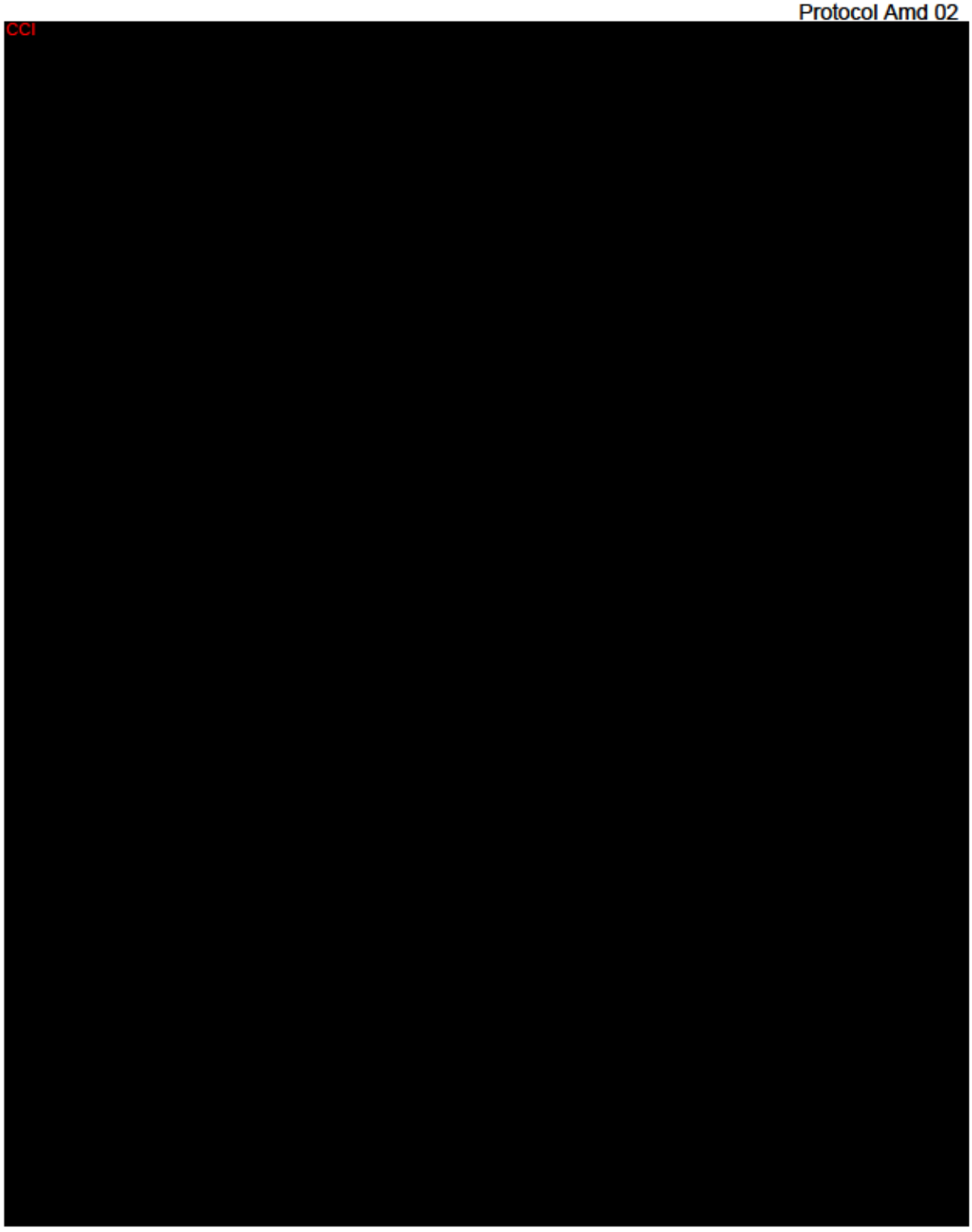
Female participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- The initial information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Appendix 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 will discontinue study intervention.

Note: The collection of pregnancy information will also apply to participants who continue to receive study intervention after the DCO date until last visit.

CCI



10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase I/II liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I/II Liver Chemistry Stopping Criteria and Required Follow up Assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event **Including participants with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT >2.5 x ULN but ≤5 x ULN**	
ALT-absolute	**Both** ALT ≥5 x ULN **and** ≥2 x baseline value
ALT Increase	**Both** ALT ≥3 x ULN **and** ≥1.5 x baseline value that persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3 x ULN **and** bilirubin ≥2 x ULN (**>**35% direct bilirubin)
INR[2]	ALT ≥3 x ULN **and** INR >1.5, if INR measured
Cannot Monitor	**Both** ALT ≥3 x ULN **and** ≥1.5 x baseline value that cannot be monitored for 4 weeks
Symptomatic[3]	**Both** ALT ≥3 x ULN **and** ≥1.5 x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the CRF within one week of occurrence and complete an SAE data collection tool if the event also meets the criteria for an SAE**²** • Perform liver event follow up assessments • Monitor the participant until liver chemistries ʳesolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant • If restart/rechallenge **not allowed per protocol or not granted**, permanently	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend. • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained approximately 48hrs after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN

discontinue study treatment and may continue as a participant in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use in the SAE form if reported as an SAE **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT≥ 3 x ULN **and** bilirubin ≥2 x ULN (>35% direct bilirubin) or ALT ≥3 x ULN **and** INR >1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase I/II Oncology Liver Chemistry Increased Monitoring Criteria With Continued Therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
Participant <u>with</u> entry criteria ALT ≤2.5 x ULN ALT ≥3 x ULN **but** <5 x ULN **and** bilirubin <2 x ULN, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks **Participant <u>with documented</u> liver metastases/tumor infiltration at baseline AND entry criteria ALT>2.5 x ULN but ≤5 x ULN** ALT ≥3 x ULN and 1.5 x baseline value **but** ALT <5 x ULN and 2 x baseline value **and** bilirubin <2 x ULN**, without** symptoms believed to be related to liver injury, or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above **For participants with entry criteria ALT ≤2.5 x ULN** • If, after 4 weeks of monitoring, ALT <3 x ULN and bilirubin <2 x ULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline. **For participants with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT >2.5 x ULN but ≤5 x ULN** • If, after 4 weeks of monitoring, ALT <3 x ULN and <1.5 x baseline value, and bilirubin <2 x ULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline

Reference:

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009;37:1779-1784.

10.7. Appendix 7: Country-specific requirements

There are no country specific requirements.

10.8. Appendix 8: Abbreviations and Trademarks

Abbreviations

CCI [redacted]	
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ASCO	The American Society of Clinical Oncology
β-hCG	Beta-human Chorionic Gonadotropin
CCI [redacted]	
CCI [redacted]	
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CrCl	Creatinine Clearance
CRP	C Reactive Protein
CSR	Clinical Study Report
CT	Computed Tomography
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
CCI [redacted]	
cSCC	cutaneous Squamous-cell Carcinoma
CV	Cardiovascular
DCO	Data Cut-off
CCI [redacted]	
CCI [redacted]	
ECHO	Echocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EU	European Union
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FTIH	First-Time-in-Human
GI	Gastrointestinal
GSK	GlaxoSmithKline
Hgb	Hemoglobin
HRT	Hormone Replacement Therapy
Hypothesis	H
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

CCI [redacted]	
IEC	Independent Ethics Committees
CCI [redacted]	
Ig	Immunoglobulin
CCI [redacted]	
IL	Interleukin
INR	International Normalized Ratio
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
IRR	Infusion-related Reaction
IV	Intravenous
KA	Keratoacanthoma
kg	Kilogram(s)
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MIBC	Muscle-Invasive Bladder Cancer
µg	Microgram(s)
mg	Milligram(s)
mL	Milliliter(s)
MRI	Magnetic Resonance Imaging
MSDS	Material Safety Data Sheet
MSEC	Millisecond(s)
MUGA	Multigated Acquisition Scan
NCI-CTCAE v5	National Cancer Institute - Common Terminology Criteria for Adverse Events, version 5
ORR	Overall Response Rate
CCI [redacted]	
CCI [redacted]	
PD	Progressive Disease
PD-1	Programmed Death 1
PD-L1	Programmed Death-Ligand 1
CCI [redacted]	
CCI [redacted]	
PR	Partial Response
PS	Performance Status
PV	Pharmacovigilance
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
Q6W	Every 6 Weeks
Q12W	Every 12 Weeks
QTc	QT interval duration corrected
QTcF	QT interval duration corrected by Fredericia formula
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
CCI [redacted]	

RP2D	Recommended Phase 2 Dose
SCC	Squamous-cell Carcinoma
SD	Stable Disease
SoA	Schedule of Activities
SRM	Study Reference Manual
TCR	T Cell Receptor
TGF-β	Transforming Growth Factor β
TEAE	Treatment Emergent Adverse Event
TNFα	Tumor Necrosis Factor, alpha
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
WOCBP	Woman of Childbearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

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10.9. Appendix 9: The Recommendations for irAE Management, in Accordance with the Joint American Society of Clinical Oncology Clinical Practice Guidelines and National Comprehensive Cancer Network

Adapted from:
Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline [Brahmer, 2018].

