Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase II, Multicenter, Open-label Study to Investigate the Clinical Efficacy of M7824 Monotherapy in Participants With Locally Advanced or Metastatic Biliary Tract Cancer Who Fail or are Intolerant to First-line Platinum-Based Chemotherapy
Study Number:	MS200647_0047
Merck Compound:	M7824
Merck Registered Compound Name in Japan:	Not applicable
Study Phase:	Phase II
Short Title:	Phase II Study of M7824 Monotherapy in Participants With Locally Advanced or Metastatic Biliary Tract Cancer Who Fail or are Intolerant to First-line Platinum-Based Chemotherapy
Coordinating Investigator:	PPD
Sponsor Name and Legal Registered Address:	For all countries, except the USA and Japan: Merck KGaA Frankfurter Str. 250 Darmstadt, Germany In the USA: EMD Serono Research & Development Institute, Inc. An affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, 01821, USA In Japan: Merck Biopharma Co., Ltd.: Japan (Affiliate of Merck KGaA, Darmstadt, Germany) Arco Tower, 1-8-1 Shimomeguro Meguro-ku, Tokyo 153-8926, Japan
Regulatory Agency Identifying Numbers:	IND: CCI EudraCT: 2018-003707-19 ClinicalTrials.gov: NCT03833661

Protocol Version:	22 June 2021/Version 5.0

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	08-Nov-2018
1.1-VHP	Region-specific amendment (European Union for countries participating in the Voluntary Harmonisation Procedure [VHP])	15-Jan-2019
1.2-FDA	Region-specific amendment (United States Food and Drug Administration request)	01-Feb-2019
1.3-CHN	Country-specific amendment (China)	31-May-2019
2.0	Global Protocol Amendment	26-Aug-2019
3.0	Global Protocol Amendment	10-Oct-2019
3.1-CHN	Country-specific amendment (China)	14-Mar-2020
4.0	Global Protocol Amendment	20-Oct-2020
4.1	Country-specific amendment (China)	21-Oct-2020
5.0	Global Protocol Amendment	22-Jun-2021

Protocol Version 5.0 (22 June 2021)

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

Overall Rationale for the Amendment

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

Section # and Name	Description of Change	Brief Rationale
Title Page	Removed “Medical Responsible” field Removed “Replaces Version” and “Approval Date” rows.	To be consistent with current Sponsor protocol template (Version 15).
2.3 Benefit/Risk Assessment	Risk classification has been revised and the list of events has been updated accordingly. The statement referring to the number of patients treated with M7824 monotherapy has been removed.	The risk reclassification was based on in-depth analysis of a pooled safety dataset of N = 765 participants who received M7824 monotherapy at 1200 mg Q2W. The information on the number of patients treated with M7824 is provided in the IB.
5 Study Population Appendix 2 Study Governance	Edits related to informed consent process.	To be consistent with current Sponsor protocol template (Version 15).
6.9 Management of Adverse Events of Special Interest and other Potential Risks Appendix 4 Adverse Events: Definitions and Procedures for Recording, evaluating, Follow-up, and Reporting	Risk categorization has been revised and the list of events has been updated accordingly.	The risk reclassification was based on in-depth analysis of a pooled safety dataset of N = 765 participants who received M7824 monotherapy at 1200 mg Q2W.
6.9.1 Infusion-related Reactions Including Immediate Hypersensitivity	Infusion-related reactions are reclassified from “important identified risk” to “identified risk” for M7824.	
6.9.2 Immune-related Adverse Events	Risk categorization has been revised and the list of events has been updated accordingly.	
6.9.3 TGF-β Inhibition Mediated Skin Reactions	Skin Adverse Events have been renamed to TGF-β Inhibition Mediated Skin Reactions.	
6.9.4 Anemia	Term “treatment-related anemia events” has been revised to “anemia” and reclassified from “important potential risk” to “important identified risk” for M7824.	
6.9.5 Bleeding Events	Bleeding events are reclassified from “potential risk” to “important identified risk” for M7824.	
6.9.6.1 Impaired Wound Healing	The risk name “Alterations in Wound Healing or Repair of Tissue Damage” has been changed to “Impaired Wound Healing”.	
7.3 Lost to Follow-up	Edits are done related to Lost to Follow-up information.	To be consistent with current Sponsor protocol template (Version 15).
Note: Minor changes have been performed throughout the protocol to address consistency pertaining to major changes made in the protocol or to add further clarity and precision.		

[redacted]

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

A Phase II, Multicenter, Open-label Study to Investigate the Clinical Efficacy of M7824 Monotherapy in Participants With Locally Advanced or Metastatic Biliary Tract Cancer Who Fail or are Intolerant to First-line Platinum-Based Chemotherapy

Short Title:

Phase II Study of M7824 Monotherapy in Participants With Locally Advanced or Metastatic Biliary Tract Cancer Who Fail or are Intolerant to First-line Platinum-Based Chemotherapy

Rationale:

There is no established second-line therapy for biliary tract cancer (BTC) as the standard of care according to the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines. M7824 (bintrafusp alfa) targets the programmed death-ligand 1 (PD-L1) and transforming growth factor β, the 2 major mechanisms of immunosuppression in the tumor microenvironment and provides a rationale to overcome the resistance of checkpoint inhibitor monotherapy. A preclinical study showed that M7824 demonstrated enhanced antitumor activity and prolonged survival compared with checkpoint inhibitors in in vivo models. A clinical study of M7824 showed a promising result with a clinical efficacy signal of 23.3% (7 of 30 participants) confirmed objective response rate (ORR) assessed by Investigators and 20% assessed by Independent Review Committee (IRC) in second-line BTC. Therefore, the current clinical study is supported by scientific evidence and promising clinical efficacy data with the goal of fulfilling an unmet medical need and bringing clinical benefits to patients.

Objectives and Endpoints:

Objectives	Endpoints (Outcome Measures)
Primary	
• To evaluate clinical efficacy of M7824 based on ORR	• Confirmed objective response (OR) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) assessed by IRC
Secondary	
• To evaluate clinical efficacy of M7824 based on duration of response (DOR)	• DOR assessed from complete response (CR) or partial response (PR) until progression of disease (PD), death, or last tumor assessment assessed by IRC
• To evaluate clinical efficacy of M7824 based on durable response rate (DRR)	• Durable response of at least 6 months according to RECIST 1.1 assessed by IRC
• To evaluate clinical safety of M7824	• Occurrence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (AEs), including adverse events of special interest (AESIs)

Objectives	Endpoints (Outcome Measures)
• To evaluate clinical efficacy based on progression-free survival (PFS)	• PFS according to RECIST 1.1 assessed by IRC
• To evaluate ORR, DOR, DRR and PFS by Investigator read	• OR, DOR, DRR, and PFS according to RECIST 1.1 assessed by Investigator read
• To evaluate clinical efficacy based on overall survival (OS)	• OS
• To characterize the pharmacokinetic (PK) profile of M7824	• The concentration observed immediately at the end of infusion (C_{EOI}) of M7824 • The concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration [C_{trough}] for multiple dosing) of M7824
• To characterize the immunogenicity of M7824	• Immunogenicity of M7824 as measured by antidrug antibody (ADA) assay, from Screening through 12 weeks (± 2 weeks) after last treatment
• To evaluate clinical efficacy of M7824 based on ORR, DOR, and DRR according to PD-L1 expression and microsatellite instability (MSI) status retrospectively	• Confirmed OR according to RECIST 1.1 assessed by IRC according to PD-L1 expression and MSI status • DOR and durable response of at least 6 months according to RECIST 1.1 assessed by IRC according to PD-L1 expression and MSI status

Overall Design:

This is a Phase II, multicenter, international, single-arm, open-label, study to evaluate M7824 monotherapy in participants with locally advanced or metastatic BTC who failed or were intolerant to first-line chemotherapy.

The study plans to enroll 141 eligible BTC participants. The participants will be included from the USA, Europe, and Asian countries with competitive enrollment. The study will enroll 3 major subtypes of BTC, including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer, with a minimum of 30 participants in each subtype. If one subtype does not reach a minimum of 30 participants by the end of competitive enrollment of 141 participants, the study will continue to enroll only in this subtype to reach 30 participants.

Participants will receive M7824 at a dose of 1200 mg once every 2 weeks until confirmed PD, death, unacceptable toxicity, or study withdrawal.

This study includes:

- 28-day Screening period.
- Treatment until confirmed PD per RECIST 1.1, death, unacceptable toxicity, or study withdrawal. In the case of PD, treatment may continue past the initial determination of PD or confirmed PD if the participant's performance status has remained at least stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment and if other criteria are fulfilled as outlined in the protocol. Participants who have experienced a confirmed CR should continue treatment for a maximum of 24 months after confirmation of response. If the Investigator believes that a participant with confirmed CR may benefit from treatment beyond 24 months, it may be permissible to continue treatment after discussion with the

Medical Monitor and the Sponsor Medical Responsible. Participants with stable disease or PR should continue treatment until disease progression or any other discontinuation criterion is met.

- Safety Follow-up will continue until 12 weeks after the last dose of M7824. The 12-week Safety Follow-up is allowed to be conducted via phone 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. Long-term Follow-up can be performed by chart reviews or telephone calls.
- Survival Follow-up will continue until each participant was followed up for at least 3 years after the End-of-Treatment.

Number of Participants:

The planned total sample size is 141 participants based on the following assumptions:

1. ORR of 18%
2. Alpha = 0.025 (1-sided) for the Exact test of the null hypothesis of an ORR ≤ 10%.

Under the given assumptions, the power to reject the null hypothesis at the primary analysis is 80%.

Statistical Analysis:

There will be 2 data cutoff time points in this study:

- An CCI [redacted] per BTC subtype will be performed once 15 participants of each subtype have reached at least one postbaseline tumor assessment. Each subtype will be analyzed separately once criteria are met.
- The primary analysis will be conducted 9 months after the accrual of the last of 141 planned participants.
- Second analysis for DRR and DOR will be conducted 15 months after the accrual of the last of 141 planned participants. The analysis will comprise a full evaluation of all efficacy and safety endpoints.

Study Intervention Groups and Duration:

The study duration for a participant is estimated to be up to 3 years. This includes a 28-day Screening period (decision will be made in this period for participants' study inclusion if all eligibility criteria are met); a treatment duration until confirmed PD, unacceptable toxicity, or study withdrawal occurs, a 28-day Safety Follow-up visit and a 12-week Safety Follow-up phone call after the last dose of M7824.

Involvement of Special Committee(s): Yes

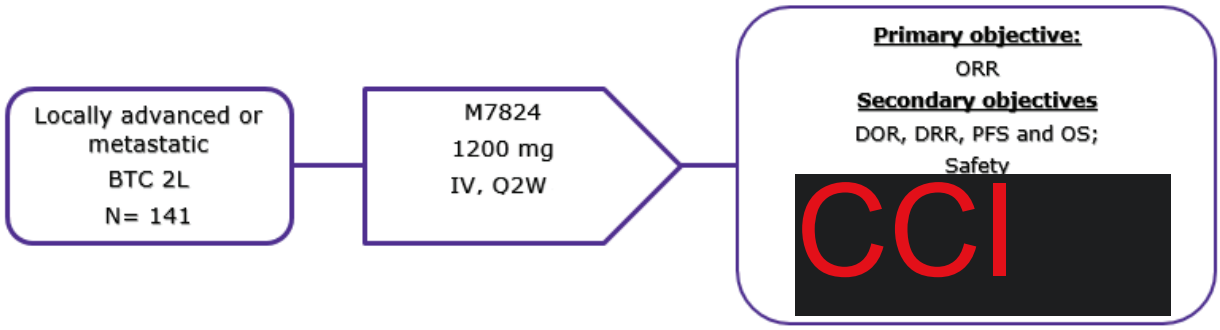
The following committees will be involved in the study: Independent Data Monitoring Committee (IDMC), IRC, and Study Steering Committee.

To ensure participants' safety during the study, an external IDMC will periodically review safety data. The IDMC will be composed of a minimum of 3 voting members, including an independent biostatistician, and 2 independent oncologists (BTC experts). The full membership, mandate, and processes of the IDMC are detailed in the IDMC charter.

1.2 Schema

The overall study design is shown in Figure 1.

Figure 1 Overall Study Design Schema



2L=second-line, BTC=biliary tract cancer, DOR=duration of response, DRR=durable response rate, IV=intravenous, CCI, N=number of participants, ORR=objective response rate, OS=overall survival, PD-L1=programmed death-ligand 1, PFS=progression-free survival, Q2W=every 2 weeks.

1.3 Schedule of Activities

The Schedule of Activities is provided in Table 1. The M7824 pharmacokinetic and immunogenicity sampling times are provided in Table 2.

Table 1 Schedule of Activities

Assessments & Procedures	Screen-ing/ Base-line	Treatment Phase (± 3 days)								End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day -28 to First Treat-ment	V1	V2	V3	V4	V5	V6	V7	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13						
		D1	D15	D29	D43	D57	D71	D85						
Administrative Procedures														
Written informed consent	X													
Inclusion/ exclusion criteria/ Enrollment (if eligible)	X	X[a]												Enrollment will be after the confirmation of fulfilling all inclusion criteria and without matching any exclusion criterion. [a] Confirmation of eligibility is required prior to dosing on W1D1.
Demographic data	X													
Medical history	X													Medical history should include history of BTC with stages at diagnosis, tumor locations (intrahepatic, extrahepatic, and gallbladder cancer) environmental / occupational exposure to chemicals and baseline medical condition.
Prior anticancer drug/radio-therapy / procedures for Baseline visit	X													Prior anticancer procedures and therapies should at least include prior adjuvant therapy, surgical resection and recurrence, and details on first-line chemotherapy agents, treatment duration, and treatment responses.

Assessments & Procedures	Screen-ing/ Base-line	Treatment Phase (± 3 days)								End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day -28 to First Treat-ment	V1	V2	V3	V4	V5	V6	V7	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13						
		D1	D15	D29	D43	D57	D71	D85						
Documentation of concomitant medication and procedures	X	X	X	X	X	X	X	X	Q2W	X	X			
Documentation of non-protocol related hospitalization, emergency room visits, and outpatient hospital visits		X	X	X	X	X	X	X	Q2W	X	X			

Assessments & Procedures	Screen-ing/ Base-line	Treatment Phase (± 3 days)								End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day -28 to First Treat-ment	V1	V2	V3	V4	V5	V6	V7	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13						
		D1	D15	D29	D43	D57	D71	D85						
Tumor Biopsies/Archival Tissue Collection														
CCI														CCI

Assessments & Procedures	Screen-ing/ Base-line	Treatment Phase (± 3 days)								End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day -28 to First Treat-ment	V1	V2	V3	V4	V5	V6	V7	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13						
		D1	D15	D29	D43	D57	D71	D85						
Premedication and M7824 Drug Administration														
Premedication and M7824 administration		X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	Q2W[d]					[d] See Section 6.9.1 for premedication details. The first 15 participants will not receive premedication before first and second M7824 infusions to establish whether mandatory use of premedication is required. If two or more Grade 2 infusion-related reactions are seen during the first 2 infusions for the first 15 participants, IDMC will determine if mandatory premedication is needed. Study enrollment will continue in parallel to this review and sites will be notified accordingly if premedication becomes a requirement. If IDMC determines mandatory premedication is justified, premedication with an antihistamine and with paracetamol (acetaminophen) (e.g., 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] IV or oral equivalent) prior to each dose of M7824 is mandatory for the first 2 infusions. After 2 infusions, premedication is optional and at the discretion of the Investigator. If Grade 2 infusion-related reactions are seen during the first 2 infusions, then premedication should not be stopped. Steroids as premedication are not permitted.