Table of Tables

Table A1 Management of Skin irAEs in Patients Treated With ICPis

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

1.0 Skin Toxicities	
G4: All severe rashes unmanageable with prior interventions and intolerable	Immediately hold ICPi and consult dermatology to determine appropriateness of resuming ICPi therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) ≤10 mg Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves Monitor closely for progression to severe cutaneous adverse reaction Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology Consider alternative antineoplastic therapy over resuming ICPis if the skin irAE does not resolve to G1 or less; if ICPIs are the patient's only option, consider restarting once these adverse effects have resolved to a G1 level
1.2 Bullous dermatoses	
Definition: Including bullous pemphigoid or other autoimmune bullous dermatoses, bullous drug reaction Diagnostic work-up Physical examination Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease If needed, a biologic check-up, including a blood cell count, liver, and kidney tests; consider serum antibody tests to rule out bullous pemphigoid or, under the guidance of dermatology, sending patient serum for indirect immunofluorescent testing to rule out other autoimmune blistering diseases Referral to dermatology for blisters that are not explained by infectious or transient other causes (eg, herpes simplex, herpes zoster, bullous impetigo, bullous insect bite, friction or pressure blister) Consider skin biopsy (both hematoxylin and eosin evaluation of lesional skin and direct immunofluorescence evaluation of perilesional skin)	
Grading	Management
G1: Asymptomatic, blisters covering <10% BSA and no associated erythema	If blisters are <10% BSA, asymptomatic, and noninflammatory (such as the case with friction blisters or pressure blisters), cessation of ICPi is not necessary, and only observation and/or local wound care is warranted. When symptomatic bullae or erosions, which are deroofed vesicles or bullae, are observed on the skin or mucosal surfaces, the cutaneous irAE is by definition considered at least G2 See G2 management recommendations
G2: Blistering that affects quality of life and requires intervention based on diagnosis not meeting criteria for Grade >2 Blisters covering 10%-30% BSA	Hold ICPi therapy and consult with dermatology for work-up and to determine appropriateness of resuming

1.0 Skin Toxicities	
	Attention given to general local wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions, which are left over on the skin after the blister has popped or if the roof of the blister easily sloughs off Counsel patients to avoid skin irritants and overexposure to sun, wear protective clothing, use sunscreens Work-up for autoimmune bullous disease as above Initiate Class 1 high-potency topical corticosteroid (eg, clobetasol, betamethasone or equivalent) and reassess every 3 days for progression or improvement Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg dosing and taper over at least 4 weeks Monitor patients with G2 irAEs closely for progression to involvement of greater BSA and/or mucous membrane involvement. Consider following patients closely using serial photography Primer on monitoring for complicated cutaneous adverse drug reactions:
	Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements
	Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN
G3: Skin sloughing covering >30% BSA with associated pain and limiting self-care ADL	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming

1.0 Skin Toxicities	
	Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab, as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.
G4: Blisters covering >30% BSA with associated fluid or electrolyte abnormalities	Permanently discontinue ICPi Admit patient immediately and place under supervision of a dermatologist Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg with tapering over at least 4 weeks when the toxicity resolves If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc
1.3 SCARs, including SJS, TEN, acute generalized exanthematous pustulosis, and DRESS/DIHS	
Definition: Severe changes in either structure or functions of skin, the appendages or the mucous membranes due to a drug Diagnostic work-up	
Total body skin examination with attention to examining all mucous membranes as well as complete review of systems Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease A biologic checkup, including a CBC with differential test, and liver and kidney function tests, including urinalysis, in addition to the blood work; if the patient is febrile, blood cultures should be considered as well Skin biopsies to assess for full-thickness epidermal necrosis, as is seen in SJS/TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses or other drug reactions, such as acute generalized exanthematous pusulosis Consider following patients closely using serial clinical photography If mucous membrane involvement or blistering is observed on the skin, consider early admission to a burn center for further monitoring and management Primer on monitoring for complicated cutaneous adverse drug reactions: Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements	

1.0 Skin Toxicities	
Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN	
Grading	Management
All Grades	In cases of suspected SJS or any mucous membrane involvement, discontinue ICPi treatment and monitor closely for improvement, regardless of grade
G1: NA	For SCARs, there is no G1 category; if lower BSA is involved with bullae or erosions, there should remain a high concern that this reaction will progress to G3 or G4
G2: Morbilliform ("maculopapular") exanthem covering 10%-30% BSA with systemic symptoms, lymphadenopathy, or facial swelling	Hold ICPi and monitor patients closely every 3 days with G2 irAEs for progression to involvement of greater BSA and/or mucous membrane involvement Consider following patients closely using serial photography Initiate therapy with topical emollients, oral antihistamines, and medium- to high-strength topical corticosteroids Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks
G3: Skin sloughing covering <10% BSA with mucosal involvement associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment)	Hold ICPi therapy and consult with dermatology Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum Administer IV (methyl)prednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks Admit to burn and/or consult wound services with attention to supportive care, including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (eg, ophthalmology; ear, nose, and throat; urology; gynecology; etc, as appropriate)

1.0 Skin Toxicities	
G4: Skin erythema and blistering/sloughing covering ≥10% to >30% BSA with associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (eg, liver function test elevations in the setting of DRESS/DIHS)	Permanently discontinue ICPi Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services Consider further consultations based on management of mucosal surfaces (eg, ophthalmology; urology; gynecology; ear, nose, and throat surgery; etc) Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal IVIG or cyclosporine may also be considered in severe or corticosteroid-unresponsive cases Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations
Additional considerations: The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immunodirected toxicity Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS/DIHS All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate	

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

Table A2 Management of GI irAEs in Patients Treated With ICPis

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

2.0 GI Toxicities	
	discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less Concurrent immunosuppressant maintenance therapy (10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases May also include supportive care with medications such as Imodium if infection has been ruled out Should consult with gastroenterology for G2 or higher Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent When symptoms improve to G1 or less, taper corticosteroids over at least 4-6 weeks before resuming treatment, although resuming treatment while on low-dose corticosteroid may also be an option after an evaluation of the risks and benefits EGD/colonoscopy, endoscopy evaluation should be highly recommended for cases Grade ≥2 to stratify patients for early treatment with infliximab based on the endoscopic findings and to determine the safety of resuming PD-1, PD-L1 therapy Stool inflammatory markers can be considered (lactoferrin and calprotectin) in cases of G2 or higher to differentiate functional versus inflammatory diarrhea, and use calprotectin to monitor treatment response if provider prefers Repeat colonoscopy is optional for cases of G2 or higher for disease activity monitoring to achieve complete remission, especially if there is a plan to resume ICPi
G3: Increase of seven or more stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL	Should consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less. Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent) Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance If symptoms persist ≥3-5 days or recur after improvement, consider administering IV corticosteroid or noncorticosteroid (eg, infliximab) Consider colonoscopy in cases where patients have been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (ie, CMV colitis) and for those who are anti-TNF or corticosteroid refractory
G4: Life-threatening consequences; urgent intervention indicated	Permanently discontinue treatment Should admit patient when clinically indicated; patients managed as outpatients should be very closely monitored

2.0 GI Toxicities	
	Administer 1-2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks Consider early infliximab 5-10 mg/kg if symptoms refractory to corticosteroid within 2-3 days Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections
Additional considerations The use of vedolizumab (not approved in Japan) may be considered in patients refractory to infliximab and/or contraindicated to TNF-a blocker. The decision should be made on an individual basis from gastroenterology and oncology evaluation. This is based on case series showing promising results Patients with hepatitis and irAE colitis are rare, and management should include permanently discontinuing ICPi and offering other immunosuppressant agents that work systemically for both conditions Currently, enteritis alone as the cause of diarrhea is uncommon and requires small bowel biopsy as the evaluation tool. It may be managed similar as colitis, including corticosteroid and/or infliximab, etc	
2.2 Hepatitis (management based on guidelines by Brahmer et al., 2018, with modifications)	
Definition: A disorder characterized by a viral pathologic process involving the liver parenchyma Diagnostic work-up Monitor patient for abnormal liver blood tests: AST, ALT, and bilirubin prior to each infusion and/or weekly if G1 liver function test elevations. No treatment is recommended for G1 liver function test abnormality For G2 or higher: Work-up for other causes of elevated liver enzymes should be tested, viral hepatitis, alcohol history, iron study, thromboembolic event, liver ultrasound, cross-sectional imaging for potential liver metastasis from primary malignancy. If suspicion for primary autoimmune hepatitis is high, can consider ANAs, antismooth muscle antibodies, antineutrophil cytoplasmic antibodies. If patients with elevated alkaline phosphatase alone, g-glutamyl transferase should be tested. For isolated elevation of transaminases, consider checking CK for other etiologies	
Grading	Management
All patients	Counsel all patients to be aware of and inform their health care provider immediately if they experience: Yellowing of skin or whites of the eyes Severe nausea or vomiting Pain on the right side of the abdomen Drowsiness Dark urine (tea colored) Bleeding or bruising more easily than normal Feeling less hungry than usual
G1: Asymptomatic (AST or ALT > ULN to 3.0 x ULN and/or total bilirubin > ULN to 1.5 x ULN)	Continue ICPi with close monitoring; consider alternate etiologies Monitor laboratories one to two times weekly Manage with supportive care for symptom control
G2: Asymptomatic (AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN). For participants with metastatic disease to liver and elevated transaminases at baseline, see Appendix 6 for grading that accommodates baseline liver chemistry values.	Permanently discontinue ICPi if: - ALT ≥3 x ULN persists for ≥4 weeks - ALT ≥3 x ULN **and** bilirubin ≥2 x ULN (>35% direct bilirubin) - ALT ≥3 x ULN **and** INR >1.5, if INR measured

2.0 GI Toxicities	
	- ALT ≥3 x ULN **and** cannot be monitored weekly for 4 weeks In the absence of criteria above, hold ICPi temporarily. Consider corticosteroid 0.5-1 mg/kg/d prednisone or equivalent if the abnormal elevation persists. Increase frequency of monitoring. See Appendix 6 for additional details. May resume ICPi treatment followed by taper only when symptoms improve to G1 or less and corticosteroid ≤10 mg/d; taper over at least 1 month Participants should be advised to stop unnecessary medications and any known hepatotoxic drugs. Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of idiosyncratic liver failure (Note: No clear evidence shows the liver toxicity from infliximab from other studies) Participants should be advised to stop unnecessary medications and any known hepatotoxic drugs
G3: Symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis (AST or ALT 5-20 x ULN and/or total bilirubin 3-10 x ULN). For participants with metastatic disease to liver and elevated transaminases at baseline, see Appendix 6 for grading that accommodates baseline liver chemistry values.	Permanently discontinue ICPi Immediately start corticosteroid 1-2 mg/kg methylprednisolone or equivalent If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using azathioprine should test for thiopurine methyltransferase deficiency) Laboratories at daily or every other day; consider inpatient monitoring for patients with AST/ALT >8 x ULN and/or elevated TB 3 x ULN Increase frequency of monitoring to every 1-2 days Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of liver failure (Note: No clear evidence shows that the liver toxicity from infliximab from other studies); alternatives include non–TNF-a agents as systemic immunosuppressants If no improvement is achieved with corticosteroids or for patients on combination therapy with a novel agent, with standard chemotherapy, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis Corticosteroid taper can be attempted around 4-6 weeks; re-escalate if needed; optimal duration unclear
G4: Decompensated liver function (eg, ascites, coagulopathy, encephalopathy, coma; AST or ALT > 20 x ULN and/or total bilirubin > 10 x ULN)	Permanently discontinue ICPi Administer 2 mg/kg/d methylprednisolone equivalents If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil

2.0 GI Toxicities	
	Monitor laboratories daily; consider inpatient monitoring Avoid the use of infliximab in the situation of immune-mediated hepatitis Hepatology consult if no improvement was achieved with corticosteroid Corticosteroid taper can be attempted around 4-6 weeks when symptoms improve to G1 or less; re-escalate if needed; optimal duration unclear Consider transfer to tertiary care facility if necessary
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations is moderate.	

*not approved in Japan.

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

Table A3 Management of Lung irAEs in Patients Treated with ICPis

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

Abbreviations: ADL = activities of daily living; BAL = bronchoalveolar lavage; CT = computed tomography; CXR = chest x-ray; DLCO = diffusing capacity of lung for carbon monoxide; G = Grade; GI = gastrointestinal; ICPi = immune

checkpoint inhibitor; irAE = immune-related adverse event; IV = intravenous; IVIG = intravenous immunoglobulin; PPI = proton pump inhibitor.

Table A4 Management of Endocrine irAEs in Patients Treated with ICPis

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

4.0 Endocrine Toxicity	
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate supplementation Endocrine consultation May admit for IV therapy if signs of myxedema (bradycardia, hypothermia) Thyroid supplementation and reassessment as in G2
Additional considerations For patients without risk factors, full replacement can be estimated with an ideal body weight–based dose of approximately 1.6 µg/kg/d For elderly or fragile patients with multiple comorbidities, consider titrating up from low dose, starting at 25-50 mg Extreme elevations of TSH can be seen in the recovery phase of thyroiditis and can be watched in asymptomatic patients to determine whether there is recovery to normal within 3-4 weeks Under guidance of endocrinology, consider tapering hormone replacement and retesting in patients with a history of thyroiditis (initial thyrotoxic phase) Adrenal dysfunction, if present, must always be replaced before thyroid hormone therapy is initiated	
4.1.2 Hyperthyroidism	
Definition: Suppressed TSH and high normal or elevated FT4 and/or triiodothyronine Diagnostic work-up Monitor TSH, FT4 every 4-6 weeks from the start of therapy or as needed for case detection in symptomatic patients Consider TSH receptor antibodies if there are clinical features and suspicion of Grave disease (eg, ophthalmopathy) Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch transition to hypothyroidism in patients with thyroiditis and hyperthyroidism	
Grading	**Management**
G1: Asymptomatic or mild symptoms	Can continue ICPi with close follow-up and monitoring of TSH, FT4 every 2-3 weeks until it is clear whether there will be persistent hyperthyroidism (see below) or hypothyroidism (see 4.1.1 of Table A4- Appendix 9) Consider holding ICPi until symptoms return to baseline Consider endocrine consultation b-Blocker (eg, atenolol, propranolol) for symptomatic relief Hydration and supportive care Corticosteroids are not usually required to shorten duration For persistent hyperthyroidism (>6 weeks) or clinical suspicion, work-up for Graves disease (TSI or TRAb) and consider thionamide (methimazole or PTU) Refer to endocrinology for Graves disease
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate therapy Endocrine consultation b-Blocker (eg, atenolol, propranolol) for symptomatic relief

4.0 Endocrine Toxicity	
	For severe symptoms or concern for thyroid storm, hospitalize patient and initiate prednisone 1-2 mg/kg/d or equivalent tapered over 1-2 weeks; consider also use of SSKI or thionamide (methimazole or PTU).
Additional considerations Thyroiditis is transient and resolves in a couple of weeks to primary hypothyroidism or normal. Hypothyroidism can be treated as above. Graves disease is generally persistent and is due to increased thyroid hormone production that can be treated with antithyroid medical therapy. Physical examination findings of ophthalmopathy or thyroid bruit are diagnostic of Graves and should prompt early endocrine referral.	
4.2 Adrenal – primary adrenal insufficiency	
Definition: Adrenal gland failure leading to low morning cortisol, high morning ACTH, as well as hyponatremia and hyperkalemia with orthostasis and volume depletion due to loss of aldosterone	
Diagnostic work-up for patients in whom adrenal insufficiency is suspected: Evaluate ACTH (AM), cortisol level (AM) Basic metabolic panel (Na, K, CO_2, glucose) Consider ACTH stimulation test for indeterminate results If primary adrenal insufficiency (high ACTH, low cortisol) is found biochemically: Evaluate for precipitating cause of crisis such as infection Perform an adrenal CT for metastasis/hemorrhage	
Grading	Management
G1: Asymptomatic or mild symptoms	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Replacement therapy with prednisone (5-10 mg daily) or hydrocortisone (10-20 mg orally every morning, 5-10 mg orally in early afternoon) May require fludrocortisone (0.1 mg/d) for mineralocorticoid replacement in primary adrenal insufficiency Titrate dose up or down as symptoms dictate
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Initiate outpatient treatment at two to three times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg in the morning, and 10-20 mg in the afternoon) to manage acute symptoms. Taper stress-dose corticosteroids down to maintenance doses over 5-10 days Maintenance therapy as in G1.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormone Endocrine consultation