Assessments & Procedures	Screen-ing/ Base-line	Treatment Phase (± 3 days)								End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day -28 to First Treat-ment	V1	V2	V3	V4	V5	V6	V7	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13						
		D1	D15	D29	D43	D57	D71	D85						
Safety Assessments														
Documentation of AEs[e]	X	X	X	X	X	X	X	X	Q2W	X	X	X[e]	X[e]	AEs will be documented at each study visit (see Appendix 4) for safety assessment. Any SAE assessed as related to study intervention must be reported whenever it occurs, irrespective of the time elapsed since the last administration of study intervention. [e] The 12-week Safety Follow-up and Long-term Follow-up should be conducted via telephone calls or patient chart reviews unless there is medical necessity requiring a clinical visit. See Sections 8.3.1, 8.3.2 and Appendix 4 for definition of the AE reporting period and Follow-up.
Physical examination	X	X	X	X	X	X	X	X	Q2W	X	X			Complete physical examination at Screening; at least focused physical examinations should be performed at subsequent clinical visits per local standard practice.
Skin assessment	X				X			X	Q6W	X	X	X[f]		[f] The 12-week Safety Follow-up is to be conducted via a telephone call unless there is medical necessity requiring a clinical visit.
Vital signs	X	X	X	X	X	X	X	X	Q2W	X	X			Including weight and height (height at Screening only).
ECOG PS	X	X[g]	X	X	X	X	X	X	Q2W	X	X			[g] ECOG PS 0 or 1 is required at W1D1.
12-lead ECG	X									X	X			

Assessments & Procedures	Screen-ing/ Base-line	Treatment Phase (± 3 days)								End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day -28 to First Treat-ment	V1	V2	V3	V4	V5	V6	V7	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13						
		D1	D15	D29	D43	D57	D71	D85						
SpO_2	X	X	X	X	X	X	X	X	Q2W	X	X			Using pulse oximeter.
Laboratory Assessments														
Virology serology (HBV and HCV)	X	As clinically indicated in participants with a history of HBV or HCV infection												HIV testing is not mandated for study inclusion; and if it is performed at any point in Screening or while on study, a site must consent the participant for HIV testing as per local standard guidance.
Hematology	X	X	X	X	X	X	X	X	Q2W	X	X			Details on blood tests under this category are listed in Appendix 5. Samples must also be drawn prior to study intervention administration and results of selected laboratory tests (see Appendix 5) must be reviewed within 48 hours prior to dosing.
Full serum chemistry	X	X	X	X	X	X	X	X	Q2W	X	X			Full serum chemistry is listed in Appendix 5. Samples must be drawn prior to dose administration and results of selected laboratory tests (see Appendix 5) must be reviewed within 48 hours prior to dosing.
Coagulation parameters (aPTT, prothrombin time and INR)	X	X		X		X		X	Q4W	X	X			See Appendix 5.
CA 19.9	X	X			X			X	Q6W	X	X			
Urinalysis	X									X	X			Details on urinalysis under this category are listed in Appendix 5. Full urinalysis (dipstick plus microscopic evaluation) at the Screening only and a basic urinalysis (dipstick only) should be performed during treatment if clinically indicated.

Assessments & Procedures	Screen-ing/ Base-line	Treatment Phase (± 3 days)								End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day -28 to First Treat-ment	V1	V2	V3	V4	V5	V6	V7	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13						
		D1	D15	D29	D43	D57	D71	D85						
β-HCG pregnancy test	X	X		X		X		X	Q4W		X	X[h]		β-HCG should be determined from serum or highly sensitive urine β-HCG pregnancy test. Results of the most recent pregnancy test should be available prior to dosing of study intervention. See Section 5.1 and 8.2.3 for details. [h] participants should go to local laboratory to perform pregnancy test. Clinical visit is not required.
Free T4 and TSH	X				X			X	Q6W		X			
KL-6, SP-A and SP-D[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	Q4W[i] after D85 until PD	X[i]	X[i]			[i] Only applicable for Japanese sites.

Assessments & Procedures	Screen-ing/ Base-line	Treatment Phase (± 3 days)								End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day -28 to First Treat-ment	V1	V2	V3	V4	V5	V6	V7	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13						
		D1	D15	D29	D43	D57	D71	D85						
Patient Reported Outcomes (PRO)														
CCI														

Assessments & Procedures	Screen-ing/ Base-line	Treatment Phase (± 3 days)								End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day -28 to First Treat-ment	V1	V2	V3	V4	V5	V6	V7	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13						
		D1	D15	D29	D43	D57	D71	D85						
Patient interviews	X									X				Participants will be asked to participate in an interview performed by a third-party vendor. Participants will be selected from all sites in the USA, Germany, and Korea.
Tumor Assessments														
Tumor evaluation /staging (CT scan/MRI/other established methods)	X					X			Q8W up to 12 months, then Q12W				X[m]	A brain CT/MRI scan should be done as clinically indicated at Screening. Confirmation of CR or PR should be performed preferably at the regularly scheduled assessment intervals, but no sooner than 4 weeks after the initial documentation. See Section 8.1.1. The IRC should confirm measurable disease before enrollment as well as verify unconfirmed PD by Investigator read. [m] In case treatment is discontinued due to another reason than PD, tumor assessments should be continued according to original protocol schedule until confirmed PD.
Subsequent anticancer therapy (any line)											X	X	X	
Survival follow-up[n]													X[n]	[n] Survival Follow-up will continue until each participant was followed up for at least 3 years after the End-of-Treatment.

Assessments & Procedures	Screen-ing/ Base-line	Treatment Phase (± 3 days)								End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Day -28 to First Treat-ment	V1	V2	V3	V4	V5	V6	V7	Until PD	On the Day of or Within 7 Days of Decision to Discontinue	28 Days (± 5 Days) After Last Treatment	12 Weeks (± 2 Weeks) After Last Treatment	Every 12 Weeks (± 2 Weeks)	
		W1	W3	W5	W7	W9	W11	W13						
		D1	D15	D29	D43	D57	D71	D85						
PK, ADA and CCI														
PK and ADA sampling	See Table 2 for PK and ADA sampling times													
CCI														s

ADA=antidrug antibody, AE=adverse events, aPTT= activated partial thromboplastin time, β-HCG=β-human chorionic gonadotropin, CCI item module, BTC=biliary tract cancer, CCI, CR=complete response, CT=computed tomography, D=Day, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group performance status, CCI, CCI, HBV=hepatitis B virus, HCC-18=Hepatobiliary Cancer 18 item module, HCV=hepatitis C virus, HIV=human immunodeficiency virus, IDMC=Independent Data Monitoring Committee, INR=international normalized ratio, IRC=Independent review committee, IV=intravenous, MRI=magnetic resonance imaging, CCI, PD=progression of disease, PD-L1=programmed death ligand 1, PGIS=patient global impression of severity, PK=pharmacokinetics, PR=partial response, CCI ome, Q2W=every 2 weeks, Q4W=every 4 weeks, Q6W=every 6 weeks, Q12W=every 12 weeks, SAE=serious adverse event, SP-A=Surfactant protein A, SP-D=Surfactant protein D, SpO2=blood oxygen saturation, T4=thyroxine, CCI TSH=thyroid-stimulating hormone, V=visit, W=Week, W1D1=Week 1 Day 1.

Table 2 M7824 Pharmacokinetic, Immunogenicity Sampling

M7824 Measure	Screening / Baseline Assessments	Treatment Phase (± 3 days)						End-of-Treatment Visit	Safety Follow-up Visit		Notes
		V1	V2	V3	V4	V7					
		W1	W3	W5	W7	W13					
	Day -28 to First Treatment	D1 Pre/End Infusion	D15 Pre/End Infusion	D29 Pre/End Infusion	D43 Pre/End Infusion	D85 Pre/End Infusion	Until Progression Pre-infusion	On the Day of or Within 7 Days of Decision	Up to 28 Days (± 5 days) After Last Treatment	12 Weeks (± 2 weeks) After Last Treatment	
Blood sample for PK		X/X	X/-	X/X	X/-	X/-	Q6W up to/including W25, then Q12W	X	X		Samples for PK analysis to be taken before (pre) infusion (as close to the start of the infusion as possible), immediately after the completion of infusion (as close to the completion as possible but no later than 30 minutes post end of infusion). The pre-dose sample should still be drawn even if dosing is ultimately deferred at the study visit. The exact time of each draw must be recorded. A protocol deviation will be defined by a sample not being drawn or time not being recorded.
Blood sample for ADA	X		X/-	X/-	X/-	X/-	Q6W up to/including W25, then Q12W	X	X		Pre-dose ADA samples to be collected within 2 hours prior to study intervention infusions as scheduled.

ADA=antidrug antibody, D=days, PK=pharmacokinetics, Q6W=every 6 weeks, Q12W=every 12 weeks; V=visit, W=Week.

2 Introduction

M7824 (bintrafusp alfa) is a first-in-class, intravenously administered bifunctional fusion protein that combines an antiprogrammed death-ligand 1 (anti-PD-L1) antibody and the soluble extracellular domain of the human transforming growth factor-β (TGF-β) receptor as a TGF-β neutralizing "trap" into a single molecule. M7824 is being developed for the treatment of participants with locally advanced or metastatic biliary tract cancer (BTC) who failed or are intolerant to first-line (1L) chemotherapy. Bintrafusp alfa is the international nonproprietary name for M7824.

M7824, as a monotherapy, has shown an acceptable safety profile and a promising clinical efficacy signal in a Phase Ib study of second-line (2L) BTC.

Detailed information on the chemistry, pharmacology, efficacy, and safety of M7824 is in the Investigator's Brochure (IB).

2.1 Study Rationale

There is no established 2L therapy for BTC as the standard of care according to the National Comprehensive Cancer Network (NCCN 2018) and European Society for Medical Oncology (Valle 2016) guidelines. The TGF-β pathway mutation is one of the key underlying molecular alterations of BTC tumorigenesis (Nakamura 2015). M7824 is designed to target PD-L1 and TGF-β, 2 of the major mechanisms of immunosuppression in the tumor microenvironment and provides a rationale to overcome resistance of checkpoint inhibitor monotherapy.

A preclinical study showed that M7824 demonstrated enhanced antitumor activities and prolonged survival compared with checkpoint inhibitors in in vivo models (Lan 2018). A clinical study of M7824 showed a promising result with a clinical efficacy signal of 23.3% (7 of 30 participants) confirmed objective response rate (ORR) by Investigator read and 20% by Independent Review Committee (IRC) in 2L BTC. Therefore, the current clinical study is supported by scientific evidence and promising clinical efficacy data with the goal of fulfilling an unmet medical need and bringing clinical benefits to patients.

2.2 Background

BTC is a heterogeneous group of rare tumors that include intrahepatic and extrahepatic cholangiocarcinoma (CCA) and gallbladder cancer (NCCN 2018; Valle 2016). Ampullary cancer can originate from the pancreas, duodenum, distal common bile duct, or the structures of the ampullary complex based on the anatomic location. For this reason, this study excludes ampullary cancer. There were approximately 12,190 estimated new cases and 3,790 estimated deaths in 2018 in the USA (Siegel 2018). More than 90% of BTCs are adenocarcinomas (Hezel 2008). Most patients with BTC have advanced disease at presentation and relapse despite surgery; BTC cases have a poor prognosis, with an estimated 5-year overall survival (OS) of about 17.5% (Noone 2018). The recurrence rates are about 67% at 24 months among the few patients who undergo curative resection (Jarnagin 2003). Unresectable BTC is treated with chemotherapy, but the median survival time is < 1 year (Valle 2010). For patients with advanced-stage or unresectable

BTCs, current standard of care is 1L systemic chemotherapy, that is a combination of gemcitabine and cisplatin. However, this 1L standard of care has limited effectiveness, with median OS < 1 year (Valle 2010).

There is no established 2L therapy for BTC as the standard of care for 2L chemotherapy. Based on an update of a systematic review published in 2014 (Lamarca 2014) from available literature conducted in August 2018, which included 2L BTC studies reporting ORR results for chemotherapy alone or in association with an approved systemic anticancer therapy restricted to studies with > 20 participants (to avoid imprecise ORR estimates reported in smaller samples), 32 studies were identified reporting outcomes for 2137 participants globally. The ORR estimate derived from a regression model with a random effect was 7.2% with a 95% confidence interval (CI) ranging from 5.5% to 9.2%. Using the upper limit of this CI we assumed the benchmark ORR to be 10%.

M7824 has shown promising clinical efficacy signal in BTC patients progressing after platinum-based 1L treatment (Study MS200647-0008). Thirty Asian participants were treated with M7824 at dose of 1200 mg every 2 weeks. As of 20 March 2018, 30 participants who had previously received 1L treatment for BTC, received M7824 for a median duration of 8.9 weeks (range: 2 to 57.6 weeks); 5 participants remained on treatment at the time of data cutoff. Seven participants had a confirmed objective response (OR) by Investigator read (ORR 23.3%) and 6 participants had a confirmed OR by IRC (ORR 20%), including 1 confirmation of response after cutoff. Per anatomical location, the ORR was 14.3% (1 out of 7) in study participants with extrahepatic CCA and 40% (4 out of 10) in study participants with intrahepatic CCA, 16.6% (2 out of 12) in study participants with gallbladder carcinoma. No responses were observed in ampullary cancer (0 out of 1). With a minimum follow-up of 8 months, the duration of response (DOR) ranged from 0.7 to 6.9 months with 5 of 7 responses ongoing at the data cutoff date. Besides the confirmed ORR, 1 additional participant had an ongoing partial response (PR) for 7.6+ months after initial progression. The observed clinical efficacy, therefore, compares favorably to the calculated benchmark of existing 2L treatment options and there is a strong rationale with preclinical and clinical data to justify further clinical development of M7824 in 2L BTC, with the potential to establish M7824 as the standard of care.

In the Phase I Asian 2L BTC study, 2 treatment-related Grade 5 interstitial lung disease (ILD) events have been reported in Japanese participants with an incidence of approximately 6.6%: 1 on treatment after 3 doses and 1 with Grade 3 ILD after 3 doses that recovered, and then worsened with fatal outcome 6 months after initial ILD diagnosis and last M7824 dose. These 2 cases of treatment-related Grade 5 interstitial pneumonitis represent an incidence of approximately 0.3% in overall M7824 studies (2 adverse events [AEs] reports out of more than 670 treated participants). According to the literature reference, a higher ILD incidence is observed in the Japanese population (Takada 2014; Azuma 2007; Vansteenkiste 2017). For proper and early detection of ILD/pneumonitis events occurring in Japanese participants, serum KL-6, surfactant protein A (SP-A), and surfactant protein D (SP-D) levels will be measured in study sites in Japan. Inclusion of these markers will potentially help to identify treatment-emergent lung toxicity early on, which can be further confirmed by imaging (Kubo 2013).

2.3 Benefit/Risk Assessment

At the time of study initiation, in Study MS200647-0008, a Phase Ib study of 2L BTC, M7824 has demonstrated promising clinical efficacy with a confirmed ORR of 23.3% (7 of 30 participants) by Investigator read and 20% by IRC, suggesting that the clinical benefit could be substantially better than the historical benchmark.

The following have been identified as important identified risks for M7824: Immune-related adverse events (immune-related pneumonitis, immune-related hepatitis, immune-related colitis, immune-related nephritis and renal dysfunction, immune-related endocrinopathies [thyroid disorders, adrenal insufficiency, Type 1 diabetes mellitus, pituitary disorders], immune-related rash and other immune-related adverse events (irAEs) [myositis, myocarditis, encephalitis]), TGF-β inhibition mediated skin reactions, anemia and bleeding adverse events. Infusion-related reactions are classified as identified risk for the treatment with bintrafusp alfa.

The identified and potential risks with M7824 monotherapy across tumor types were overall manageable and no new safety signals emerged in the EMR200647-001/MS200647-0008 studies compared with therapies targeting PD-(L)1 or TGF-β. M7824 infusion-related reactions (IRRs) were similar to those seen with monoclonal antibodies. The overall M7824 related IRRs was observed to be 5% with severity of low grade, well managed, and did not lead to permanent treatment discontinuation. The overall safety profile for irAEs is found to be consistent across M7824 studies and aligned with the known safety profile of approved anti-PD-(L)1 agents.

Dermatologic AEs related to TGF-β-inhibition (including keratoacanthomas [KA] and cutaneous squamous cell cancers) are an important identified risk with M7824 not seen with other programmed death-1 (PD-1)/PD-L1 antibodies. These lesions were previously observed in participants with genetic mutations in the TGF-β receptor (i.e., Ferguson-Smith syndrome), and participants treated with the TGF-β-targeting agent fresolimumab (Goudie 2011; Morris 2014). In the EMR200647-001/MS200647-0008 studies, treatment-emergent TGF-β inhibition mediated skin reactions were observed in approximately 7% of participants, were well-managed with simple excision (or spontaneous resolution) and did not require any participant to discontinue treatment. The risk of these lesions with M7824 was considered manageable in this study, especially in the context of encouraging clinical activity in several tumor types.

In view of the observed clinical efficacy in 2L BTC in M7824 and the manageable safety profile observed in the Phase I studies, the benefit/risk assessment is considered favorable to conduct this global study in 2L BTC participants, in consideration of the high unmet medical need and the current absence of an efficacious standard of care.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of M7824 can be found in Section 4.2 and the current IB. Based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

3 Objectives and Endpoints

The objectives and endpoints of M7824 monotherapy are shown in Table 3.