4.0 Endocrine Toxicity	
	See in clinic or, for after hours, make an emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation (hydrocortisone 100 mg or dexamethasone 4 mg (if the diagnosis is not clear and stimulation testing will be needed) Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge Maintenance therapy as in G1
Additional considerations Primary and secondary adrenal insufficiency can be distinguished by the relationship between ACTH and cortisol. If the ACTH is low with low cortisol, then management is as per 4.3. Patients on corticosteroids for management of other conditions will have low morning cortisol as a result of iatrogenic, secondary adrenal insufficiency. ACTH will also be low in these patients. A diagnosis of adrenal insufficiency is challenging to make in these situations (see next section on hypophysitis). Emergent therapy for someone with suspected adrenal insufficiency is best done with dexamethasone as a stimulation test can still be performed. If the diagnosis is already confirmed, can use hydrocortisone 100 mg. All patients need education on stress dosing and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS. Endocrine consultation prior to surgery or any procedure for stress-dose planning.	
4.3 Pituitary - hypophysitis	
Definition: Inflammation of the pituitary with varying effects on hormone function. Most commonly presenting with central adrenal insufficiency. May also have central hypothyroidism, diabetes insipidus, and hypogonadism. Diagnostic work-up Diagnosis: Low ACTH with a low cortisol. Low or normal TSH with a low FT4. Hypernatremia and volume depletion with diabetes insipidus. Low testosterone or estradiol with low LH and FSH. Testing: Evaluate ACTH, cortisol (AM), TSH, FT4, electrolytes Consider evaluating LH, FSH, and testosterone levels in males or estrogen in premenopausal females with fatigue, loss of libido, and mood changes Consider MRI of the brain with or without contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities ± new severe headaches or complaints of vision changes	
Grading	Management
G1: Asymptomatic or mild symptoms	Consider holding ICPi until patient is stabilized on replacement hormones Endocrine consultation Hormonal supplementation as in G1
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormones Endocrine consultation Hormonal supplementation as in G1 Consider initial pulse dose therapy with prednisone 1-2 mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks
Additional considerations Be aware of the need to start corticosteroids first when planning hormone replacement therapy for multiple deficiencies All patients need instruction on doubling doses for illness (stress dosing) and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS	

4.0 Endocrine Toxicity	
Corticosteroid use can cause isolated central adrenal insufficiency Work-up cannot be done with a simple AM cortisol in a patient on corticosteroids for other conditions Laboratory confirmation of adrenal insufficiency should not be attempted until treatment with corticosteroids for other disease is ready to be discontinued. For long-term exposure, consult endocrinology for recovery and weaning protocol using hydrocortisone.	
4.4 Diabetes	
Definition: T2DM is a combination of insulin resistance and insufficiency that may require oral or insulin therapy. It may be new onset or exacerbated during therapy for nonimmunologic reasons, such as corticosteroid exposure. Autoimmune T1DM results from islet cell destruction and is often acute onset, with ketosis and an insulin requirement Diagnostic work-up Monitor patients for hyperglycemia or other signs and symptoms of new or worsening DM, including measuring glucose at baseline and with each treatment cycle during induction for 12 weeks, then every 3-6 weeks thereafter. To guide the work-up in new-onset hyperglycemia, clinicians should consider a patient's medical background, exposure history, and risk factors for each subtype of DM. Laboratory evaluation in suspected T1DM should include testing for ketosis in urine and an assessment of the anion gap on a metabolic panel. Anti–glutamic acid decarboxylase, anti–islet cell, or anti–insulin antibodies are highly specific for autoimmune diabetes. Insulin and C-peptide levels can also assist in the diagnosis.	
Grading	Management
G1: Asymptomatic or mild symptoms; fasting glucose value > ULN (160 mg/dL); fasting glucose value > ULN (8.9 mmol/L); no evidence of ketosis or laboratory evidence of T1DM	Can continue ICPi with close clinical follow-up and laboratory evaluation May initiate oral therapy for those with new-onset T2DM Screen for T1DM if appropriate, for example, acute onset with prior normal values or clinical concern for ketosis
G2: Moderate symptoms, able to perform ADL, fasting glucose value >160-250 mg/dL; fasting glucose value >8.9-13.9 mmol/L, ketosis or evidence of T1DM at any glucose level	May hold ICPi until glucose control is obtained Titrate oral therapy or add insulin for worsening control in T2DM Should administer insulin for T1DM (or as default therapy if there is confusion about type) Urgent endocrine consultation for any patient with T1DM; in the absence of endocrinology, internal medicine may suffice Consider admission for T1DM if early outpatient evaluation is not available or signs of ketoacidosis are present
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL G3: >250-500 mg/dL (>13.9-27.8 mmol/L) G4: >500 mg/dL (>27.8 mmol/L)	Hold ICPi until glucose control is obtained on therapy with reduction of toxicity to G1 or less Urgent endocrine consultation for all participants Initiate insulin therapy for all patients Admit for inpatient management: Concerns for developing DKA, Symptomatic participants regardless of diabetes type, New-onset T1DM unable to see endocrinology
Additional considerations Insulin therapy can be used as the default in any case with hyperglycemia	

4.0 Endocrine Toxicity
Long-acting therapy alone is not usually sufficient for T1DM, where half of daily requirements are usually given in divided doses as prandial coverage and half as long acting. Insulin doses will be lower in T1DM because of preserved sensitivity (total daily requirement can be estimated at 0.3-0.4 units/kg/d). In T2DM, sliding-scale coverage with meals over a few days provides data to estimate a patient's daily requirements and can be used to more rapidly titrate basal needs. All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.

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

Table A5 Management of Musculoskeletal irAEs in Patients Treated With ICPis

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

5.0 Musculoskeletal Toxicities	
	Referral to rheumatology
G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL	For G3: Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to G1 or less For G4: permanently discontinue ICPi Initiate oral prednisone 0.5-1 mg/kg If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD Synthetic: methotrexate, leflunomide Biologic: consider anticytokine therapy such as TNF-a or IL-6 receptor inhibitors. (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis.) Test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment Referral to rheumatology.
Additional considerations Early recognition is critical to avoid erosive joint damage. Corticosteroids can be used as part of initial therapy in inflammatory arthritis, but due to likely prolonged treatment requirements, physicians should consider starting corticosteroid-sparing agents earlier than one would with other irAEs Oligoarthritis can be treated early on with intra-articular corticosteroids; consider early referral. Consider PCP prophylaxis for patients treated with high dose of corticosteroids for 12 weeks, as per local guidelines.	
5.2 Myositis	
Definition: A disorder characterized by muscle inflammation with weakness and elevated muscle enzymes (CK). Muscle pain can be present in severe cases. Can be life threatening if respiratory muscles or myocardium are involved Diagnostic work-up Complete rheumatologic and neurologic history regarding differential diagnosis; rheumatologic and neurologic examination, including muscle strength; and examination of the skin for findings suggestive of dermatomyositis. Muscle weakness is more typical of myositis than pain. Consider preexisting conditions that can cause similar symptoms. Blood testing to evaluate muscle inflammation CK, transaminases (AST, ALT), LDH, and aldolase can also be elevated Troponin to evaluate myocardial involvement and other cardiac testing, such as echocardiogram, as needed Inflammatory markers (ESR and CRP) Consider EMG, imaging (MRI), and/or biopsy on an individual basis when diagnosis is uncertain and overlap with neurologic syndromes, such as myasthenia gravis, is suspected Consider paraneoplastic autoantibody testing for myositis and neurologic conditions, such as myasthenia gravis Monitoring: CK, ESR, CRP	
G1: Complete examination and laboratory work-up as above G2: Complete history and examination as above; autoimmune myositis blood panel; EMG, MRI of affected joints Early referral to a rheumatologist or neurologist G3-4: As for G2 Urgent referral to a rheumatologist or neurologist	

5.0 Musculoskeletal Toxicities	
Grading	Management
G1: Mild weakness with or without pain	Continue ICPi If CK is elevated and patient has muscle weakness, may offer oral corticosteroids, and treat as G2 Offer analgesia with acetaminophen or NSAIDs if there are no contraindications
G2: Moderate weakness with or without pain, limiting age-appropriate instrumental ADL	Hold ICPi temporarily and may resume upon symptom control, if CK is normal and prednisone dose 10 mg; if worsens, treat as per G3 NSAIDs as needed Referral to rheumatologist or neurologist If CK is elevated three times or more), initiate prednisone or equivalent at 0.5-1 mg/kg May require permanent discontinuation of ICPi in most patients with G2 symptoms and objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy)
G3-4: Severe weakness with or without pain, limiting self-care ADL	For G3: Hold ICPi until G1 or less and permanently discontinue if any evidence of myocardial involvement For G4: permanently discontinue ICPi Consider hospitalization for severe weakness Referral to rheumatologist or neurologist Initiate prednisone 1 mg/kg or equivalent. Consider 1-2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia) Consider plasmapheresis Consider IVIG therapy Consider other immunosuppressant therapy, such as methotrexate, azathioprine, or mycophenolate mofetil, if symptoms and CK levels do not improve or worsen after 4-6 weeks; rituximab is used in primary myositis but caution is advised given its long biologic duration In case of management with rituximab, ICPi treatment should be discontinued
Additional considerations: Caution is advised with rechallenging	
5.3 Polymyalgia-like syndrome	
Definition: Characterized by marked pain and stiffness in proximal upper and/or lower extremities and no signs of true muscle inflammation such as CK elevation or EMG findings of myositis. No true muscle weakness, difficulty in active motion related to pain Diagnostic work-up	
G1 Complete rheumatologic history regarding differential diagnosis and examination of all joints and skin Check for symptoms of temporal arteritis, such as headache or visual disturbances; refer to ophthalmologist if present, and consider temporal artery biopsy ANA, RF, anti-CCP CK to evaluate differential diagnosis of myositis Inflammatory markers (ESR, CRP)	

5.0 Musculoskeletal Toxicities	
Monitoring: ESR, CRP	
G2: Complete history and examination as above; autoimmune tests as required for differential diagnosis; early referral to a rheumatologist G3-4: As for G2; see rheumatologist advice and review	
Grading	Management
G1: Mild stiffness and pain	Continue ICPi Initiate analgesia with acetaminophen and/or NSAIDs if there are no contraindications
G2: Moderate stiffness and pain, limiting age-appropriate instrumental ADL	Consider holding ICPi and resuming upon symptom control, prednisolone <10 mg; if worsens, treat as per G3 Initiate prednisone 20 mg/d or equivalent; if symptoms improve, start to taper dose after 3-4 weeks If no improvement or need for higher dosages after 4 weeks, escalate to G3 Consider referral to rheumatology
G3-4: Severe stiffness and pain, limiting self-care ADL	For G3: Hold ICPi and may resume, in consultation with rheumatology, if recover to G1 or less; however, note that cases of toxicity returning upon rechallenge have been reported. ICPi should be permanently discontinued in such cases For G4: permanently discontinue ICPi Referral to rheumatology Should initiate prednisone 20 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a corticosteroid-sparing agent such as methotrexate or IL-6 inhibition with tocilizumab (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis or GI metastases). Consider admission for pain control
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

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

Table A6 Management of Renal irAEs in Patients Treated With ICPis

6.0 Renal Toxicities	
Nephritis and renal dysfunction: diagnosis and monitoring For any suspected immune-mediated adverse reactions, exclude other causes Monitor patients for elevated serum creatinine prior to every dose Routine urinalysis is not necessary, other than to rule out UTIs, etc; nephrology may consider further If no potential alternative cause of AKI identified, then one should forego biopsy and proceed directly with immunosuppressive therapy Swift treatment of autoimmune component important	
6.1 Nephritis	
Definition: Inflammation of the kidney affecting the structure	
Grading	Management
G1: Creatinine level increase of >0.3 mg/dL; creatinine 1.5-2.0 x over baseline	Consider temporarily holding ICPi, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status) and baseline renal function. A change that is still <1.5 x ULN could be meaningful
G2: Creatinine 2-3 x above baseline	Hold ICPi temporarily Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc); if other etiologies ruled out, administer 0.5-1 mg/kg/d prednisone equivalents If worsening or no improvement: 1 to 2 mg/kg/d prednisone equivalents and permanently discontinue treatment If improved to G1 or less, taper corticosteroids over 4-6 weeks If no recurrence of chronic renal insufficiency, discuss resumption of ICPI with patient after taking into account the risks and benefits.
G3: Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Permanently discontinue ICPi
G4: Life-threatening consequences; dialysis indicated	Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc) Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent)
Additional considerations Monitor creatinine weekly Reflex kidney biopsy should be discouraged until corticosteroid treatment has been attempted	
6.2 Symptomatic nephritis: follow-up	
Grading	Management
G1	Improved to baseline, resume routine creatinine monitoring
G2	If improved to G1, taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring If elevations persist >7 days or worsen and no other cause found, treat as G3

6.0 Renal Toxicities	
G3	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist 3-5 days or worsen, consider additional immunosuppression (eg, mycophenolate)
G4	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist 2-3 days or worsen, consider additional immunosuppression (eg, mycophenolate)
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

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

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

7.0 Nervous System Toxicities	
7.1 Myasthenia gravis	
Definition: Fatigable or fluctuating muscle weakness, generally more proximal than distal. Frequently has ocular and/or bulbar involvement (ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, dysarthria, facial muscle weakness). May have neck and/or respiratory muscle weakness. (Note: May occur with myositis and/or myocarditis. Respiratory symptoms may require evaluation to rule out pneumonitis, myocarditis. Miller Fisher variant of Guillain-Barré syndrome (ophthalmoparesis) and the oculobulbar myositis (ptosis, ophthalmoparesis, dysphagia, neck and respiratory weakness) with ICPi may have overlapping symptoms.	
Diagnostic work-up AChR and antistriated muscle antibodies in blood; if AChR antibodies are negative, consider muscle specific kinase and lipoprotein-related 4 antibodies in blood Pulmonary function assessment with NIF and VC CPK, aldolase, ESR, CRP for possible concurrent myositis Consider MRI of brain and/or spine, depending on symptoms to rule out CNS involvement by disease or alternate diagnosis If respiratory insufficiency or elevated CPK, troponin T, perform cardiac examination with ECG and TTE for possible concomitant myocarditis Neurologic consultation Electrodiagnositic studies, including neuromuscular junction testing with repetitive stimulation and/or jitter studies, NCS to exclude neuropathy, and needle EMG to evaluate for myositis	
Grading	Management
All grades	All grades warrant work-up and intervention given potential for progressive myasthenia gravis to lead to respiratory compromise
No G1	
G2: Some symptoms interfering with ADL MGFA severity class 1 (ocular symptoms and findings only) and MGFA severity class 2 (mild generalized weakness)	Hold ICPi and may resume in G2 patients (MGFA 1 and 2) only if symptoms resolve Should consult neurology Pyridostigmine starting at 30 mg orally three times a day and gradually increase to maximum of 120 mg orally four times a day as tolerated and based on symptoms Administer corticosteroids (prednisone, 1-1.5 mg/kg orally daily) if symptoms G2; wean based on symptom improvement
G3-4: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms, or MGFA severity class 3-4 moderate to severe generalized weakness to myasthenic crisis	Permanently discontinue ICPi Admit patient, may need ICU-level monitoring Neurology consult Continue corticosteroids and initiate IVIG 2 g/kg IV over 5 days (0.4 g/kg/d) or plasmapheresis for 5 days Frequent pulmonary function assessment Daily neurologic review
Additional considerations Avoid medications that can worsen myasthenia: β-blockers, IV magnesium, fluoroquinolones, aminoglycosides, and macrolides Initially a 5-day course of plasmapheresis or a 2 g/kg course of IVIG over 5 days	