Table 3 Study Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)
Primary	
• To evaluate clinical efficacy of M7824 based on objective response rate (ORR)	• Confirmed objective response (OR) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) assessed by Independent Review Committee (IRC)
Secondary	
• To evaluate clinical efficacy of M7824 based on duration of response (DOR)	• DOR assessed from complete response (CR) or partial response (PR) until progression of disease (PD), death, or last tumor assessment assessed by IRC
• To evaluate clinical efficacy of M7824 based on durable response rate (DRR)	• Durable response of at least 6 months according to RECIST 1.1 assessed by IRC
• To evaluate clinical safety of M7824	• Occurrence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events, including adverse events of special interest (AESIs)
• To evaluate clinical efficacy based on progression-free survival (PFS)	• PFS according to RECIST 1.1 assessed by IRC
• To evaluate ORR, DOR, DRR, and PFS by Investigator read	• OR, DOR, DRR, and PFS according to RECIST 1.1 assessed by Investigator read
• To evaluate clinical efficacy based on overall survival (OS)	• OS
• To characterize the pharmacokinetic (PK) profile of M7824	• The concentration observed immediately at the end of infusion (C_{EOI}) of M7824 • The concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration [C_{trough}] for multiple dosing) of M7824
• To characterize the immunogenicity of M7824	• Immunogenicity of M7824 as measured by antidrug antibody (ADA) assay, from Screening through 12 weeks (± 2 weeks) after last treatment
• To evaluate clinical efficacy of M7824 based on ORR, DOR and DRR according to programmed death-ligand 1 (PD-L1) expression and microsatellite instability (MSI) status retrospectively	• Confirmed OR according to RECIST 1.1 assessed by IRC according to PD-L1 expression and MSI status • DOR and durable response of at least 6 months according to RECIST 1.1 assessed by IRC according to PD-L1 expression and MSI status

Objectives	Endpoints (Outcome Measures)
CCI	

* Items noted above with an * symbol are not collected in sites in China.

4 Study Design

4.1 Overall Design

This is a Phase II, multicenter, international, single-arm, open-label study to evaluate M7824 monotherapy in participants with locally advanced or metastatic BTC who failed or were intolerant to 1L chemotherapy.

The study plans to enroll 141 eligible BTC participants from USA, Europe, and Asian countries, with competitive enrollment. The study will enroll 3 major subtypes of BTC: intrahepatic CCA, extrahepatic CCA, and gallbladder cancer, with a minimum of 30 participants enrolled per each subtype. If one subtype does not reach a minimum of 30 participants by the end of competitive enrollment of 141 participants, the study will continue to enroll only in this subtype to reach 30 participants. Ampullary cancer is excluded from the study, since it originates from the pancreas, duodenum, distal common bile duct, or the structures of the ampullary complex.

Participants will receive M7824 at a dose of 1200 mg once every 2 weeks until confirmed progression of disease (PD), death, unacceptable toxicity, or study withdrawal. The primary objective is to evaluate the clinical efficacy of M7824 based on the ORR in 2L BTC. The secondary efficacy objectives are summarized in Figure 1. Tumor response evaluation based on RECIST 1.1 (Eisenhauer 2009) will be performed every 8 weeks until 12 months after the first administration of M7824 and then every 12 weeks until confirmed disease progression.

This study includes:

- 28-day Screening period
- Treatment until confirmed PD per RECIST 1.1, death, unacceptable toxicity, or study withdrawal. In the case of PD, treatment may continue past the initial determination of PD or confirmed PD if the participant's performance status (PS) has remained at least stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment and if other criteria are fulfilled as outlined in the protocol. Participants who have experienced a confirmed complete response (CR) should continue treatment for a maximum of 24 months after confirmation of response. If the Investigator believes that a participant with a confirmed CR may benefit from treatment beyond 24 months, it may be permissible to continue treatment after discussion with the Medical Monitor and the Sponsor Medical Responsible. Participants with stable disease or PR should continue treatment until disease progression or any other discontinuation criterion is met.
- Safety Follow-up will continue until 12 weeks after the last dose of M7824. The 12-week Safety Follow-up is allowed to be conducted via telephone calls or patient chart reviews unless there is medical necessity requiring a clinical visit.
- Long-term Follow-up should be performed every 12 weeks after the Safety Follow-up according to the Schedule of Activities (Table 1). Long-term Follow-up should be performed by chart reviews or telephone calls.
- Survival Follow-up will continue until each participant was followed up for at least 3 years after the End-of-Treatment.

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

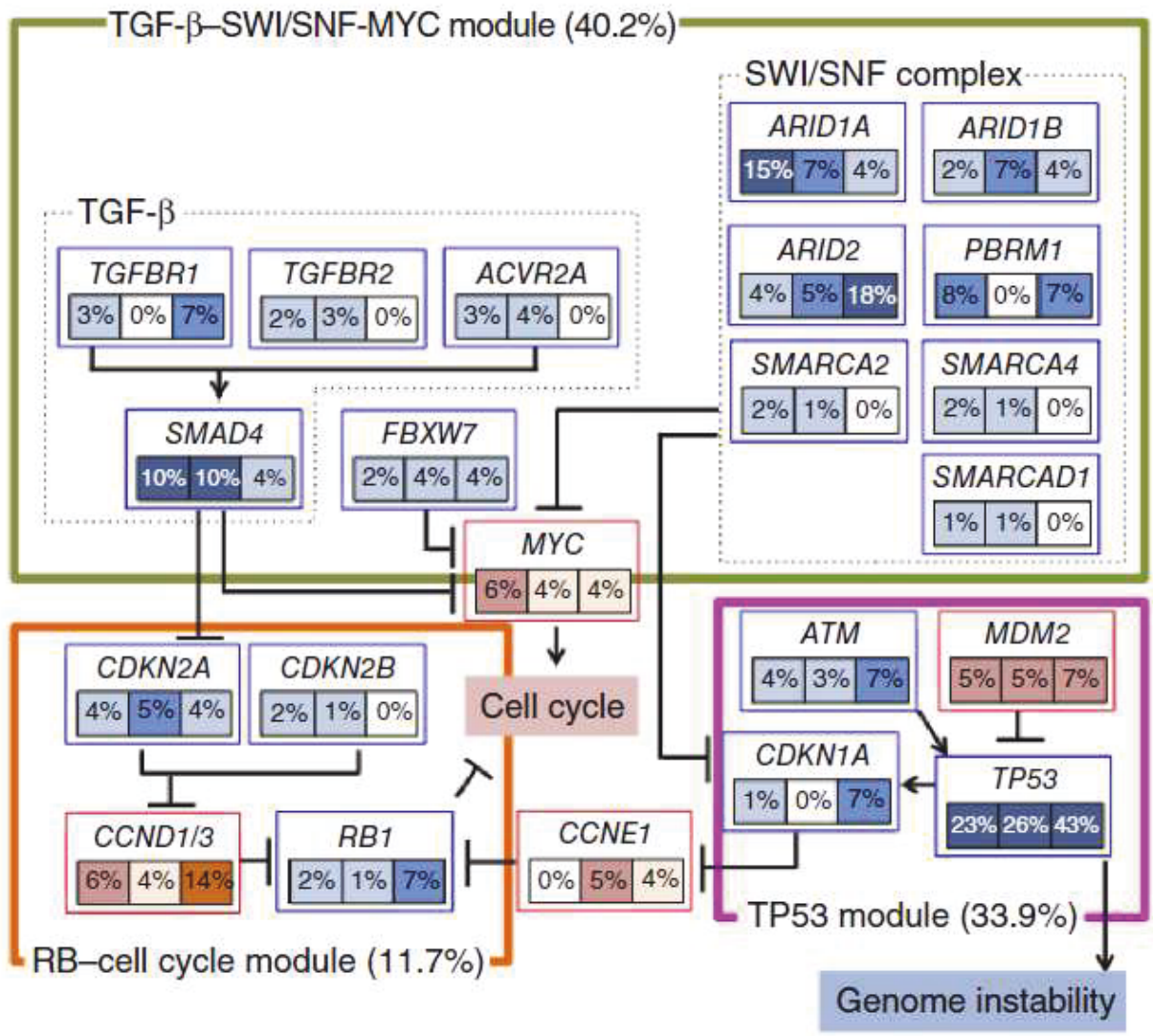
4.2 Scientific Rationale for Study Design

In benign and early-stage cancers, TGF-β acts as a potent inducer of cell growth arrest and apoptosis. In advance stage the TGF-β pathway promotes tumor progression and metastasis by promoting cancer cell motility, invasion, epithelial-to-mesenchymal transition, and cell stemness. TGF-β can function as both a tumor suppressor and tumor promoter. This functional switch is known as TGF-β paradox. The pathway is inactivated either through mutation, allelic loss of heterozygosity, or through epigenetic changes in various types of cancers. Cancer genomic analysis of 260 BTCs showed that 15% to 20% of BTC has TGF-β pathway mutations suggesting that the TGF-β pathway alteration has high selection pressure and is important in BTC tumorigenesis (Nakamura 2015).

The TGF-β signaling inhibition is an emerging strategy for cancer therapy. TGF-β signaling influences the tumor microenvironment by promoting fibrosis, angiogenesis, and metastasis, and suppressing immune-related host response. TGF-β inhibition is considered primarily to normalize tumor microenvironment homeostasis by down-regulating stromal stimulation resulting from excess TGF-β production by tumor and tumor-related tissues, reduce immunosuppression, as well as suppress epithelial-to-mesenchymal transition that might further contribute to immune escape.

Spectra of molecular alterations in BTC (Nakamura 2015) are shown in Figure 2.

Figure 2 Spectra of Molecular Alterations in Biliary Tract Cancers



Source: Nakamura 2015.

M7824, as a monotherapy, has shown a manageable safety profile and promising clinical efficacy signal in 2L BTC. Thirty Asian participants with BTC refractory to platinum-based 1L treatment were treated with M7824 1200 mg every 2 weeks. As of 20 March 2018, the median treatment duration was 8.9 weeks (range: 2 to 57.6 weeks). Five participants remained on treatment. Seven participants had a confirmed OR by Investigator read (ORR 23.3%) and 6 participants had a confirmed OR by IRC (ORR 20%), including 1 confirmation of response after cutoff. With a minimum follow-up of 8 months, the DOR ranged from 0.7 to 6.9 months, with 5/7 responses ongoing at the data cutoff date. One additional participant had ongoing PR for 7.6+ month after initial progression. Therefore, there is a strong rationale with preclinical and clinical data to justify further clinical development of M7824 in 2L BTC with the potential to establish M7824 as the standard of care.

Since there is no established standard of care for 2L BTC, a Phase II, multicenter, international, single-arm, open-label study to evaluate M7824 monotherapy in participants with locally advanced or metastatic BTC who fail 1L gemcitabine plus cisplatin chemotherapy has been proposed.

In this study participants who benefit from treatment will stay on treatment with frequent safety monitoring visits until unacceptable toxicity or loss of clinical benefit. Participants with confirmed CR will continue treatment for up to 24 months since confirmation of CR. In the M7824 program, participants have been exposed to M7824 beyond 12 months and the treatment was well tolerated. In Study MS200647-0008, some participants with OR had long lasting reduction in tumor size beyond 12 months under ongoing treatment. Treatment up to 24 months was also used with other checkpoint inhibitors published in 2L BTC (Ueno 2018). In addition, recent data showed continuous treatment beyond 12 months of nivolumab significantly improved progression-free survival (PFS) in non-small cell lung cancer compared to 12-month treatment duration (Spigel 2017).

4.3 Justification for Dose

The recommended Phase II dose (RP2D) for M7824 is 1200 mg administered as an intravenous infusion once every 2 weeks. The selection of RP2D is based on the available clinical data from the Phase I Studies EMR200647-001 and MS200647-0008, including safety/tolerability, pharmacokinetic (PK), and pharmacodynamics (PD-L1 target occupancy in peripheral blood mononuclear cell and TGF-β plasma concentrations), as well as efficacy in 2L non-small cell lung cancer cohorts from the EMR200647-001 study. The selection of RP2D is also supported by population pharmacokinetic (PopPK) and exposure-response modeling and simulation.

The completed and detailed data and analysis for dose justification can be found in IB.

4.4 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 Section 1.3.

The end of the study is defined as the date when each participant was followed up for at least 3 years after the End-of-Treatment.

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

5 Study Population

The study will aim at enrolling a balanced number of participants across the 3 major subtypes of BTC (intrahepatic CCA, extrahepatic CCA, and gallbladder cancer), with a minimum of 30 participants in each subtype. If one subtype does not reach a minimum of 30 participants by the end of competitive enrollment of 141 participants, the study will continue to enroll only in this subtype to reach 30 participants in principle.

The criteria in Sections 5.1 (Inclusion Criteria) and 5.2 (Exclusion Criteria) are designed to enroll only participants who are appropriate for the study, thereby ensuring that the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this study.

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

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

5.1 Inclusion Criteria

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

Age

1. Are ≥ 18 years of age at the time of signing the informed consent. In Japan, if a participant is at least 18 but < 20 years of age, written informed consent from his/her parent or guardian will be required in addition to the participant's written consent.

Type of Participant and Disease Characteristics

2. Are participants with histologically or cytologically confirmed locally advanced or metastatic BTC.

3. Availability of tumor (primary or metastatic) archival material or fresh biopsies is mandatory. Fine needle aspirates, transductal aspirates, or cell blocks are not acceptable. Endoscopic retrograde cholangiography or intraductal ultrasounds assisted biopsy is acceptable, needle or excisional biopsies, or resected tissue, are preferable. Tumor biopsies and tumor archival material must be suitable for biomarker assessment as described in the Laboratory Manual.

4. Participants with BTC must have failed or be intolerant to 1L systemic platinum-based chemotherapy administered for locally advanced or metastatic disease. Only one prior treatment line is allowed. Participants who received adjuvant platinum-based chemotherapy and had evidence of disease recurrence within 6 months of completion of the adjuvant treatment are also eligible. If recurrence occurs during or within 6 months after the adjuvant chemotherapy, adjuvant platinum-based chemotherapy is counted as 1L chemotherapy.

5. Disease must be measurable with at least 1 unidimensionally measurable lesion by RECIST 1.1 and verified independently by IRC.

6. Eastern Cooperative Oncology Group (ECOG) PS of 0 to 1 at study entry and Day 1 of treatment with M7824.

7. Life expectancy ≥ 12 weeks as judged by the Investigator.

8. Adequate hematological function defined by white blood cell count ≥ 3 × 10^9/L with absolute neutrophil count ≥ 1.5 × 10^9/L, lymphocyte count ≥ 0.5 × 10^9/L, platelet count ≥ 75 × 10^9/L, and hemoglobin (Hgb) ≥ 9 g/dL.

9. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × upper limit of normal (ULN), an aspartate aminotransferase level ≤ 2.5 × ULN, and an alanine aminotransferase (ALT) level ≤ 2.5 × ULN. For participants with liver involvement in their tumor, aspartate aminotransferase ≤ 5.0 × ULN and ALT ≤ 5.0 × ULN is acceptable.
    - Participants with biliary obstruction should have an adequate biliary drainage with no evidence of ongoing infection. Biliary duct obstruction should be relieved by internal endoscopic drainage/stenting at least 2 weeks prior to dosing or by palliative bypass surgery or percutaneous drainage prior to study entry, and the participant should have no active or suspected infection. Participants fitted with a biliary stent should be clinically stable and free of signs of infection for ≥ 2 weeks prior to dosing.

10. Adequate coagulation function defined as prothrombin time (PT) or international normalized ratio (INR) ≤ 1.5 × ULN unless the participant is receiving anticoagulant therapy.

11. Albumin ≥ 3.0 g/dL.

12. Hepatitis B virus (HBV) deoxyribonucleic acid (DNA) positive participants must be treated and on a stable dose of antivirals (e.g., entecavir, tenofovir, or lamivudine; adefovir or interferon are not allowed) at study entry and with planned monitoring and management including baseline HBV DNA quantity according to appropriate labeling guidance. Participants receiving active hepatitis C virus (HCV) therapy must be on a stable dose at study entry and with planned monitoring and management according to appropriate labeling guidance of an approved antiviral.

13. Adequate renal function defined by either creatinine ≤ 1.5 × ULN or an estimated creatinine clearance (CCr) > 40 mL/min according to the Cockcroft-Gault formula or by measure of CCr from 24-hour urine collection.
    - CCr (mL/min) = (140-age) × weight (kg)/(72 × serum Cr jaffe)
    - If female, × 0.85
    - If Cr is measured by enzymatic method, add 0.2 and use as $Cr_{jaffe} = 0.2 + Cr_{enzyme}$.

Sex

14. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 4 months after the last dose of study intervention:

- Refrain from donating sperm

PLUS, either

- Abstain from intercourse with a female

  OR

- Use a male condom:
  - When having sexual intercourse with a woman of childbearing potential (WOCBP), who is not currently pregnant, **and** advise her to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 3, since a condom may break or leak
  - When engaging in any activity that allows for exposure to ejaculate.

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

- Not a WOCBP

  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 3 for the following time periods:
  - Before the first dose of the study intervention, 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 after the last dose of study intervention.

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

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

- Additional requirements for pregnancy testing during and after study intervention are in Section 8.2.3.
- The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.

Informed Consent

16. Can give signed informed consent, as indicated in Appendix 2 (Study Governance), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

5.2 Exclusion Criteria

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

Medical Conditions

1. Ampullary cancer is excluded.

2. Rapid clinical deterioration other than malignancy which, in the opinion of the Investigator, may predispose to inability to tolerate treatment or study procedures.

3. Participants with active central nervous system (CNS) metastases causing clinical symptoms or metastases that require therapeutic intervention are excluded. Participants with a history of treated CNS metastases (by surgery or radiation therapy) are not eligible unless they have fully recovered from treatment, demonstrated no progression for at least 2 months, and do not require continued steroid therapy.