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

<table>
<tr><th colspan="2">7.0 Nervous System Toxicities</th></tr>
<tr><td colspan="2">7.3 Peripheral neuropathy</td></tr>
<tr><td colspan="2">Definition: Can present as asymmetric or symmetric sensory, motor, or sensory motor deficit. Focal mononeuropathies, including cranial neuropathies (eg, facial neuropathies/Bell palsy) may be present. Numbness and paresthesias may be painful or painless. Hypo- or areflexia or sensory ataxia may be present.</td></tr>
<tr><td colspan="2">Diagnostic work-up
G1
Screen for reversible neuropathy causes: diabetic screen, B12, folate, TSH, HIV, consider serum protein electrophoresis, and other vasculitic and autoimmune screen Neurologic consultation
Consider MRI of spine with or without contrast
G2: in addition to above
MRI spine advised/MRI of brain if cranial nerve Consider EMG/NCS
Consider neurology consultation
G3-4: go to Guillain-Barré syndrome algorithm</td></tr>
<tr><td>Grading</td><td>Management</td></tr>
<tr><td>G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate</td><td>Low threshold to hold ICPi and monitor symptoms for a week If to continue, monitor very closely for any symptom progression</td></tr>
<tr><td>G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation)</td><td>Hold ICPi and resume once return to G1
Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild)
Neurontin, pregabalin, or duloxetine for pain</td></tr>
<tr><td>G3-4: Severe, limiting self-care and aids warranted, weakness limiting walking or respiratory problems (ie, leg weakness, foot drop, rapidly ascending sensory changes) Severe may be Guillain-Barré syndrome and should be managed as such</td><td>Permanently discontinue ICPi
Admit patient
Neurologic consultation
Initiate IV methylprednisolone 2-4 mg/kg and proceed as per Guillain-Barré syndrome management</td></tr>
<tr><td colspan="2">7.4 Autonomic neuropathy</td></tr>
<tr><td colspan="2">Definition: Nerves that control involuntary bodily functions are damaged. This may affect blood pressure, temperature control, digestion, bladder function, and sexual function. A case of severe enteric neuropathy with ICPi has been reported. Can present with GI difficulties such as new severe constipation, nausea, urinary problems, sexual difficulties, sweating abnormalities, sluggish pupil reaction, and orthostatic hypertension.</td></tr>
<tr><td colspan="2">Diagnostic work-up
An evaluation by neurologist or relevant specialist, depending on organ system, with testing that may include
Screening for other causes of autonomic dysfunction: diabetic screen, adrenal insufficiency, HIV, paraproteinemia, amyloidosis, botulism; consider chronic diseases such as Parkinson and other autoimmune screening
AM orthostatic vitals
Consider electrodiagnostic studies to evaluate for concurrent polyneuropathy
Consider paraneoplastic Lambert-Eaton myasthenic syndrome, antineutrophil cytoplasmic antibodies, and ganglionic AChR antibody testing</td></tr>
</table>

7.0 Nervous System Toxicities	
Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient	Low threshold to hold ICPi and monitor symptoms for a week; if to continue, monitor very closely for any symptom progression
G2: Moderate, some interference with ADL, symptoms concerning to patient	Hold ICPi and resume once return to G1 Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild) Neurologic consultation
G3-4: Severe, limiting self-care and aids warranted	Permanently discontinue ICPi Admit patient Initiate methylprednisolone 1 g daily for 3 days followed by oral corticosteroid taper Neurologic consultation
7.5 Aseptic meningitis	
Definition: may present with headache, photophobia, and neck stiffness; often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis). Diagnostic work-up MRI of brain with or without contrast + pituitary protocol AM cortisol, ACTH to rule out adrenal insufficiency Consider lumbar puncture: measure opening pressure; check cell count and protein glucose; and perform Gram stain, culture, PCR for HSV, and other viral PCRs depending on suspicion, cytology May see elevated WBC count with normal glucose, normal culture, and Gram stain; may see reactive lymphocytes or histiocytes on cytology	
Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	For G1-3: Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits For G4: permanently discontinue ICPi. In case of any aseptic meningitis events (G1-4), consider empirical antiviral (IV acyclovir) and antibacterial therapy until CSF results Once bacterial and viral infection are negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg or IV methylprednisolone 1 mg/kg if moderate/severe symptoms
7.6 Encephalitis	
Definition: As for aseptic meningitis, need to exclude infectious causes, especially viral (ie, HSV). Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality	
Diagnostic work-up Neurologic consultation MRI of brain with or without contrast may reveal T2/fluid-attenuated inversion recovery changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal Lumbar puncture: check cell count and protein glucose and perform Gram stain, culture, PCR for HSV and other viral PCRs depending on suspicion, cytology, oligoclonal bands, autoimmune encephalopathy, and paraneoplastic panels. May see elevated WBC count with lymphocytic predominance and/or elevated protein EEG to evaluate for subclinical seizures	

<table>
<tr><th colspan="2">7.0 Nervous System Toxicities</th></tr>
<tr><td colspan="2">Blood: metabolic, CBC, ESR, CRP, ANCA (if suspect vasculitic process), thyroid panel including TPO and thyroglobulin Rule out concurrent anemia/thrombocytopenia, which can present with severe headaches and confusion</td></tr>
<tr><td>Grading</td><td>Management</td></tr>
<tr><td>G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate.
G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation)
G3-4: Severe, limiting self-care and aids warranted</td><td>For G1, 2, and 3: Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits
For G4: permanently discontinue ICPi
As above for aseptic meningitis, in case of any encephalitis events, suggest concurrent IV acyclovir until PCR results obtained and negative
Trial of methylprednisolone 1-2 mg/kg
If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids methylprednisolone 1 g IV daily for 3-5 days plus IVIG 2 g/kg over 5 days If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab or plasmapheresis in consultation with neurology.
In case of management with rituximab, ICPi treatment should be discontinued</td></tr>
<tr><td colspan="2">7.7 Transverse myelitis</td></tr>
<tr><td colspan="2">Definition: Acute or subacute weakness or sensory changes bilateral, often with increased deep tendon reflexes</td></tr>
<tr><td colspan="2">Diagnostic work-up
Neurologic consultation
MRI of spine (with thin axial cuts through the region of suspected abnormality) and MRI of brain
Lumbar puncture: cell count, protein, glucose, oligoclonal bands, viral PCRs, cytology, onconeural antibodies Blood: B12, HIV, RPR, ANA, Ro/La, TSH, aquaporin-4 IgG
Evaluation for urinary retention, constipation</td></tr>
<tr><td>Grading</td><td>Management</td></tr>
<tr><td>G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate.
G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation)
G3-4: Severe, limiting self-care and aids warranted</td><td>Permanently discontinue ICPi
Methylprednisolone 2 mg/kg
Strongly consider higher doses of 1 g/d for 3-5 days Strongly consider IVIG</td></tr>
<tr><td colspan="2">All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.</td></tr>
</table>

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

TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone; TTE = transthoracic echocardiogram; VC = vital capacity; WBC = white blood cell count.

Table A8 Management of Hematologic irAEs in Patients Treated With ICPis

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

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

8.0 Hematologic Toxicities	
	Administer methylprednisolone 1 g IV daily for 3 days, with the first dose typically administered immediately after the first PEX May offer rituximab In case of management with rituximab, ICPi treatment will be discontinued
8.3 Hemolytic uremic syndrome	
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia. Signs and symptoms of hemolytic uremic syndrome can include: Bloody diarrhea Decreased urination or blood in the urine Abdominal pain, vomiting, and occasionally fever Pallor Small, unexplained bruises or bleeding from the nose and mouth Fatigue and irritability Confusion or seizures High blood pressure Swelling of the face, hands, feet, or entire body	
Diagnostic work-up History and physical examination (special consideration for new history of high-risk drugs, hypertension, or cardiac causes) CBC with indices Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis. Serum creatinine ADAMTS13 (to rule out TTP) Homocysteine/methylmalonic acid Complement testing C3, C4, CH50 (complement inhibitory antibodies for suspected familial) Evaluate reticulocyte count and mean corpuscular volume Evaluation of infectious cause, including screening for EBV, CMV, HHV6 Evaluation for nutritional causes of macrocytosis (B12 and folate) Pancreatic enzymes Evaluation for diarrheal causes, shiga toxin, Escherichia coli 0157, etc Direct antibody test (Coombs test), haptoglobin, LDH, and other etiologies of anemia Evaluation for common drugs causing hemolysis (tacrolimus, cyclosporine, sirolimus, etc) Evaluation for concurrent confusion	
Grading	Management
G1-2: Evidence of RBC destruction (schistocytosis) without clinical consequences of anemia, thrombocytopenia Grade 2 G3: Laboratory findings with clinical consequences (eg, renal insufficiency, petechiae) G4: Life-threatening consequences (eg, CNS thrombosis/ embolism or renal failure)	For G1 and G2: Continue ICPi with close clinical follow-up and laboratory evaluation Supportive care For G3 and G4: Permanently discontinue ICPi Begin therapy with eculizumab therapy 900 mg weekly for four doses, 1,200 mg week 5, then 1,200 mg every 2 weeks Red blood transfusion according to existing guidelines
8.4 Aplastic anemia	
Definition: Condition in which the body stops producing enough new blood cells	
Diagnostic work-up	