4. Receipt of any organ transplantation, including allogeneic stem-cell transplantation, but with the exception of transplants that do not require immunosuppression (e.g., corneal transplant, hair transplant).

5. Other previous and/or intercurrent malignancy except for curatively treated cancers with no recurrence in > 3 years since treatment completion, or early cancers treated with curative intent, including cervical carcinoma in situ, superficial, noninvasive bladder cancer, or basal cell or squamous cell carcinoma in situ. Endoscopically resected early gastrointestinal cancers limited in mucosal layer (esophageal, gastric, and colorectal) that are without recurrence in > 1 year are allowed.

6. Significant acute or chronic infections, including:
    - Uncontrolled biliary infection. Biliary tract obstruction should be released by stenting or percutaneous transhepatic biliary drainage.
    - Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (no testing at Screening required). If an Investigator has a strong suspicion of HIV infection without known history for a participant in Screening, and the participant refuses testing, discuss with the Medical Monitor to assess eligibility. (Note: HIV testing is not mandated for study inclusion; however, if it is performed at any point in Screening or while on study, a site must consent the participant for HIV testing as per local standard guidance.)
    - Active tuberculosis infection (clinical symptoms, physical or radiographic, and laboratory findings).

- Active bacterial or fungal infection requiring intravenous systemic therapy (except as indicated, discuss alternative scenarios with the Medical Monitor).

7. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:
   - Participants with diabetes type 1, vitiligo, alopecia, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible
   - Participants requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg of prednisone or equivalent per day
   - Administration of steroids for other conditions through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) is acceptable.

8. History of non-infectious (e.g., drug-induced) ILD requiring systemic steroid treatment, or current pneumonitis.

9. Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before enrollment.

10. Known severe hypersensitivity (Grade ≥ 3 National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 [NCI-CTCAE v5.0]) to investigational product (M7824) or any components in their formulations, any history of anaphylaxis, or recent, within 5 months, history of uncontrolled asthma.

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

12. Clinically significant cardiovascular/cerebrovascular disease as follows: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia.

13. Clinically relevant diseases (e.g., inflammatory bowel disease) and/or uncontrolled medical conditions, which, in the opinion of the Investigator, might impair the participant's tolerance or ability to participate in the study. Participants with history of bleeding diathesis or recent major bleeding events considered by the Investigator as high risk for study intervention are also excluded.

14. Any psychiatric condition that would prohibit the understanding or rendering of informed consent.

Prior/Concomitant Therapy

15. Participants who are not eligible for or have not been treated with 1L systemic chemotherapy will be excluded.

16. Systemic anticancer treatment after failing 1L platinum-based chemotherapy.

17. Concurrent treatment with nonpermitted drugs.

18. Prior participation in a M7824 clinical trial.

19. Prior therapy with other immunotherapy or checkpoint inhibitors, such as anti-PD-1, anti-PD-L1, anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibodies.

20. Prior therapy with any antibody or inhibitors targeting the TGF-β/TGF-β receptor pathway.

21. Anticancer treatment within 21 days before the start of study intervention, e.g., cytoreductive therapy, radiotherapy involving > 30% of the bone marrow (with the exception of palliative bone-directed radiotherapy), immune therapy, or cytokine therapy.

22. Anticancer treatment with antibody within 28 days before the start of study intervention.

23. Systemic therapy with immunosuppressive agents within 7 days before the start of study intervention; or use of any investigational drug within 28 days before the start of study intervention.

24. Vaccine administration within 4 weeks of M7824 administration. Vaccination with live vaccines while on study is prohibited. Administration of inactivated vaccines is allowed (e.g., inactivated influenza vaccines).

Prior/Concurrent Clinical Study Experience

25. Participation in experimental clinical studies after failure of 1L systemic chemotherapy.

Diagnostic Assessments

26. Unable to tolerate computed tomography (CT) or magnetic resonance imaging (MRI) in the opinion of the Investigator and/or allergy to contrast material.

Other Exclusions

27. Major surgery within 28 days before the start of study intervention (excluding prior diagnostic biopsy and stenting/percutaneous transhepatic biliary drainage for releasing biliary tract obstruction).

28. Pregnancy or breast feeding.

29. Known active or recent alcohol or drug abuse within 2 years.

30. Legal incapacity or limited legal capacity.

31. Other severe acute or chronic medical conditions.

5.3 Lifestyle Considerations

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

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants will be assigned a new participant number. Rescreening is allowed within 14 days since date of screen failure. Baseline tumor assessments must be repeated if outside of 28-day window from the first dose of study intervention. Participants can be rescreened only 1 (one) time after initial screen failure.

Participants who have an abnormal liver function test at Screening that may normalize with biliary drainage or stenting can be rescreened once appropriate drainage has been put in place (see inclusion criterion #9). For participants with other laboratory abnormalities that may resolve, concomitant medication that will be discontinued, or undergoing a prohibited procedure that will be completed, it is recommended to discuss with the Medical Monitor as to whether the participant may be rescreened.

In other situations, when a potential participant fails screening and wants to be rescreened, the site should contact the Medical Monitor to discuss whether the participant can be rescreened.

6 Study Intervention(s)

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Study Intervention Administration

Study Intervention Name:	M7824
Dose Formulation:	Sterile concentrate solution for infusion
Unit Dose Strength(s)/Dosage Level(s):	10 mg/mL in single-use glass vials
Route of Administration:	Intravenous infusion
Dosing Instructions:	Flat dose of 1200 mg over 1 hour (- 10 minutes/+ 20 minutes, i.e., over 50 to 80 minutes) once every 2 weeks
Sourcing:	Provided centrally by the Sponsor
Supplier/Manufacturer:	Merck KGaA/PPD
Packaging and Labeling:	Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines

6.2 Study Intervention Preparation, Handling, Storage, and Accountability

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

Upon receipt of the study intervention, the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the Pharmacy Manual.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply it. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.

Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.

Study intervention accountability records at the study site will include the following:

- Confirmation of receipt, in good condition, and in the defined temperature range.
- The inventory provided for the clinical study and prepared at the site.
- The dose(s) each participant used during the study.
- The disposition (including return, if applicable) of any unused study intervention.

- Dates, quantities, batch numbers, vial numbers, expiry dates, formulations, and the participant numbers.

The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and that all study intervention provided were fully reconciled.

Unused study intervention must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be redispensed to a different participant.

A Study Monitor will periodically collect the study intervention accountability forms.

Destruction of used and unused study intervention should be performed at the site if allowed by local law only after Sponsor authorization. If that is not possible, the Sponsor/designee will be responsible.

Further guidance and information for the final disposition of unused study intervention is provided in the Operations Manual.

M7824 should be stored in a CCI (CCI) until use. M7824 must not be frozen and should be stored in the original packaging.

Additional instructions for the preparation, handling, storage, and disposal of M7824 will be provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

The Sponsor or delegate will assign a unique participant identifier number to participants in chronological order at the time of informed consent signature. Participant identifiers will be comprised of digits representing the study number, the site number, and the participant number, which is allocated sequentially. Enrollment will utilize an Interactive Voice/Web Response System.

6.3.2 Blinding

Not applicable.

6.4 Study Intervention Compliance

In this study, participants will receive study intervention at the study site. Well-trained medical staff will monitor and perform the study intervention administration. The information of each study intervention administration, including the date, time, and dose of study intervention, will be recorded on the electronic case report forms (eCRF). The Investigator will make sure that the

information entered into the eCRF regarding study intervention administration is accurate for each participant. Any reason for noncompliance should be documented.

Noncompliance is defined as a participant missing > 1 infusion of study intervention for nonmedical reasons and barring any extenuating circumstances in the opinion of the Investigator. Extenuating circumstances should be documented, and when possible, discussed with the Sponsor in advance. If 1 infusion is missed and the interval between the subsequent infusion and the last administered treatment is longer than 4 weeks for nonmedical reasons, the criterion of insufficient compliance is met as well.

Consequences of noncompliance may lead to discontinuation of study interventions as described in Section 7.1. In case of overdose, see Section 8.4.

6.5 Concomitant Therapy

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

Any additional concomitant therapy that becomes necessary during the study and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

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

6.5.1 Rescue Medicine

Not applicable.

6.5.2 Permitted Medicines

The only permitted medications are the following:

- Any medications (other than those excluded by the clinical study protocol) that are considered necessary for the participants' welfare and will not interfere with the study intervention may be given at the Investigator's discretion.
- Other drugs to be used for nonsteroid premedication as described in Table 1 (antihistamine and acetaminophen), treatment of anaphylactic reactions, IRRs, and severe hypersensitivity reactions/flu-like symptoms and irAEs.
- Blood transfusions and erythroid growth factors are permitted for Hgb ≤ 7 g/dL as clinically indicated and/or for life-threatening bleeding.

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

Permitted Procedures

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

6.5.3 Prohibited Medicines

The following treatments must not be administered during Screening and for the duration of study intervention:

- Immunotherapy, immunosuppressive drugs (i.e., chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions or for the treatment of irAEs), or other experimental pharmaceutical products.
  - Short-term administration of systemic steroid (i.e., for allergic reactions or the management of irAEs) is allowed.
  - Steroids with no or minimal systemic effect (topical, intranasal, intro-ocular, inhalation) are allowed.
  - Hormone replacement with corticosteroids for adrenal insufficiency is allowed if the steroids are administered only for the purpose of hormonal replacement and at doses $\leq$ 10 mg or equivalent prednisone per day.
  - Prophylactic use of corticosteroids for IRRs is prohibited.
- Concomitant local or regional treatment (radio/chemo-embolization) is not permitted.
- Vaccination with live vaccines while on study intervention is prohibited. Administration of inactivated vaccines is allowed (e.g., inactivated influenza vaccines).
- If the administration of a nonpermitted concomitant drug becomes necessary during the study, the participant will be withdrawn from study intervention (the Sponsor may be contacted to discuss whether the study intervention must be discontinued).
- Any traditional Chinese medication with approval for use as anticancer treatment (regardless of the type of cancer) will not be permitted. Traditional Chinese medication for indications other than anticancer treatment, such as supportive care, may be administered at the discretion of the Investigator.
- Medications other than those specifically excluded in this study (see above) may be administered for the management of symptoms associated with the administration of M7824 as required. These might include analgesics, antinausea medications, antihistamines, diuretics, antianxiety medications, and medication for pain management, including narcotic agents.

6.5.4 Other Interventions

The following procedures must not be performed, and supplements must not be taken during the study and within 28 days before the study.

- Major surgery (excluding prior diagnostic biopsy and stenting/percutaneous transhepatic biliary drainage for releasing biliary tract obstruction) within 4 weeks before the start of the study. Discuss with the Medical Monitor if unplanned major surgery is required on study to plan for timing of retreatment. Any diagnostic biopsies collected for clinical reasons during the study should be documented as a concomitant procedure including the outcome of available pathological reports.
- Herbal remedies with immuno-stimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin).

6.6 Dose Selection and Modification

Participants will receive an intravenous infusion of M7824 at a dose of 1200 mg over 1 hour (- 10 minutes/+ 20 minutes, i.e., over 50 to 80 minutes) once every 2 weeks as detailed in the Schedule of Activities (Table 1).

Dose modification of M7824 is not allowed. Special precautions for monitoring of participants and management of IRRs/hypersensitivity, including premedication, modifications of the infusion rate and stopping of study intervention, are described in Section 6.9.

6.6.1 Adverse Drug Reactions Requiring Treatment Modification

Any adverse drug reaction (ADR) assessed as related to M7824 may require permanent or transient discontinuation of M7824 treatment. For the management of certain ADRs assessed to be irAEs, follow the American Society of Clinical Oncology (ASCO) guideline in Appendix 6. Single laboratory values out of the normal range that do not have any clinical correlate do not necessarily need treatment interruption. Questions or concerns with regard to management and/or follow-up of ADRs should be discussed with the Medical Monitor.

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

- For suspected irAEs, irAE management and guidance is presented in Appendix 6. General management by NCI-CTCAE v5.0 toxicity grading, as per ASCO, is listed below:
  - Grade 1: study intervention should be continued with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities.
  - Grade 2: study intervention may be suspended for most Grade 2 toxicities, with consideration of resuming when symptoms revert to Grade 1 or less. Corticosteroids may be administered (initial dose of 0.5 to 1 mg/kg/day of prednisone or equivalent).
  - Grade 3: study intervention is generally suspended and the high-dose corticosteroid treatment (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) should be initiated. Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy.

- Grade 4: in general, permanent discontinuation of study intervention is recommended, with the exception of endocrinopathies that have been controlled by hormone replacement.

- IRRs and hypersensitivity reactions guidance are presented in Section 6.9.1.
- Guidance on anemia is presented in Section 6.9.4.
- Guidance and management for TGF-β inhibition mediated skin reactions are discussed in Section 6.9.3.
- Guidance and management of bleeding events are discussed in Section 6.9.5.

In general, the following applies for ADRs related to M7824 that are not covered by the ASCO guideline:

Any Grade 4 ADRs require permanent treatment discontinuation, except endocrinopathies that have been controlled by hormone replacement, or single laboratory values out of normal range that do not have clinical relevance.

Any Grade 3 ADRs require treatment discontinuation, except for any of the following:

- Transient Grade 3 flu-like symptoms or fever that is controlled with medical management
- Transient Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to ≤ Grade 1
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumors
- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis
- Grade 3 Hgb decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor use
- Keratoacanthoma (KA) and cutaneous squamous cell carcinoma (cSCC).

Any Grade 2 ADRs should be managed as follows:

If a Grade 2 ADR resolves to Grade ≤ 1 by the day before the next infusion, study intervention may be continued.

If a Grade 2 ADR does not resolve to Grade ≤ 1 by the day before the next infusion, but it is manageable and/or not clinically relevant, the Medical Monitor should be consulted to assess if it is clinically reasonable to administer the following infusion.

Note that treatment recommendations regarding continuation, hold, or discontinuation by grade are different depending on the specific toxicity (see Appendix 6). Toxicity grading is assigned based on NCI-CTCAE v5.0. The ASCO guideline should be used only for the management of immune-related toxicity due to M7824.

6.7 Study Intervention After the End of the Study

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

On withdrawal from the study, participants may receive whatever care they and their physicians agree upon.

6.8 Special Precautions

As a part of safety-related precautionary measures, a standardized risk management approach is planned for M7824 for IRRs, irAEs, TGF-β inhibition mediated skin reactions, anemia, and bleeding AEs. The approach is mainly based on the mechanism of PD-L1 inhibition and TGF-β inhibition.

6.9 Management of Adverse Events of Special Interest and other Potential Risks

Adverse events of special interest (AESIs) are serious or non-serious AEs specific to the known mechanism of action of the study intervention that are of clinical interest requiring ongoing monitoring.

For this study, AESIs include the following:

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

6.9.1 Infusion-Related Reactions Including Hypersensitivity

Infusion-related reactions, including hypersensitivity, are defined in this section. Infusion-related reactions are AESIs and identified risks for M7824.

Infusion-Related Reactions

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

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

Management of Infusion-Related Reactions

Based on the observed low IRR incidence in Phase I studies in over 670 participants treated with M7824 single agent, and with low-grade IRRs without leading to treatment discontinuation, the first 15 participants will not receive premedication before first and second M7824 infusions in this study in order to establish whether mandatory use of premedication is required. If IRR is observed at the first or second infusion, premedication should be used for subsequent infusions at the discretion of the Investigator.

If two or more Grade 2 IRRs are seen during the first 2 infusions for the first 15 participants, an Independent Data Monitoring Committee (IDMC) will determine if mandatory premedication is needed. Study enrollment will continue in parallel to this review and sites will be notified accordingly if premedication will be required.

If IDMC determines mandatory premedication is justified in order to mitigate potential IRRs, premedication with an antihistamine and with paracetamol (acetaminophen) (e.g., 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] intravenous or oral equivalent) prior to each dose of M7824 is mandatory for the first 2 infusions. After the first 2 infusions, premedication is optional and at the discretion of the Investigator. If Grade 2 IRRs are seen during the first 2 infusions, then premedication should not be stopped. Steroids as premedication are not permitted.

Management of symptoms should follow the guidelines shown in Table 4.

Table 4 Treatment Modification of M7824 for Symptoms of Infusion-Related Reactions Including Immediate Hypersensitivity

NCI-CTCAE v5.0 Grade	Treatment Modification
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator.
Grade 2 – moderate • Therapy or infusion interruption indicated but if responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	• Stop the infusion of the study intervention caused IRR. • Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator. • If symptoms resolve quickly or decreased to Grade 1, resume infusion at 50% of original rate with close monitoring of any worsening otherwise dosing held until resolution of symptoms with mandated premedication for the next scheduled visit. • If worsens to Grade 3 or 4, follow treatment modification guidelines accordingly.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the infusion of study intervention-caused IRR immediately and disconnect infusion tubing from the participant with additional appropriate medical measures and closely monitor until deemed medically stable by the attending Investigator. Hospitalization and/or close monitoring is recommended • Administration of glucocorticoids may be required • Restart the medication taking out the drug that is the cause of IRRs from the next scheduled visit
IRR=infusion-related reaction, IV=intravenous, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, NSAIDs=nonsteroidal anti-inflammatory drugs. Once the M7824 infusion is interrupted or rate reduced to 50% of previous infusion rate, it must remain decreased for all subsequent infusions. For Grade 3 or 4 IRRs, M7824 discontinuation is mandated. For all types and grades of infusion reactions, details about drug physical constitution, method of preparation, and infusion must be recorded.	