8.0 Hematologic Toxicities	
History and physical examination (close attention to medications, exposure to radiation, toxins, recent viral infections) CBC, smear, reticulocyte count Viral studies, including CMV, HHV6, EBV, parvovirus Nutritional assessments including B12, folate, iron, copper, ceruloplasmin, vitamin D Serum LDH, renal function Work-up for infectious causes Identify marrow hypo/aplasia Bone marrow biopsy and aspirate analysis Peripheral blood analysis, including neutrophil count, proportion of GPI-negative cells by flow for PNH Flow cytometry to evaluate loss of GPI-anchored proteins Type and screen patient for transfusions and notify blood bank that all transfusions need to be irradiated and filtered	
Grading	Management
G1: Nonsevere, <0.5 polymorphonuclear cells x 10^9/L hypocellular marrow, with marrow cellularity <25%, peripheral platelet count >20,000, reticulocyte count <20,000	Hold ICPi and provide growth factor support and close clinical follow-up, and laboratory evaluation Supportive transfusions as per local guidelines
G2: Severe, hypocellular marrow <25% and two of the following: ANC < 500, peripheral platelet <20,000, and reticulocyte <20,000	Hold ICPi and provide growth factor support and close clinical laboratory evaluations daily Administer ATG + cyclosporine; HLA typing and evaluation for bone marrow transplantation if patient is candidate; all blood products should be irradiated and filtered Supportive care with granulocyte colony-stimulating factor may be added in addition
G3-4: Very severe, ANC >200, platelet count >20,000, reticulocyte count >20,000, plus hypocellular marrow >25%	For G3: Hold ICPi and monitor weekly for improvement; if not resolved, discontinue treatment until AE has reverted to G1 For G4: permanently discontinue ICPi Hematology consult, growth factor support Horse ATG plus cyclosporine If no response, repeat immunosuppression with rabbit ATG plus cyclosporine, cyclophosphamide For refractory patients, consider eltrombopag plus supportive care
8.5 Lymphopenia	
Definition: An abnormally low level of lymphocytes in PB; for adults, counts of < 1,500/mm^3	
Diagnostic work-up History and physical examination (special attention for lymphocyte-depleting therapy such as fludarabine, ATG, corticosteroids, cytotoxic chemotherapy, radiation exposure, etc, as well as history of autoimmune disease, family history of autoimmune disease) Evaluation of nutritional state as cause Spleen size CBC with differential, peripheral smear and reticulocyte counts CXR for evaluation of presence of thymoma Bacterial cultures and evaluation for infection (fungal, viral, bacterial specifically CMV/HIV)	
Grading	Management
G1-2: 500-1,000 PB lymphocyte count G3: 250-499 PB lymphocyte count	Continue ICPi

8.0 Hematologic Toxicities	
G4: <250 PB lymphocyte count	Continue ICPi, checking CBC weekly for monitoring, initiation of CMV screening Consider holding ICPi Initiate *Mycobacterium avium* complex prophylaxis and *Pneumocystis jirovecii* prophylaxis, CMV screening. HIV/hepatitis screening if not already done May consider EBV testing if evidence of lymphadenopathy/hepatitis, fevers, hemolysis consistent with lymphoproliferative disease
8.6 Immune thrombocytopenia	
Definition: An autoimmune disorder characterized by immunologic destruction of otherwise normal platelets	
Diagnostic work-up History and physical examination (special attention for lymphocyte-depleting therapy, such as fludarabine, ATG, corticosteroids, cytotoxic therapy) Family history of autoimmunity or personal history of autoimmune disease History of viral illness CBC Peripheral blood smear, reticulocyte count Bone marrow evaluation only if abnormalities in the above test results and further investigation is necessary for a diagnosis Patients with newly diagnosed immune thrombocytopenia should undergo testing for HIV, hepatitis C virus, hepatitis B virus, and Helicobacter pylori Direct antigen test should be checked to rule out concurrent Evan syndrome Nutritional evaluation Bone marrow evaluation if other cell lines affected and concern for aplastic anemia	
Grading	Management
G1: Platelet count <100/µL G2: Platelet count <75/µL	Continue ICPi with close clinical follow-up and laboratory evaluation Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1 Administer prednisone 1 mg/kg/d (dosage range, 0.5-2 mg/kg/d) orally for 2-4 weeks after which time this medication should be tapered over 4-6 weeks to the lowest effective dose IVIG may be used in conjunction with corticosteroids if a more-rapid increase in platelet count is required.
G3: Platelet count <50/µL	Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1
G4: Platelet count <25/µL	Hematology consult Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue treatment IVIG used with corticosteroids when a more-rapid increase in platelet count is required

8.0 Hematologic Toxicities	
	If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary If previous treatment with corticosteroids and/or IVIG unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more-potent immunosuppression (From American Society of Hematology guideline on immune thrombocytopenia97; consult for further details)
8.7 Acquired hemophilia	
Definition: Disorder caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors	
Diagnostic work-up Full blood count to assess platelet number, fibrinogen, PT, PTT, INR; the typical finding in patients with acquired hemophilia A is a prolonged activated PTT with a normal PT MRI, CT, and ultrasonography may be indicated to localize, quantify, and serially monitor the location and response of bleeding Medication review to assess for alternative causes Determination of Bethesda unit level of inhibitor	
Grading	Management
G1: Mild, 5%-40% of normal factor activity in blood, 0.05-0.4 IU/mL of whole blood	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits Administer 0.5-1 mg/kg/d prednisone Transfusion support as required Treatment of bleeding disorders with hematology consult
G2: Moderate, 1%-5% of normal factor activity in blood, 0.01- 0.05 IU/mL of whole blood	Hematology consult Administration of factor replacement (choice based on Bethesda unit of titer) Administer 1 mg/kg/d prednisone ± rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d); choice of rituximab v cyclophosphamide is patient specific and should be done with assistance of hematology consult; prednisone, rituximab, and cyclophosphamide should be given for at least 5 weeks Factors should be provided to increase level during bleeding episodes, with choice of factor based on presence or absence of inhibitor
G3-4: Severe, <1% of normal factor activity in blood, <0.01 IU/mL of whole blood	Permanently discontinue ICPi Admit patient Hematology consult Administration of factor replacement, choice based on Bethesda unit level of inhibitor Bypassing agents may be used (factor VII, factor VIII inhibitor bypass activity); caution should be taken in the elderly and those with coronary artery disease Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) ± rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d).

8.0 Hematologic Toxicities	
	Transfusion support as required for bleeding If worsening or no improvement add cyclosporine or immunosuppression/immunoadsorption
Additional considerations: The American Heart Association requires specialist clinical and laboratory expertise. Consult and/or transfer to a specialist center is often appropriate. If consultation with or transfer to a hemophilia center is not immediately possible, then investigation and treatment should be initiated while a liaison is being established. All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