In the event of a Grade 2 IRR that does not improve or worsens after implementation of the treatment modifications indicated in Table 4 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids and the infusion should be stopped for that day. At the next infusion, the Investigator may consider the addition of H2 blocker antihistamines (e.g., famotidine or ranitidine), in addition to premedication, for select participants. However, prophylactic steroids are not permitted. At the next dose, if the participant has a second IRR Grade ≥ 2 on the slower infusion rate, with the addition of further medication to premedication, the infusion should be stopped, and the participant should be removed from the study intervention.

Hypersensitivity Reaction

If a hypersensitivity reaction occurs, the participant must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council United Kingdom and can be found

at https://www.resus.org.uk/pages/reaction.pdf. Participants should be instructed to report any delayed reactions to the Investigator immediately.

Symptoms may include, but are not limited to:

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

Management of hypersensitivity includes:

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

Prophylaxis of Flu-Like Symptoms:

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

6.9.2 Immune-Related Adverse Events

In general, the spectrum of irAEs is similar for M7824 compared with other checkpoint inhibitors. Immune-related AEs are considered AESIs. Effective risk management of these toxicities (irAEs) primarily caused due to inhibition of PD-L1 and PD-1 pathways is based on key recommendations (Champiat 2016). Participant education for on-time reporting of symptoms of potential irAEs and prompt clinical assessment is critical for effective management and quicker resolution of immune-mediated toxicities, thus preventing progression into severe forms of toxicity that otherwise may become life-threatening and difficult to manage or warrant permanent discontinuation from the study.

Immune-related AEs are specific to immunotherapies and vary by organ system.

The following immune-related AEs are important identified risks for M7824:

- Immune-related hepatitis
- Immune-related pneumonitis
- Immune-related colitis

- Immune-related nephritis and renal dysfunction
- Immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, Type 1 diabetes mellitus, pituitary disorders)
- Immune-related rash
- Other immune-related events (myositis, myocarditis, encephalitis)

The following irAEs are important potential risks for M7824:

- Guillain-Barré syndrome
- Uveitis
- Pancreatitis
- Myasthenia gravis/myasthenic syndrome

The Medical Monitor may be involved as needed for follow-up. Details of the diagnostic work-up will be requested by the study team.

For treatment management of irAEs per NCI-CTCAE v5.0 criteria, refer to the ASCO Clinical Practice Guidelines and National Comprehensive Cancer Network (NCCN) irAE management guidelines.

The recommendations for irAE management are guided by the joint ASCO Clinical Practice Guidelines (Brahmer 2018) and NCCN guidelines, listed in Appendix 6.

Treatment of irAEs is mainly dependent upon severity as defined by NCI-CTCAE v5.0. In general, management by NCI-CTCAE v5.0 grading, as per ASCO, is listed below:

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

Permanent treatment discontinuation is required in case of immune-related Grade 4 rash/inflammatory dermatitis, nephritis, autoimmune hemolytic anemia, hemolytic uremic syndrome, aplastic anemia, immune thrombocytopenia and acquired thrombotic thrombocytopenic purpura (TTP).

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

For additional organ/system specific management guidelines, see the guideline tables in Appendix 6.

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

6.9.3 TGF-β Inhibition Mediated Skin Reactions

TGF-β inhibition mediated skin reactions, including hyperkeratosis, KA, and/or cSCCs, are important identified risks and AESIs for M7824.

Skin assessments are performed at Baseline and every 6 weeks for all participants per Schedule of Activities (Table 1). Referral to a dermatologist is recommended in case of suspicious lesions. Baseline skin assessments include a detailed medical history of genetic or iatrogenic skin conditions, skin type, geographical location, significant UV exposure/sun damage of skin, and occupational or environmental exposure to radiation or chemicals.

Skin AEs appear to be related to both mechanisms of M7824; anti-PDL1 and anti-TGF-β:

1. Immune-related skin AEs possibly mediated by PD-L1 inhibition (e.g., rash or maculopapular rash, distributed typically on trunk and uniformly on limbs).

2. Immune-related skin AEs should be managed according to ASCO Clinical Practice Guidelines (Appendix 6). Treatment typically includes use of emollients, non-sedating antihistamines for pruritus, and targeted use of potent topical steroids to most inflamed lesions; oral corticosteroids can be used in highly symptomatic cases.

Skin AEs, possibly due to TGF-β inhibition, including hyperkeratosis, KA and/or cSCC, are important identified risks for M7824. The distribution of lesions tends to be in sun-exposed areas.

Management guidelines for potential TGF-β inhibition mediated skin reactions:

- Discontinuation or interruption is not required in most cases. 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 inhibition mediated skin reactions 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.
  - In case of multiple lesions or location not suitable for full excision:
    - Other treatment options may be offered by the dermatologist, such as:
      - Mohs surgery, cryotherapy, or other standard treatment options depending on the pathology.
      - Use of retinoids if recommended by dermatologist, may be considered after discussion with Medical Monitor.
- 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 M7824.
- The number and localization of lesions, diagnosis (including histopathological diagnosis), treatment and outcome should be appropriately documented in the eCRF.

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

6.9.4 Anemia

Anemia is an AESI (refer to IB) and important identified risk for M7824. Notably, there are many reasons for anemia in patients with advanced cancer, which is why a thorough investigation of new anemia cases of unspecified etiology is requested.

For new anemia events, 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:

- Participants must enter the study with Hgb values at least 9 g/dL; routine blood test parameters are required in the Schedule of Activities (Table 1).
- All relevant hematologic testing for anemias should be done prior to a blood transfusion, if clinically feasible.
- Transfusion should be performed at the discretion of the Investigator based on clinical assessment and considered when the participant experiences significant anemia. An attempt should be made to initiate work-up (as specified below) for the cause of anemia prior to transfusion, if clinically feasible, to not confound this work-up. In general, blood transfusions and erythroid growth factors are permitted for Hgb ≤ 7 g/dL and/or for life-threatening bleeding.

Guidance for evaluation of suspected anemias is provided in Table 5.

Table 5 Evaluation Guidance of Suspected Anemia

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

6.9.5 Bleeding Events

Bleeding events are AESIs and considered an important identified risk for M7824 (refer to the IB).

6.9.5.1 Mucosal/Non-Tumor Bleeding

Mucosal bleeding events of mild to moderate severity were observed in participants treated with M7824 in ongoing studies. Events may include epistaxis, hemoptysis, gingival bleeding, or hematuria amongst others. In general, these reactions resolve without discontinuation of treatment.

For all participants:

For Grade 2 non-tumor bleeding, see Section 6.6.1 for general management of Grade 2 ADRs.

For Grade 3 non-tumor bleeding, study intervention 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 intervention should be held until the event recovers to Grade ≤ 1.

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

6.9.5.2 Tumor Bleeding

Participants treated with M7824 were reported in lower frequencies, with Grade ≥ 3 hemorrhages including tumor bleeding.

For Grade ≥ 2 tumor bleeding, study intervention must be held until the event recovers to Grade ≤ 1. Treatment should be permanently discontinued if the Investigator considers the participant to be at risk for additional severe bleeding.

6.9.6 Other Potential Risks

6.9.6.1 Impaired Wound Healing

Impaired wound healing is considered an important potential risk (a theoretical risk based on literature findings) for M7824, given the role of TGF-β in wound healing. Management should be discussed with the Medical Monitor for participants requiring surgery on study. It is recommended to hold study intervention for approximately 4 weeks post major surgery for observation. Postoperative wound healing will be closely monitored.

6.9.6.2 Embryofetal Toxicity

Embryofetal toxicities are a known risk of the PD-1/PD-L1 targeting class and are considered important potential risks for M7824. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Embryofetal toxicity is an important potential risk of M7824. An appropriate contraception warning is provided as part of the inclusion criteria. Pregnant and breastfeeding women are not allowed in the M7824 study, and adequate contraceptive measures are recommended during the study to minimize or eliminate the potential risk to the developing fetus.

Respective safety measures comprise inclusion/exclusion criteria for participation in clinical studies with M7824, guidance for prevention, monitoring, and medical management of potential risks, as well as guidance on study intervention interruption or discontinuation.

6.9.6.3 Disease Specific Risk: Hepatic Impairment

Biliary tract cancer can cause obstructive cholestasis complicated by acute cholangitis. Acute cholangitis is a clinical syndrome characterized by fever, jaundice, and abdominal pain that develops as a result of stasis and infection in the biliary tract. Patients with acute cholangitis may develop septic shock and thus require frequent monitoring for evaluation of signs of shock.

If biliary infection is suspected, the study intervention must be withheld. The Investigator should consider biliary drainage as well as treatment with antibiotics. If biliary tract infection is clinically improved, the study intervention can be resumed.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Participants will be withdrawn from study intervention for any of the following reasons:

- A participant may withdraw 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 withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- 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 stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment (See Section 7.1.2.1).
- Unacceptable toxicity
- Some ADRs require withdrawal from treatment. See Section 6.6.1 for additional details.
- Occurrence of pregnancy
- Use of a nonpermitted concomitant drug as defined in Section 6.5.3, where the predefined consequence is withdrawal from the study intervention.

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

Obstructive jaundice and/or biliary tract infection without radiological PD, should not be cause for study intervention discontinuation if patients can be treated with prompt biliary drainage.

7.1.1 Temporary Discontinuation

See Section 6.9 for information on temporary study intervention discontinuation.

7.1.2 Rechallenge

One reinitiation course of treatment after treatment discontinuation at the same dose and schedule is allowed at the discretion of the Investigator and upon agreement of the Study Medical Responsible for the following:

- Participants who are experiencing CR at the time of discontinuation, and then subsequently develop disease progression after stopping therapy, but prior to the end of the study.

Prior to reinitiation, the Investigator will need to confirm that the benefit of reinitiating treatment outweighs any risk involved, such as that which led to initial treatment discontinuation. For participants with only stable disease at the time of discontinuation, the Investigator should confirm

that no other reasonable treatment options are available. In addition, to be eligible for reinitiation, the participant must not have previously withdrawn consent for this trial and should have been followed up with regular eCRF documented evaluation scans up to reinitiation of treatment.

A re-Baseline scan must be performed prior to reinitiation of study intervention. Additionally, relevant safety laboratory assessments, including both full hematology and full chemistry results within 2 weeks, must be available and verified. The clinical Investigator will determine whether additional evaluation and workup are required on a case-by-case basis. A discussion with the study team is warranted to determine whether PK/CCI testing is indicated upon restarting treatment.

The participant should reinitiate treatment at the treatment phase visit where they left off according to the Schedule of Activities (Table 1). Participants who reinitiate treatment should stay on study and should be treated and monitored according the Schedule of Activities for the rest of the study.

7.1.2.1 Treatment Beyond Initial Progression

Treatment with M7824 should continue from the initial determination of disease progression by the IRC (verified PD) according to RECIST 1.1 until confirmed PD if the following criteria are met:

- No new unacceptable treatment or disease-related toxicity
- Tolerance of study interventions
- Stable or improving ECOG PS
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases).
- Participants must sign a separate informed consent to ensure that they are aware of being treated beyond initial progression.

If the treatment continues after the verified PD, a radiographic assessment should be performed to confirm the PD at the next scheduled imaging.

7.1.2.2 Treatment Beyond Confirmed Progression

After confirmed PD, if the Investigator believes per clinical judgment that the participant continues to achieve clinical benefit by continuing treatment with M7824, the participant can remain in the study and continue to receive monitoring according to the Schedule of Activities. The decision to continue treatment beyond confirmed PD should be discussed with the Medical Monitor and documented in the study records.

To qualify for treatment beyond confirmed progression:

- Participants must sign a separate informed consent to ensure that they are aware of being treated beyond confirmed progression.
- Investigators must document clinical judgment to justify the continuation of study intervention rather than other possible alternative treatments.

Participants who continue treatment beyond progression will be evaluated for further tumor response as per the protocol Schedule of Activities (Table 1). Treatment should be discontinued permanently in case of any overall, meaningful and unequivocal further increase in tumor burden after confirmation of PD. As a general guidance, a meaningful increase, for example, may represent an approximately 10% increase in tumor burden, considering the totality of all existing target lesions, non-target lesion burden, existing new lesions, and any further new lesions. Note: This 10% increase is provided as a general guide to be interpreted considering the clinical condition of the participant and any other considerations which the Investigator feels relevant, such as the availability of alternative treatments. In unclear situations, the Investigator should consult with the Medical Monitor, and the wellbeing of the individual participant should be the key consideration in determining the continuation of study intervention after confirmed progression.

7.1.2.3 Continuation of Study Intervention After Local Treatment of Disease Progression

If disease progression is due to brain metastasis, participants may continue study interventions after local treatment of the brain lesions provided that the above criteria are met in addition to the following:

- PD is verified by the IRC.
- Brain metastases have been treated locally and are clinically stable for at least 2 weeks prior to reinitiation of study interventions.
- There are no ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable).
- Participants must be either off steroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).
- Benefit-risk assessment to continue study intervention is favorable after consideration of any alternative treatment options as assessed by the Investigator.

In addition, if disease progression is mainly due to a metastatic lesion, which in the opinion of the Investigator may be treated with radiotherapy or surgically removed, participants may continue study interventions after the local treatment of such a lesion provided that:

- PD is verified by IRC.
- It has been at least 2 weeks and the participant has fully recovered from the surgery or radiotherapy.
- Benefit-risk assessment to continue study intervention is favorable after consideration of any alternative treatment options as assessed by the Investigator.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time, at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

- At the time of discontinuing from the study, if possible, a discontinuation visit will be conducted, as listed in the Schedule of Activities. The Schedule of Activities specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.
- If the participant withdraws consent for future involvement in the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed (refer to the ICF).
- A participant has the right at any time to request destruction of any biological samples taken. The Investigator must document this in the site study records.

The Investigator will secure the safety of the study participants and make every attempt to collect data.

In case of discontinuation/withdrawal from the study:

- At study intervention discontinuation, the day of End-of-Treatment will correspond to the day of withdrawal (or within 7 days).
- The assessments scheduled for the End-of-Treatment visit should be performed, if possible, with a focus on the most relevant assessments and the appropriate eCRFs for the End-of-Treatment visit must be completed.
- Participants will be asked to continue Safety and Survival Follow-ups, which include the collection of data on survival, CCI [redacted], and subsequent anticancer therapy. After completion of the follow-up period or after the End-of-Treatment visit, whichever is applicable, the appropriate eCRF section for Study Termination must be completed.

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

Survival follow-up will continue until each participant has been followed up for at least 3 years after End-of-Treatment.

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 will be taken if a participant fails to return to the study site for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee will make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner or caretaker (where allowed by local regulations) for information. These contact attempts should be documented in the participant's medical record.
- If the participant continues to be unreachable, he or she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the Schedule of Activities (Table 1).
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All Screening evaluations will be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for Screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2 (Study Governance).
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

A maximum of 145 mL of blood will be collected in any one-month period from each participant in the study, including any extra assessments that may be required.

8.1 Efficacy Assessments and Procedures

8.1.1 Tumor Response

Contrast-enhanced CT of chest/abdomen and 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 should not receive iodinated contrast medium, or due to radiation protection reasons, MRI of the same area, using gadolinium enhancement according to local protocol as permitted in conjunction with unenhanced CT of the chest from the thoracic inlet to the inferior costophrenic recess should be done. The same method should be used per participant throughout the study.

A brain CT/MRI scan should be performed if clinically indicated by development of new specific symptoms. In this study, RECIST 1.1 was modified so that skin metastases cannot be used as target lesions using measurements by caliper but may be selected if they fulfill RECIST 1.1 requirements for target lesions using CT/MRI scan (refer to RECIST 1.1 criteria).

A central imaging laboratory will be used to read and interpret all CT/MRI data; however, treatment decisions will be made by the treating Investigator, except for verification of measurable disease at Baseline and verification of initial PD, which will be made by the IRC following a local site Investigator-assessed first radiologic evidence of PD. Response will be evaluated according to RECIST 1.1CCI [redacted] by the IRC. Tumor responses to treatment assessed according to RECIST 1.1 by the Investigator will be documented in the eCRF (all measurements should be recorded in metric notation). CCI [redacted]

Baseline scans are taken within 28 days prior to treatment. Disease must be measurable with at least 1 unidimensionally measurable lesion by RECIST 1.1 and verified by independent image review. All the scans performed at Baseline need to be repeated at subsequent visits for tumor assessment using the same method. In general, lesions detected at Baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

Participants will be evaluated every 8 weeks with radiographic imaging to assess response to treatment within the first 12 months of the participant's first dose, then every 12 weeks until confirmed disease progression, as scheduled in the Schedule of Activities (Table 1).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8.2 Safety Assessments and Procedures

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

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information).

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

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

If a liver function test is elevated in an HBV- or HCV-positive participant, HBV DNA or HCV ribonucleic acid (RNA) must be monitored to exclude the possibility of reactivation of viral hepatitis. In case of viral reactivation, follow the HBV and HCV management guidelines.

8.2.1 Physical Examinations and Vital Signs

- Vital signs, physical examinations, and ECOG PS will be conducted at Screening and at subsequent visits as indicated in the Schedule of Activities (Table 1). These should be documented in the eCRF.
- A complete physical examination at Screening will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height (at Screening Visit only) and weight will also be measured and recorded.
- A brief physical examination (at all other scheduled visits other than Screening) will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- General status, such as asthenia or appetite, should be evaluated at Baseline, as these are usually affected. Pre-existing symptoms of underlying conditions and/or signs of infection should be investigated as clinically indicated.
- Abnormal findings are to be reassessed at subsequent visits.
- Vital signs including heart rate, body temperature, pulse rate, respiratory rate, and blood pressure will be assessed and recorded in the eCRF.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse and respiratory rate.
- Blood oxygen saturation will be measured with a pulse oximeter and recorded in the eCRF.

8.2.2 Electrocardiograms

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

8.2.3 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 5 at the time points listed in the Schedule of Activities (Table 1). All samples should be clearly identified.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- The tests will be performed by the local laboratory.

- The Sponsor will receive a list of the local laboratory normal ranges before shipment of study intervention. Any changes to the ranges during the study will be forwarded to the Sponsor or designated organization.
- The Investigator will review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.
- If a participant has a clinically significant abnormal laboratory test value that is not present at Baseline, the test should be closely monitored until the test value has returned to the normal range or the Investigator has determined that the abnormality is chronic or stable.
- The report of the results must be retained as a part of the participant's medical record or source documents.
- Serum KL-6, SP-A, and SP-D levels will be measured at sites in Japan for potential early detection of pneumonitis. Inclusion of these markers are for indicating potential lung-related toxicity only; further investigations, like chest CT, etc., will be performed for a confirmatory diagnosis.
- Pregnancy testing (serum or highly sensitive urine test, as required by local regulations) will be conducted at monthly intervals during study intervention administration and at the time points specified in the Schedule of Activities (Table 1), including at the end of relevant systemic exposure of the study intervention.

8.2.4 Review Committees

The following committees will be involved in the study: IDMC, IRC, and Study Steering Committee.

Independent Data Monitoring Committee (IDMC)

To ensure participants' safety during the study, an external IDMC will periodically review safety data. The IDMC will be composed of a minimum of 3 voting members, including an independent biostatistician, and 2 independent oncologists (BTC experts). The full details on membership, mandate, and processes of the IDMC are outlined in the IDMC charter.

Independent Radiology (Review) Committee (IRC)

The IRC will be composed of a minimum of 3 members. The role of the IRC will be to review radiographic image findings, physical findings, and other clinical data for the determination of the best overall response (OR) and date of disease progression for each participant. The full membership, mandate, and processes of the IRC will be detailed in the IRC charter.

8.3 Adverse Events and Serious Adverse Events

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

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

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

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

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

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

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

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

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

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

All SAEs ongoing at the 28-day Safety Follow-up visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up." Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is given in Appendix 4 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reports).

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

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

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

8.3.5 Pregnancy

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

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

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

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

8.4 Treatment of Overdose

- For this study, any dose of M7824 greater than 2 times (i.e., > 2400 mg) than the planned dose administered within a 24-hour time period will be considered an overdose. Of note: In the dose-escalation study (EMR200647-001), participants safely received up to 30 mg/kg M7824 every 2 weeks (including those with doses > 2400 mg) with no observed maximum tolerated dose (refer to the IB). Safety at significantly higher doses has not been clinically evaluated.
- In case of overdose with clinical correlation, symptomatic treatment must be used; there are no known antidotes for the compound.
- In the event of an overdose, the study intervention infusion should be discontinued, and participants should be observed closely for any signs of toxicity. Supportive treatment should be provided if clinically indicated.
- Even if it not associated with an AE or a SAE, any overdose is recorded in the CRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 4, section on Reporting Serious Adverse Events.
- If an AE occurs resulting from an overdose, it should follow SAE reporting criteria as indicated in Appendix 4.

8.5 Pharmacokinetics

- Whole blood samples of approximately 3.5 mL will be collected for measurement of serum concentrations of M7824. Collection times are specified in the Schedule of Activities (see Section 1.3; Table 2). The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration.
- The quantification of M7824 in serum will be performed using a validated assay method. Concentrations will be used to evaluate the PK of M7824.
- Remaining samples collected for analyses of M7824 concentration may also be used to evaluate immunogenicity and safety, or efficacy aspects related to concerns arising during or after the study.

- Details on processes for collection and shipment of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.
- PK and antidrug antibody (ADA) samples collected at the same time points may be used interchangeably if the dedicated sample has insufficient quantity as the participants will have consented to all collections and tests.
- PK samples will be collected according to Table 2.

The following PK parameters will be estimated and reported in the PK Analysis Set:

- C_{EOI}
- C_{trough}.

The PK parameters will be summarized using descriptive statistics. Individual as well as mean concentration-time plots will be depicted (Table 6).

The following PK parameters will be calculated, when appropriate.

Table 6 Pharmacokinetic Parameters

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


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Details on processes for collection and shipment of these samples are specified in the Laboratory Manual. The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality. Retention time and possible analyses of samples after the end of study are specified in the respective ICFs.

8.9 Health Economics

Not applicable.

8.10 Immunogenicity Assessments

- Whole blood samples of approximately 5 mL will be collected for detection of antibodies against M7824 in serum. Collection times are specified in the Schedule of Activities (see Section 1.3; Table 2). Samples will be collected prior to any M7824 administration on the same study day.

9 Statistical Considerations

9.1 Statistical Hypotheses

The primary endpoint of the study is the confirmed OR according to RECIST 1.1, based on independent review of tumor assessments.

The following null hypothesis will be tested:

$$H_0: \text{ORR} \leq 10\%.$$

9.2 Sample Size Determination

The study aims at demonstrating an ORR > 10% in the intention-to-treat (ITT) population by means of an exact binomial test.

The planned total sample size is 141 participants based on the following assumptions:

1. ORR of 18%
2. Alpha = 0.025 (1-sided) for the Exact test of the null hypothesis of an ORR ≤ 10%.

Under the given assumptions, the power to reject the null hypothesis at the primary analysis (PA) is 80%.

An observed ORR of 15.6% (22/141) would achieve a positive ORR outcome and would lead to an exact 95% CI of (10%, 22.7%).

The 2-sided 95% Clopper-Pearson CIs for different observed values for the ORR are provided in Table 8.

Table 8 Confidence Intervals for Different Objective Response Rates

N	N with CR/PR	ORR (%)	95% CI	
141	15	10.6	6.1	16.9
	20	14.2	8.9	21.1
	21	14.9	9.5	21.9
	22	15.6	10.0	22.7
	25	17.7	11.8	25.1
	30	21.3	14.8	29.0
	35	24.8	17.9	32.8

CI=confidence interval, CR=complete response, N=number of participants, ORR=objective response rate, PR=partial response.

Characterization of ORR in Individual BTC Subtypes

To characterize ORR in each individual BTC subtype (intrahepatic CCA, extrahepatic CCA and gallbladder cancer), subgroup analysis of ORR will be performed. With the planned overall sample size of 141 and assuming frequencies of 45% intrahepatic CCA, 30% extrahepatic CCA, and 25% gallbladder cancer, enrolment of at least 30 participants per subtype can be expected even in case the actual rate of participants with gallbladder cancer is below the assumed rate of 25%. A subgroup of 25% of the overall sample size of 141 participants would results in 35 participants.

Risk of observing a high ORR in a subgroup by chance if true ORR is low ("H0")

With a sample size of 30 participants and assuming a true ORR of 10%, the probability to observe at least 5 (16.7%) responders is 17.5%.

Risk of observing a low ORR in a subgroup by chance if true ORR is 18% ("H1")

With a sample size of 30 participants and assuming a true ORR of 18% (same as assumed for overall population), the probability to observe no more than 4 (13.3%) responders is 35.1%.

BTC subtype analyses are not powered for a formal statistical test, e.g., 30 participants would have 15.8% power to reject the null hypothesis of ORR $\leq$ 10%, using the same assumption of ORR of 18% and alpha = 0.025 (1-sided).

Justification of the Assumption of a Confirmed ORR of 18%

M7824, as a monotherapy, has demonstrated promising clinical efficacy signal in 2L BTC. As of 20 March 2018, 30 participants with pretreated BTC received M7824 for a median duration of 8.9 weeks (range: 2 to 57.6 weeks); 5 participants remained on treatment. Seven participants had a confirmed OR (ORR, 23.3% by Investigator read and 20% by IRC, including 1 confirmation of response after data cutoff). Therefore, it is reasonable to assume that the confirmed ORR of M7824 in 2L BTC is 18% or higher.

Justification of the Assumption of a Benchmark ORR of 10% to Define the Study Sample Size

The benchmark for the ORR for 2L treatments is based on an update of a systematic review published in 2014 (Lamarca 2014) from available literature conducted in August 2018. Based on this updated review, which included 2L BTC studies reporting ORR results for chemotherapy alone or in association with an approved systemic anticancer therapy restricted to studies with > 20 participants (to avoid imprecise ORR estimates reported in smaller samples), 32 studies were identified reporting outcomes for 2137 participants globally.

The ORR estimate derived from these studies based on a regression model with a random effect was 7.2% with a 95% CI ranging from 5.5% to 9.2%. Using the upper limit of this CI we assumed the benchmark ORR to be 10%.

9.3 Populations for Analyses

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

For purposes of analysis, the analysis populations are defined in Table 9.

Table 9 Analysis Populations

Screening (SCR)	All participants, who provided informed consent, regardless of the participant's study intervention status in the study.
Safety (SAF)/ Intention-to-treat (ITT)	All participants, who were administered at least 1 infusion of M7824. The primary analysis (PA) population for all analyses of efficacy, safety, and health-related quality of life is the Safety population.
Pharmacokinetic (PK)	All participants who complete at least 1 infusion of M7824, and who provide at least 1 sample with a measurable concentration of M7824.
Immunogenicity Analysis Set (IMM)	All participants who were administered at least 1 infusion of M7824 and have at least one valid antidrug antibody (ADA) result. All ADA analyses will be based on this analysis set.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

9.4.1.1 Analysis of Primary Endpoint

The primary endpoint is confirmed OR according to RECIST 1.1, as determined by an IRC. For an OR of PR or CR, confirmation of the response according to RECIST 1.1 will be required no sooner than 4 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR. The response at each scheduled tumor assessment and the OR will be listed for each participant. The number and proportion of OR (defined as CR + PR) will be tabulated. The ORR will be determined as the proportion of participants with a confirmed OR of PR or CR. The 95% CI for the ORR will be calculated using the Clopper-Pearson method. The test statistic of the exact

binomial test (1 sample) against the null hypothesis for the ORR will be calculated to determine whether the null hypothesis of an ORR ≤ 10% can be rejected.

Analysis of efficacy variables will also be performed on subgroup of interest, including but not restricted to

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- PD-L1 expression

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- MSI status

Further details will be specified in the integrated analysis plan (IAP).

9.4.1.2 Analysis of Secondary and CCI Endpoints

9.4.1.2.1 Analysis of Secondary Endpoints

PFS according to RECIST 1.1, is defined as the time from first administration of study intervention until date of the first documentation of PD or death due to any cause in the absence of documented PD, whichever occurs first.

PFS data will be censored on the date of the last adequate tumor assessment for participants who do not have an event (PD or death), for participants who start new anticancer treatment prior to an event, or for participants with an event after two or more missing tumor assessments. Participants who do not have a baseline tumor assessment or who do not have any postbaseline tumor assessments will be censored on the date of first administration of study intervention unless death occurred on or before the time of the second planned tumor assessment, in which case the death will be considered an event.

Sensitivity analyses of PFS will be done including but not limited to:

- Alternative censoring rules including an analysis which counts death and progression according to RECIST 1.1 as PFS event regardless of the start of a new anticancer therapy and ignoring the number of missing evaluable tumor assessments before progression or death
- PFS as assessed by the Investigator

Details will be defined in the IAP.

DOR is defined, for participants with a confirmed OR, as the time from first documentation of OR (CR or PR) to the date of first documentation of objective PD or death due to any cause whichever occurs first. The censoring rules for DOR are as described above for PFS.

A durable response is defined as an OR (CR or PR) according to RECIST 1.1, determined by an IRC, with a duration of at least 6 months. Participants for whom the DOR is censored will be treated as failures (successes) in the analysis of durable response if the censored DOR is below (at least) 6 months. The DRR is defined as the percentage of participants with durable response. The 95% CI for the DRR will be calculated using the Clopper-Pearson method.

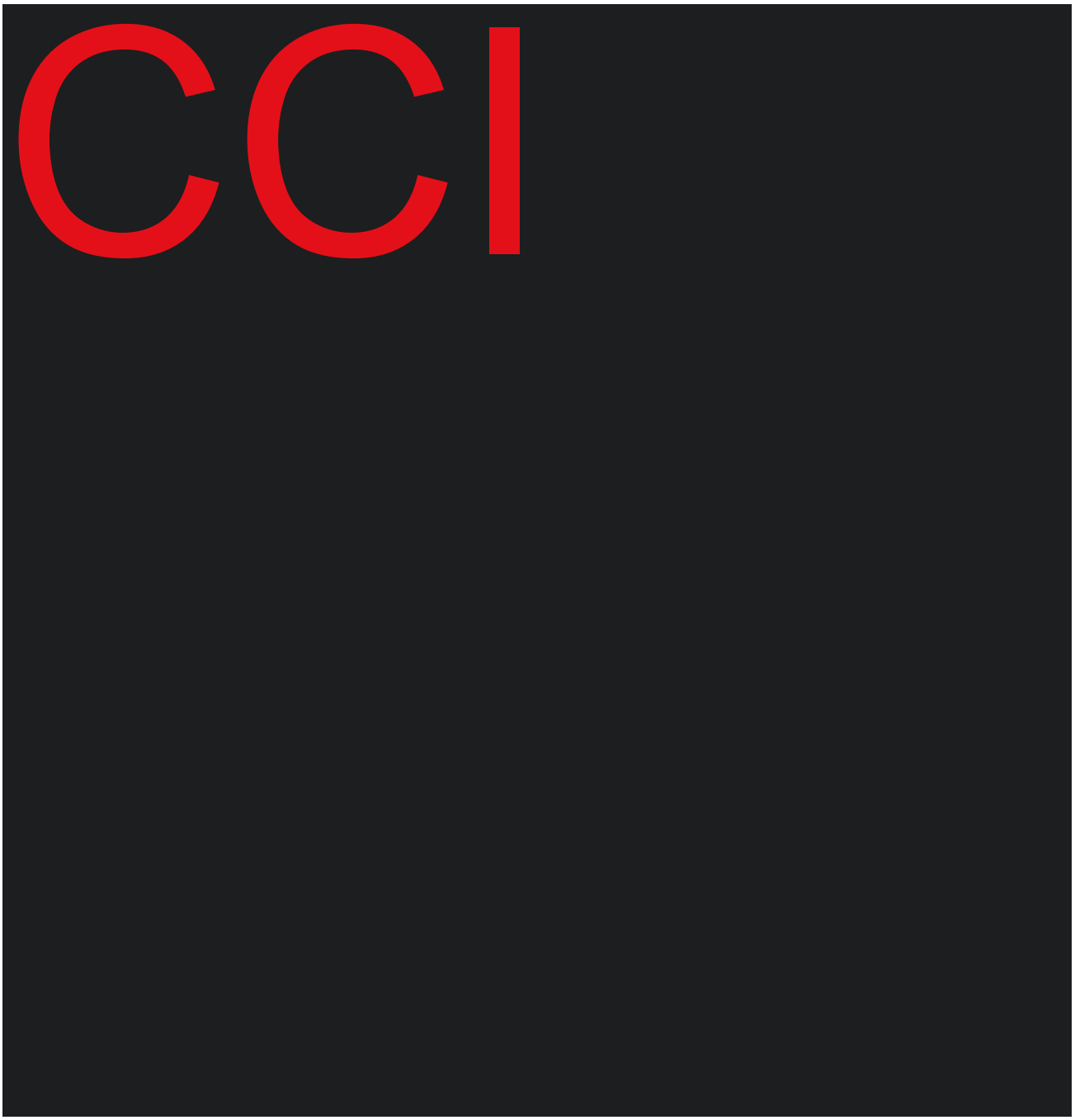
Overall survival (OS) is defined as the time from first administration of study intervention to the date of death due to any cause. Participants last known to be alive will be censored at date of last contact.