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

Table A9 Management of Cardiovascular irAEs in Patients Treated With ICPis

<table>
<tr><th colspan="2">9.0 Cardiovascular Toxicities</th></tr>
<tr><td colspan="2">9.1 Myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis</td></tr>
<tr><td colspan="2">Definition: Signs and symptoms may include chest pain, arrhythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion, fatigue</td></tr>
<tr><td colspan="2">Diagnostic work-up
At baseline
ECG
Consider troponin, especially in patient treated with combination immune therapies Upon signs/symptoms (consider cardiology consult)
ECG
Troponin
BNP Echocardiogram CXR
Additional testing to be guided by cardiology and may include
Stress test
Cardiac catherization Cardiac MRI</td></tr>
<tr><td>Grading</td><td>Management</td></tr>
<tr><td>G1: Abnormal cardiac biomarker testing, including abnormal ECG
G2: Abnormal screening tests with mild symptoms
G3: Moderately abnormal testing or symptoms with mild activity
G4: Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions</td><td>All grades warrant work-up and intervention given potential for cardiac compromise
Consider the following:
For G1: Hold ICPi
For G2, G3, and G4: Permanently discontinue ICPi
For G1-G4: High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms)
Admit patient, cardiology consultation
Immediate transfer to a coronary care unit for patients with elevated troponin or conduction abnormalities
In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin</td></tr>
<tr><td colspan="2">Qualifying statement: Treatment recommendations are based on anecdotal evidence and the life-threatening nature of cardiovascular complications. The appropriateness of rechallenging remains unknown. Note that infliximab has been associated with heart failure and is contraindicated at high doses in patients with moderate-severe heart failure.</td></tr>
<tr><td colspan="2">9.2 Venous thromboembolism</td></tr>
<tr><td colspan="2">Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream. Clinical signs and symptoms are variable and may include pain, swelling, increased skin vein visibility, erythema, and cyanosis accompanied by unexplained fever for DVT and dyspnea, pleuritic pain, cough, wheezing, or hemoptysis for PE</td></tr>
<tr><td colspan="2">Diagnostic work-up
Evaluation of signs and symptoms of PE or DVT may include Clinical prediction rule to stratify patients with suspected venous thromboembolism Venous ultrasound for suspected DVT</td></tr>
</table>

9.0 Cardiovascular Toxicities	
CTPA for suspected PE Can also consider D-dimer for low-risk patients based on risk stratification by clinical prediction rule for DVT/PE when CT or Doppler are not available or appropriate Ventilation/perfusion scan is also an option when CTPA is not appropriate Consider other testing, including ECG, CXR, BNP and troponin levels, and arterial blood gas	
Grading	Management
G1: Venous thrombosis (eg, superficial thrombosis)	Continue ICPi Warm compress Clinical surveillance
G2: Venous thrombosis (eg, uncomplicated DVT), medical intervention indicated	Continue ICPi based on benefit-risk assessment of individual patient Consider consult from cardiology or other relevant specialties LMWH is suggested over VKA, dabigatran, rivaroxaban apixaban, or edoxaban for initial and long-term treatment IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term
G3: Thrombosis (eg, uncomplicated PE [venous], nonembolic cardiac mural [arterial] thrombus), medical intervention indicated	Hold ICPi until AE reverts back to G1 or less. If reverts to G2, use benefit-risk assessment for ICPi continuation Consider consult from cardiology or other relevant specialties LMWH is suggested over VKA, dabigatran, rivaroxaban apixaban, or edoxaban for initial and long-term treatment IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term
G4: Life-threatening (eg, PE, cerebrovascular event, arterial insufficiency), hemodynamic or neurologic instability, urgent intervention indicated	Permanently discontinue ICPi Admit patient consult from cardiology or other relevant specialities Respiratory and hemodynamic support LMWH is suggested over VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial and long-term treatment IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term Further clinical management as indicated based on symptoms
Additional considerations While it may be impossible to determine the etiology of thromboembolic disease in patients with advanced cancer and the role, if any, that ICPi treatment plays, it is reasonable to permanently discontinue the potential inciting agents given the severity and life-threatening potential of G4 complications. For G3 events, ICPi must be withheld and clinicians are to use clinical judgment and take into account the risks and benefits when deciding whether to restart ICPi treatment. Anticoagulant therapy duration should continue for a minimum of 9-12 months to indefinitely in the setting of active cancer unless patient is asymptomatic, doing well, or in remission.	

9.0 Cardiovascular Toxicities
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.

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

Table A10 Management of Ocular irAEs in Patients Treated With ICPis

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

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

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

10.10. Appendix 10: ECOG Performance Status

The performance status is based on the ECOG Scale [Oken, 1982].

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655.

10.11. Appendix 11: Renal Function Measures

CKD-EPI Formula

Chronic Kidney Disease (CKD) stage: Kidney Disease Outcomes Quality Initiative (KDOQI) CKD stages 3/4/5 defined by estimated glomerular filtration rate (eGFR) using the CKD Epidemiology Collaboration (CKD-EPI) formula [Levey, 2009].

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]
where:
S_{cr} is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of S_{cr}/κ or 1, and
max indicates the maximum of S_{cr}/κ or 1.

Cockcroft-Gault Formula

The Cockcroft-Gault formula is a commonly-used surrogate marker for actual creatinine clearance (CrCl) and employs creatinine measurements and a participant's weight (kg) to predict the clearance [Cockcroft, 1976].

If the participant is obese (>30% over ideal body weight), use ideal body weight in calculation of estimated CrCl.

If the participant is below ideal body weight, use actual body weight in calculation of estimated CrCl.

Cockcroft-Gault Formula for serum creatinine in mmol/L

CrCl (mL/min)=	$\frac{Q \times (140 - \text{age [years]}) \times \text{actual body weight (kg)}^{a}}{48816 \times \text{serum creatinine (mmol/L)}}$
Q=0.85 for females Q=1.0 for males	
OR	
a. Calculation of Ideal Body Weight Using the Devine Formula [Devine, 1974]	
Male participants:	
50.0 kg + (2.3 kg X each inch over 5 feet) or 50.0 kg + (0.906 kg X each cm over 152.4 cm)	

Female participants:	
	45.5 kg + (2.3 kg X each inch over 5 feet) or 45.5 kg + (0.906 kg X each cm over 152.4 cm) c

Cockcroft-Gault Formula for serum creatinine in mg/dL

$$CrCl\,(mL/min) = \frac{Q \times (140 - age\ [years]) \times actual\ body\ weight\ (kg)^{a}}{72 \times serum\ creatinine\ (mg/dL)}$$

Q=0.85 for females
Q=1.0 for males

For example:

For a male participant with actual body weight = 90.0 kg and height = 68 inches, the calculation would be as follows:

Ideal body weight= 50.0 + (2.3) (68-60) = 68.4 kg

This participant's actual body weight is >30% over ideal body weight. In this case, the participant's ideal body weight of 68.4 kg should be used in calculating estimated creatinine clearance.

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10.12. Appendix 12: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 01 28-MAY-2020

Overall Rationale for the Amendment: Protocol is an administrative amendment to clarify wording of inclusion criteria, QTcF text in the protocol, notes in the SoA, and other typos in the original protocol.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 SoA	Clarified that use of 'intervention' and 'treatment' are interchangeable. Conmeds are to be collected during follow-up period. Brain CT/MRI added.	Administrative changes are made for clarity. Conmeds will be collected for safety follow-up. Brain CT/MRI added to align with Section 8.
Section 4.1 Overall Design	Survival Follow-up will continue until the end of study as defined in Section 4.8 is removed.	This statement was redundant.
Section 5.1 Inclusion 2	At least eighteen (18) years of age at the time of signing the informed consent.	Clarified to indicate years of age.
Inclusion 3	Renal, pelvis changed to renal pelvis. Uterus changed to ureter.	Grammar and spelling correction.
Inclusion 6	Removed language regarding NCI CTACE toxicity. Expanded ECOG acronym to full words.	Redundant to exclusion criterion 23. Expanded to full words for first usage.
Inclusion 7	Bilirubin $\leq$1.5 x ULN (isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).	Correct the cut-off for bilirubin to less than or equal to 1.5 x ULN.
Section 5.2 Exclusion 8	Excluded systemic corticosteroid use clarified to doses that are greater than 10 mg daily oral dose.	Standard dosage prescribed would be 10 mg or less therefore the protocol needs to allow for 10 mg.
Exclusion 15	F is added to QTc.	Fridericia's correction formula is to be used for standardization.
Section 8.1 Study Assessments	Complete is added to Physical Examination at screening.	Align with SoA.

Section # and Name	Description of Change	Brief Rationale
	Archival Tumor sample is mandatory. CCI [redacted]	CCI [redacted]
Section 8.3.1 Disease Response Assessments	Disease assessment clarified to include pelvis.	Chest, abdomen and pelvis are standard for this disease indication.
Section 8.4.3 Vital Signs	Vital signs will be measured after 5 minutes of rest in a semi-supine semirecumbent or supine position, and will include temperature, systolic and diastolic blood pressure, pulse rate, and oxygen saturation (measured by pulse oximetry	Correct typo – removed semi-supine
Full document		Administrative changes made throughout document to align sections for clarity and spelling corrections.

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 2	03 Mar 2022	*TMF-14396625*
Amendment 1	28 May 2020	*2019N411039_01*
Original Protocol	30 Jan 2020	*2019N411039_00*

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