The Kaplan-Meier method will be used to estimate parameters for DOR, PFS, and OS. In particular, the PFS rate at 6 and 12 months will be estimated with corresponding 2-sided 95% CIs, and the survival rate at 6 and 12 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (Brookmeyer and Crowley 1982) and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (Kalbfleisch and Prentice 1980). The estimate of the standard error will be computed using Greenwood's formula. The DOR, PFS, and OS will also be presented in participant listings.

The association between PD-L1 expression and efficacy endpoints – primarily ORR and DOR/DRR – will be analyzed. CCI

CCI

CCI



9.4.2 Safety Analyses

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

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

Adverse Events

All AEs will be coded according to the MedDRA. Severity of AEs will be graded using the NCI-CTCAE v5.0 toxicity grading scale.

The incidence of treatment-emergent adverse events (TEAEs), regardless of attribution, and TEAEs defined as possibly related to M7824 will be summarized by MedDRA preferred term and system organ class (SOC) and described in terms of intensity and relationship to M7824. 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. Any AEs with an onset or worsening date after the on-treatment period will be reported separately.

The incidence of SAEs and AESIs will be summarized by preferred term and SOC.

Descriptive statistics will be examined for indications of dose-related ADRs.

Laboratory Variables

Laboratory results will be classified by grade according to NCI-CTCAE v5.0. The worst on-study grades after the first study intervention will be summarized. Shifts in toxicity grading from first treatment to highest grade will be displayed. Results for variables that are not part of NCI-CTCAE v5.0 will be presented as below, within, or above normal limits. Only participants with postbaseline laboratory values will be included in these analyses.

Physical Examination (Including Vital Signs and 12-Lead ECGs)

Physical examination findings, including vital signs (body temperature, respiratory rate, heart rate, and blood pressure) and 12-lead ECGs, as indicated in the Schedule of Activities (Table 1) will be presented.

Further details will be provided in the IAP based on current safety experience applying the latest MedDRA version.

All safety analyses will be performed on the Safety Analysis population.

9.4.3 Other Analyses

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

Serum concentrations of M7824 will be determined by a validated method at the times listed in the Schedule of Activities (Section 1.3; Table 2).

- Details on the PK, immunogenicity, and CCI [redacted] will be in the IAP that will be finalized before database lock. The PopPK analysis and exposure-response may be performed using combined data from several M7824 clinical studies and will be specified in a separate IAP. The PopPK, exposure-response and biomarker analyses will be presented separately from the main CSR.

Estimation of Individual PK Parameters

- PK parameters will be calculated by the PK/PD Data Processing Group of QPD, Merck, Darmstadt, Germany, or by a CRO selected by the Sponsor.
- The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.4 or higher) may be used to produce tables, listings, and figures and in the calculation of PK parameters, if appropriate.

PK analyses (C_{EOI} and C_{trough}) will be specified in the IAP finalized before database lock.

ADA/Immunogenicity

Samples for ADA assessments will be collected as per the Schedule of Activities.

Immunogenicity testing strategy will be implemented and conducted in line with:

- Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins (EMEA/CHMP/BMWP/14327/2006)
- Immunogenicity Assessment of Monoclonal Antibodies Intended for In Vivo Clinical Use (EMA/CHMP/BMWP/86289/2010)
- FDA Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins (refer to FDA; December 2009, draft).

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

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

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

9.4.4 Sequence of Analyses

There will be 2 data cutoff time points in this study:

- An CCI [redacted] per BTC subtype will be performed once 15 participants of each subtype have reached at least one postbaseline tumor assessment. Each subtype will be analyzed separately once criteria are met.
- The PA will be conducted 9 months after the accrual of the last of 141 planned participants.
- Second analysis for DRR and DOR will be conducted 15 months after the accrual of the last of 141 planned participants. The analysis will comprise a full evaluation of all efficacy and safety endpoints.

10 References

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CCI

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11 Appendices

Appendix 1 Abbreviations

1L	First-line
2L	Second-line
ADA	Antidrug antibody
ADR	Adverse drug reactions
AE	Adverse events
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
CCI	[redacted]
BTC	Biliary tract cancer
CCA	Cholangiocarcinoma
CI	Confidence Interval
CCr	Creatinine clearance
CNS	Central nervous system
CR	Complete response
CRO	Contract Research Organization
cSCC	Cutaneous squamous cell carcinoma
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
C_{trough}	Trough concentration
DNA	Deoxyribonucleic acid
DOR	Duration of response
DRR	Durable response rate
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
CCI	[redacted]
CCI	[redacted]
FSH	Follicle-stimulating hormone

GCP	Good Clinical Practices
HBV	Hepatitis B virus
HCC-18	Hepatobiliary Cancer 18 item module
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
IAP	Integrated analysis plan
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
INR	International normalized ratio
ITT	Intention-to-treat
irAE	Immune-related adverse event
IRB	Institutional Review Board
CCI	[redacted]
IRC	Independent Review Committee
CCI	[redacted]
IRR	Infusion-related reaction
CCI	[redacted]
KA	Keratoacanthoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
CCI	[redacted]
NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drugs
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PA	Primary analysis
PD	Progression of disease
PD-1	Programmed death-1

PD-L1	Programmed death ligand 1
PFS	Progression-free survival
CCI	[redacted]
PK	Pharmacokinetic
PopPK	Population pharmacokinetics
PR	Partial response
CCI	[redacted]
PS	Performance status
PT	Prothrombin time
CCI	[redacted]
RECIST 1.1	Response Evaluation Criteria in Solid Tumors 1.1
RNA	Ribonucleic acid
RP2D	Recommended Phase II dose
SAE	Serious adverse event
SOC	System organ class
SP-A	Surfactant protein A
SP-D	Surfactant protein D
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
TGF-β	Transforming growth factor-beta
CCI	[redacted]
TTP	Thrombotic thrombocytopenic purpura
ULN	Upper limit of normal
VAS	Visual Analog Scale
WOCBP	Woman of childbearing potential

Appendix 2 Study Governance

Financial Disclosure

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

Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally-authorized representative (where allowed by local laws and regulations) and answer all questions on the study.

Participants must be informed that their participation is voluntary.

Participants or their legally-authorized representative (where allowed by local laws and regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; the Japanese ministerial ordinance on GCP; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.

The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

If the ICF is updated during their participation in the study, participants must be reconsented to the most current, approved version.

Participants who are rescreened are required to sign a new ICF.

Data Protection

The Sponsor will assign a unique identifier to participants after obtaining their informed consent. All participant records or datasets transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.

The Sponsor will inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant and pregnant partners (if applicable), who will be required to give consent for their data to be used, as specified in the informed consent.

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

Study Administrative

The Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the CSR.

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

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

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

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

The Clinical Trial Supplies department of the Sponsor will supply the study medication of M7824, which will be distributed to the sites by Fisher Clinical Services.

Participant enrollment will be managed by an interactive voice response system or an interactive web response system.

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

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

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

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

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

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines
- The Japanese ministerial ordinance on GCP
- Applicable laws and regulations.

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

The Sponsor initiates the study at a site after obtaining written approval from the Head of the study site, based on favorable opinion/approval from the concerned IRB.

Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.

The Investigator will be responsible for the following:

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

The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).

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

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

Clinical Study Insurance and Compensation to Participants

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

The Sponsor is entirely responsible for AEs that are associated with this study and cause damage to the health of the participants, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the study site, and/or the participant. The Sponsor takes out insurance to fulfill the responsibility.

Clinical Study Report

After study completion, the Sponsor will write a CSR in consultation with the Coordinating Investigator.

Publication

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by agreement.

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

Dissemination of Clinical Study Data

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

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

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

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

Data Quality Assurance

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

For CCI data (e.g., CCI and pain assessments), CCI will be used.

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

The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan or contracts.

The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.

Study monitors will perform ongoing source data verification to confirm that data in the eCRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, the Japanese ministerial ordinance on GCP, and all applicable regulatory requirements.

The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.

The Investigator will keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file will identify each participant, contain the following demographic and medical information for the participant, and will be as complete as possible:

- Participant's full name, date of birth, sex, height, and weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the study)
- Study identifier (i.e., the Sponsor's study number) and participant's study number.
- Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
- Any medical examinations and clinical findings predefined in the protocol
- All AEs
- Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.

All source data will be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document will have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records will be performed, documented, signed and dated by the Investigator.

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

The Study Monitors will use printouts of electronic files for source data verification. These printouts will be signed and dated by the Investigator and kept in the study file.

Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator or in Japan: a record retainer designated by the Head of the study site ensures that no destruction of medical records is performed without the Sponsor's written approval.

Definition of what constitutes source data is found in the eCRF guidelines.

Study and Site Start and Closure

First Act of Recruitment

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

Study Closure and Site Termination

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further development of the Sponsor's compound.
- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

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

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

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

- Sponsor's decision that continuation of the study is unjustifiable for medical or ethical reasons.
- Poor enrollment of participants making completion of the study within an acceptable time frame unlikely.
- Discontinuation of development of the Sponsor's study intervention.

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

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

Survival Follow-up will continue until each participant was followed up for at least 3 years after the End-of-Treatment.

Appendix 3 Contraception

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

Woman of Childbearing Potential (WOCBP)

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

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

A WOCBP is **not**:

1. Premenarchal

2. A premenopausal female with 1 of the following:

    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy.

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

For a female with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.

3. A postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.

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

CONTRACEPTIVES ALLOWED DURING THE STUDY

Highly Effective Methods That Have Low User Dependency

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

Highly Effective Methods That Are User Dependent

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

- Oral
- Intravaginal*
- Transdermal*
- Injectable*

Progestogen-only hormone contraception associated with inhibition of ovulation

- Oral
- Injectable*
- Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.

Notes:

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

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

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

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

* Not approved in Japan

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

Definitions

Adverse Event

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

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

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

Investigators will reference the NCI-CTCAE, v5.0 (publication date: 27 November 2017), a descriptive terminology that can be used for AE reporting.

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

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

The 5 general grades are:

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

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

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

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

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

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

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

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

Serious Adverse Events

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

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

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

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g., an overnight stay to facilitate intravenous therapy) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

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

AE/SAEs Observed in Association With Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an (S)AE, unless the participant's general condition is more severe than expected for the participant's condition and/or unless the outcome is fatal within the AE reporting period, as defined in Section 8.3.2.

Adverse Events of Special Interest

Infusion-related reactions including hypersensitivity, immune-related AEs, TGF-β inhibition mediated skin reactions, anemia, and bleeding AEs are all considered as AESI for M7824.

Other Adverse Events to be Reported Following a Specialized Procedure

Not applicable.

Recording and Follow-up of AE and/or SAE

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

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

Reporting Serious Adverse Events

Serious Adverse Events

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

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

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

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

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

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

Appendix 5 Clinical Laboratory Tests

The required laboratory safety tests for the full chemistry and hematology panel is summarized in Table A. See Section 1.3 for details of which panel to run at each visit.

Table A Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelets[a]		Mean Corpuscular Volume (MCV)	White blood cell (WBC) Count with Differential[a]: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Reticulocytes		Mean corpuscular hemoglobin concentration (MCHC)	
	Hemoglobin[a]		Mean corpuscular hemoglobin (MCH)	
	Hematocrit		Activated partial thromboplastin time (aPTT)[b]	
	Red blood cell count[a]		Prothrombin time[b]	
	Absolute lymphocyte count[a]		International normalized ratio (INR)[b]	
	Absolute neutrophil count[a]			
Biochemistry	Blood Urea Nitrogen	Potassium	Aspartate aminotransferase[a]	Bilirubin (total, indirect/direct)[a]
	Creatinine[a]	Sodium	Alanine aminotransferase[a]	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
	Lipase	Chloride	Albumin	
	C-reactive protein	Amylase		
Full Urinalysis	Dipstick plus microscopic evaluation. Dipstick, including physical appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen, as locally available			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, by dipstick • Microscopic examination (if blood or protein is abnormal).			
Other Tests	• FSH and estradiol (as needed if **not** a WOCBP only) • Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test • Free T4 and TSH • Hepatitis Screening[c]: Hepatitis B surface antigen; Hepatitis B core antibody and Hepatitis C antibody • KL-6, SP-A and SP-D[d] • Tumor marker: CA 19.9			

[a] Results must be reviewed by the Investigator within 48 hours prior to dosing.

[b] Coagulation parameters must be collected at Baseline, Day 1, every 4 weeks thereafter, End-of-Treatment Visit, and 28 Days Safety Follow-up Visit (See Schedule of Assessment [Table 1]).

[c] If hepatitis B surface antigen positive and hepatitis B core antibody positive, then reflex to quantitative HBV DNA (PCR); if hepatitis B core antibody positive alone, then reflex to quantitative hepatitis B DNA (PCR); if hepatitis C antibody positive, then reflex to quantitative hepatitis C RNA (PCR).

[d] Only applicable for Japanese sites.

Appendix 6 Management of irAEs

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

The management of immune-related adverse events (irAEs) in patients treated with immune checkpoint inhibitors is presented in the following tables:

Table A1 Management of Skin irAEs in Patients Treated With ICPis

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

1.0 Skin Toxicities	
G4: All severe rashes unmanageable with prior interventions and intolerable	**<u>Permanently discontinue ICPi</u>** Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves Monitor closely for progression to severe cutaneous adverse reaction Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology
1.2 Bullous dermatoses	
Definition: Including bullous pemphigoid or other autoimmune bullous dermatoses, bullous drug reaction Diagnostic work-up Physical examination Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease If needed, a biologic checkup, including a blood cell count, liver, and kidney tests; consider serum antibody tests to rule out bullous pemphigoid or, under the guidance of dermatology, sending patient serum for indirect immunofluorescent testing to rule out other autoimmune blistering diseases Referral to dermatology for blisters that are not explained by infectious or transient other causes (e.g., herpes simplex, herpes zoster, bullous impetigo, bullous insect bite, friction or pressure blister) Consider skin biopsy (both hematoxylin and eosin evaluation of lesional skin and direct immunofluorescence evaluation of perilesional skin)	
Grading	**Management**
G1: Asymptomatic, blisters covering < 10% BSA and no associated erythema	If blisters are < 10% BSA, asymptomatic, and noninflammatory (such as the case with friction blisters or pressure blisters), cessation of ICPi is not necessary, and only observation and/or local wound care is warranted When symptomatic bullae or erosions, which are deroofed vesicles or bullae, are observed on the skin or mucosal surfaces, the cutaneous irAE is by definition considered at least G2 See G2 management recommendations
G2: Blistering that affects quality of life and requires intervention based on diagnosis not meeting criteria for grade > 2 Blisters covering 10% to 30% BSA	Hold ICPi therapy and consult with dermatology for work-up and to determine appropriateness of resuming Attention given to general local wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions, which are left over on the skin after the blister has popped or if the roof of the blister easily sloughs off Counsel patients to avoid skin irritants and overexposure to sun, wear protective clothing, use sunscreens Work-up for autoimmune bullous disease as above Initiate class 1 high-potency topical corticosteroid (e.g., clobetasol, betamethasone or equivalent) and 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

1.0 Skin Toxicities	
	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 (e.g., pemphigus) and SJS/TEN
G3: Skin sloughing covering > 30% BSA with associated pain and limiting self-care ADL	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab, as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.
G4: Blisters covering > 30% BSA with associated fluid or electrolyte abnormalities	Permanently discontinue ICPi. Admit patient immediately and place under supervision of a dermatologist. Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg with tapering over at least 4 weeks when the toxicity resolves. If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.

1.0 Skin Toxicities	
1.3 SCARs, including SJS, TEN, acute generalized exanthematous pustulosis, and DRESS/DIHS	
Definition: Severe changes in either structure or functions of skin, the appendages or the mucous membranes due to a drug Diagnostic work-up	
Total body skin examination with attention to examining all mucous membranes as well as complete review of systems Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease A biologic checkup, including a CBC with differential test, and liver and kidney function tests, including urinalysis, in addition to the blood work; if the patient is febrile, blood cultures should be considered as well Skin biopsies to assess for full-thickness epidermal necrosis, as is seen in SJS/TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses or other drug reactions, such as acute generalized exanthematous pustulosis Consider following patients closely using serial clinical photography If mucous membrane involvement or blistering is observed on the skin, consider early admission to a burn center for further monitoring and management. Primer on monitoring for complicated cutaneous adverse drug reactions: Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (e.g., pemphigus) and SJS/TEN	
Grading	**Management**
All Grades	In cases of suspected SJS or any mucous membrane involvement, discontinue ICPi treatment and monitor closely for improvement, regardless of grade
G1: NA	For SCARs, there is no G1 category; if lower BSA is involved with bullae or erosions, there should remain a high concern that this reaction will progress to G3 or G4
G2: Morbilliform ("maculopapular") exanthem covering 10%-30% BSA with systemic symptoms, lymphadenopathy, or facial swelling	Hold ICPi and monitor patients closely every 3 days with G2 irAEs for progression to involvement of greater BSA and/or mucous membrane involvement Consider following patients closely using serial photography Initiate therapy with topical emollients, oral antihistamines, and medium- to high-strength topical corticosteroids Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks
G3: Skin sloughing covering < 10% BSA with mucosal involvement associated signs (e.g., erythema, purpura, epidermal detachment, mucous membrane detachment)	Hold ICPi therapy and consult with dermatology Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum

1.0 Skin Toxicities	
	Administer IV (methyl)prednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks Admit to burn and/or consult wound services with attention to supportive care, including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (e.g., ophthalmology; ear, nose, and throat; urology; gynecology; etc, as appropriate)
G4: Skin erythema and blistering/sloughing covering ≥ 10% to > 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (e.g., liver function test elevations in the setting of DRESS/DIHS)	Permanently discontinue ICPi Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services Consider further consultations based on management of mucosal surfaces (e.g., ophthalmology; urology; gynecology; ear, nose, and throat surgery; etc). Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal IVIG or cyclosporine may also be considered in severe or corticosteroid-unresponsive cases Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations
Additional considerations: The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immunodirected toxicity Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS/DIHS All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate	

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, SS-A/B= Sjogren's syndrome A/B, TEN=toxic epidermal necrolysis.

Table A2 Management of GI irAEs in Patients Treated With ICPis

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

2.0 GI Toxicities	
	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 v inflammatory diarrhea, and use calprotectin to monitor treatment response if provider prefers Repeat colonoscopy is optional for cases of G2 or higher for disease activity monitoring to achieve complete remission, especially if there is a plan to resume ICPi
G3: Increase of seven or more stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL	Should consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less. Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent) Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance If symptoms persist ≥ 3-5 days or recur after improvement, consider administering IV corticosteroid or noncorticosteroid (e.g., infliximab) Consider colonoscopy in cases where patients have been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (i.e., CMV colitis) and for those who are anti-TNF or corticosteroid refractory
G4: Life-threatening consequences; urgent intervention indicated	Permanently discontinue treatment Should admit patient when clinically indicated; patients managed as outpatients should be very closely monitored Administer 1-2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks Consider early infliximab 5-10 mg/kg if symptoms refractory to corticosteroid within 2-3 days Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections
Additional considerations The use of vedolizumab (not approved in Japan) may be considered in patients refractory to infliximab and/or contraindicated to TNF-α blocker. The decision should be made on an individual basis from gastroenterology and oncology evaluation. This is based on case series showing promising results	

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

2.0 GI Toxicities	
	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-α agents as systemic immunosuppressants. If no improvement is achieved with corticosteroids or for patients on combination therapy with a novel agent, with standard chemotherapy, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis Corticosteroid taper can be attempted around 4-6 weeks; re-escalate if needed; optimal duration unclear
G4: Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma; AST or ALT > 20 x ULN and/or total bilirubin > 10 x ULN)	Permanently discontinue ICPi Administer 2 mg/kg/d methylprednisolone equivalents If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil Monitor laboratories daily; consider inpatient monitoring Avoid the use of infliximab in the situation of immune-mediated hepatitis Hepatology consult if no improvement was achieved with corticosteroid Corticosteroid taper can be attempted around 4- 6 weeks when symptoms improve to G1 or less; re-escalate if needed; optimal duration unclear Consider transfer to tertiary care facility if necessary
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations is moderate.	

ADL=activities of daily living, ALT=alanine aminotransferase, ANA=antinuclear antibody, AST= aspartate aminotransferase, 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; 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.	

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

Table A4 Management of Endocrine irAEs in Patients Treated With ICPis

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

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

4.0 Endocrine Toxicity	
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 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

4.0 Endocrine Toxicity	
	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 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	

4.0 Endocrine Toxicity	
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 patients Initiate insulin therapy for all patients Admit for inpatient management: Concerns for developing DKA, Symptomatic patients regardless of diabetes type, New-onset T1DM unable to see endocrinology
Additional considerations Insulin therapy can be used as the default in any case with hyperglycemia Long-acting therapy alone is not usually sufficient for T1DM, where half of daily requirements are usually given in divided doses as prandial coverage and half as long acting. Insulin doses will be lower in T1DM because of preserved sensitivity (total daily requirement can be estimated at 0.3-0.4 units/kg/d). In T2DM, sliding-scale coverage with meals over a few days provides data to estimate a patient's daily requirements and can be used to more rapidly titrate basal needs. All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

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, SSKI=potassium iodide, T1DM=type 1 diabetes mellitus, T2DM=type 2 diabetes mellitus, TRAb=thyroid-stimulating hormone receptor antibody, TSH=thyroid-stimulating hormone, TSI=thyroid-stimulating immunoglobulin, ULN=upper limit of normal.

Table A5 Management of Musculoskeletal irAEs in Patients Treated With ICPis

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

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

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) 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	

5.0 Musculoskeletal Toxicities	
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.	

ADL=activities of daily living, ANA=antinuclear antibodies, CCP=citrullinated protein antibody, CK= creatine kinase, CRP=C-reactive protein, DMARD=disease-modifying antirheumatic drug, EMG=electromyography, ESR=erythrocyte sedimentation rate, ICPi=immune checkpoint inhibitor, IL=interleukin, irAE=immune-related adverse event, IV=intravenous, IVIG=intravenous immunoglobulin, LDH=lactate dehydrogenase, NSAID=nonsteroidal anti-inflammatory drug, PCP=Pneumocystis pneumonia, RF=rheumatoid factor, TNF=tumor necrosis factor.

Table A6 Management of Renal irAEs in Patients Treated With ICPis

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

6.0 Renal Toxicities	
6.2 Symptomatic nephritis: follow-up	
Grading	**Management**
G1	Improved to baseline, resume routine creatinine monitoring
G2	If improved to G1, taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring If elevations persist > 7 days or worsen and no other cause found, treat as G3
G3	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist 3-5 days or worsen, consider additional immunosuppression (e.g., mycophenolate)
G4	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist 2-3 days or worsen, consider additional immunosuppression (e.g., mycophenolate)
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

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 anti-striated 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 Electrodiagnostic studies, including neuromuscular junction testing with repetitive stimulation and/or jitter studies, NCS to exclude neuropathy, and needle EMG to evaluate for myositis	
Grading	**Management**
All grades	All grades warrant work-up and intervention given potential for progressive myasthenia gravis to lead to respiratory compromise
No G1	
G2: Some symptoms interfering with ADL MGFA severity class 1 (ocular symptoms and findings only) and MGFA severity class 2 (mild generalized weakness)	Hold ICPi and may resume in G2 patients (MGFA 1 and 2) only if symptoms resolve Should consult neurology Pyridostigmine starting at 30 mg orally three times a day and gradually increase to maximum of 120 mg orally four times a day as tolerated and based on symptoms Administer corticosteroids (prednisone, 1-1.5 mg/kg orally daily) if symptoms G2; wean based on symptom improvement
G3-4: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms, or MGFA severity class 3-4 moderate to severe generalized weakness to myasthenic crisis	Permanently discontinue ICPi Admit patient, may need ICU-level monitoring Neurology consult Continue corticosteroids and initiate IVIG 2 g/kg IV over 5 days (0.4 g/kg/d) or plasmapheresis for 5 days Frequent pulmonary function assessment Daily neurologic review
Additional considerations Avoid medications that can worsen myasthenia: β-blockers, IV magnesium, fluoroquinolones, aminoglycosides, and macrolides Initially a 5-day course of plasmapheresis or a 2 g/kg course of IVIG over 5 days 1-2 mg/kg methylprednisolone daily, wean based on symptom improvement Pyridostigmine, wean based on improvement ICPi-associated myasthenia gravis may be monophasic, and additional corticosteroid-sparing agents may not be required	

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

7.0 Nervous System Toxicities	
Diagnostic work-up G1 Screen for reversible neuropathy causes: diabetic screen, B12, folate, TSH, HIV, consider serum protein electrophoresis, and other vasculitis 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	
Grading	**Management**
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate	Low threshold to hold ICPi and monitor symptoms for a week If to continue, monitor very closely for any symptom progression
G2: Moderate, some interference with ADL, symptoms concerning to patient (i.e., pain but no weakness or gait limitation)	Hold ICPi and resume once return to G1 Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild) Neurontin, pregabalin, or duloxetine for pain
G3-4: Severe, limiting self-care and aids warranted, weakness limiting walking or respiratory problems (i.e., leg weakness, foot drop, rapidly ascending sensory changes) Severe may be Guillain-Barré syndrome and should be managed as such	Permanently discontinue ICPi Admit patient Neurologic consultation Initiate IV methylprednisolone 2-4 mg/kg and proceed as per Guillain-Barré syndrome management
7.4 Autonomic neuropathy	
Definition: Nerves that control involuntary bodily functions are damaged. This may affect blood pressure, temperature control, digestion, bladder function, and sexual function. A case of severe enteric neuropathy with ICPi has been reported. Can present with GI difficulties such as new severe constipation, nausea, urinary problems, sexual difficulties, sweating abnormalities, sluggish pupil reaction, and orthostatic hypertension.	
Diagnostic work-up An evaluation by neurologist or relevant specialist, depending on organ system, with testing that may include Screening for other causes of autonomic dysfunction: diabetic screen, adrenal insufficiency, HIV, paraproteinemia, amyloidosis, botulism; consider chronic diseases such as Parkinson and other autoimmune screening AM orthostatic vitals Consider electrodiagnostic studies to evaluate for concurrent polyneuropathy Consider paraneoplastic Lambert-Eaton myasthenic syndrome, antineutrophil cytoplasmic antibodies, and ganglionic AChR antibody testing	
Grading	**Management**
G1: Mild, no interference with function and symptoms not concerning to patient	Low threshold to hold ICPi and monitor symptoms for a week; if to continue, monitor very closely for any symptom progression
G2: Moderate, some interference with ADL, symptoms concerning to patient	Hold ICPi and resume once return to G1 Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild) Neurologic consultation

7.0 Nervous System Toxicities	
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 (i.e., pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits. Consider empirical antiviral (IV acyclovir) and antibacterial therapy until CSF results. Once bacterial and viral infection are negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg or IV methylprednisolone 1 mg/kg if moderate/severe symptoms
7.6 Encephalitis	
Definition: As for aseptic meningitis, need to exclude infectious causes, especially viral (i.e., HSV). Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality	
Diagnostic work-up Neurologic consultation MRI of brain with or without contrast may reveal T2/fluid-attenuated inversion recovery changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal Lumbar puncture: check cell count and protein glucose and perform Gram stain, culture, PCR for HSV and other viral PCRs depending on suspicion, cytology, oligoclonal bands, autoimmune encephalopathy, and paraneoplastic panels. May see elevated WBC count with lymphocytic predominance and/or elevated protein EEG to evaluate for subclinical seizures Blood: metabolic, CBC, ESR, CRP, ANCA (if suspect vasculitic process), thyroid panel including TPO and thyroglobulin Rule out concurrent anemia/thrombocytopenia, which can present with severe headaches and confusion	
Grading	**Management**
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (i.e., pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits As above for aseptic meningitis suggest concurrent IV acyclovir until PCR results obtained and negative Trial of methylprednisolone 1-2 mg/kg

7.0 Nervous System Toxicities	
	If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids methylprednisolone 1 g IV daily for 3-5 days plus IVIG 2 g/kg over 5 days If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab or plasmapheresis in consultation with neurology.
7.7 Transverse myelitis	
Definition: Acute or subacute weakness or sensory changes bilateral, often with increased deep tendon reflexes	
Diagnostic work-up Neurologic consultation MRI of spine (with thin axial cuts through the region of suspected abnormality) and MRI of brain Lumbar puncture: cell count, protein, glucose, oligoclonal bands, viral PCRs, cytology, onconeural antibodies Blood: B12, HIV, RPR, ANA, Ro/La, TSH, aquaporin-4 IgG Evaluation for urinary retention, constipation	
Grading	**Management**
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (i.e., pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Permanently discontinue ICPi Methylprednisolone 2 mg/kg Strongly consider higher doses of 1 g/d for 3-5 days Strongly consider IVIG
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

AChR=acetylcholine receptor, ACTH=adrenocorticotropic hormone, ADL=activities of daily living, ANCA=antineutrophil cytoplasmic antibodies, CNS=central nervous system, CPK=creatine phosphokinase, CRP=C-reactive protein, CSF=cerebrospinal fluid, ECG=electrocardiogram, EMG=electromyography, ESR=erythrocyte sedimentation rate, HIV=human immune deficiency, 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.

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 PT, INR, 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, penicillin, 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 - 4.9 mmol/L; < 100 to 80 g/L	Hold ICPi and strongly consider permanent discontinuation Administer 0.5-1 mg/kg/d prednisone equivalents
G3: Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated	Permanently discontinue ICPi Should use clinical judgment and consider admitting the patient Hematology consult Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms/speed of development) If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue ICPi treatment Consider RBC transfusion per existing guidelines; do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return a patient to a safe Hgb range (7-8 g/dL in stable, noncardiac inpatients) Should offer patients supplementation with folic acid 1 mg once daily
G4: Life-threatening consequences, urgent intervention indicated	Permanently discontinue ICPi Admit patient Hematology consult IV prednisone corticosteroids 1-2 mg/kg/d

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

8.0 Hematologic Toxicities	
8.3 Hemolytic uremic syndrome	
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia. Signs and symptoms of hemolytic uremic syndrome can include: Bloody diarrhea Decreased urination or blood in the urine Abdominal pain, vomiting, and occasionally fever Pallor Small, unexplained bruises or bleeding from the nose and mouth Fatigue and irritability Confusion or seizures High blood pressure Swelling of the face, hands, feet, or entire body	
Diagnostic work-up History and physical examination (special consideration for new history of high-risk drugs, hypertension, or cardiac causes), CBC with indices Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis. Serum creatinine ADAMTS13 (to rule out TTP) Homocysteine/methylmalonic acid Complement testing C3, C4, CH50 (complement inhibitory antibodies for suspected familial) Evaluate reticulocyte count and mean corpuscular volume Evaluation of infectious cause, including screening for EBV, CMV, HHV6 Evaluation for nutritional causes of macrocytosis (B12 and folate) Pancreatic enzymes Evaluation for diarrheal causes, shiga toxin, Escherichia coli O157, etc Direct antibody test (Coombs test), haptoglobin, LDH, and other etiologies of anemia Evaluation for common drugs causing hemolysis (tacrolimus, cyclosporine, sirolimus, etc) Evaluation for concurrent confusion	
Grading	**Management**
G1-2: Evidence of RBC destruction (schistocytosis) without clinical consequences of anemia, thrombocytopenia grade 2 G3: Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae) G4: Life-threatening consequences (e.g., CNS thrombosis/ embolism or renal failure)	For G1 and G2: Continue ICPi with close clinical follow-up and laboratory evaluation Supportive care **<u>For G3 and G4: Permanently discontinue ICPi</u>** Begin therapy with eculizumab therapy 900 mg weekly for four doses, 1,200 mg week 5, then 1,200 mg q2w Red blood transfusion according to existing guidelines
8.4 Aplastic anemia	
Definition: Condition in which the body stops producing enough new blood cells	
Diagnostic work-up History and physical examination (close attention to medications, exposure to radiation, toxins, recent viral infections), CBC, smear, reticulocyte count Viral studies, including CMV, HHV6, EBV, parvovirus Nutritional assessments including B12, folate, iron, copper, ceruloplasmin, vitamin D Serum LDH, renal function Work-up for infectious causes Identify marrow hypo/aplasia Bone marrow biopsy and aspirate analysis Peripheral blood analysis, including neutrophil count, proportion of GPI-negative cells by flow for PNH	

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

8.0 Hematologic Toxicities	
	For G4, for single laboratory values out of normal range without any clinical correlates, permanent treatment discontinuation is not required. Treatment should be held until the etiology is determined. Permanent treatment discontinuation will only be required, if lymphopenia is considered of immune related in nature, no clear alternative explanation exists for the event, and Grade 4 lymphopenia does not resolve within 14 days. If the event is not considered immune related and resolves to G ≤1 restarting treatment may be considered. Check 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	**Permanently discontinue ICPi.** Hematology consult Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms)

8.0 Hematologic Toxicities	
	If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue treatment IVIG used with corticosteroids when a more-rapid increase in platelet count is required If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary If previous treatment with corticosteroids and/or IVIG unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more-potent immunosuppression (From American Society of Hematology guideline on immune thrombocytopenia; consult for further details)
8.7 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

8.0 Hematologic Toxicities	
	Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms), ± rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1--2 mg/kg/d). Transfusion support as required for bleeding If worsening or no improvement add cyclosporine or immunosuppression/immunoadsorption
Additional considerations: The American Heart Association requires specialist clinical and laboratory expertise. Consult and/or transfer to a specialist center is often appropriate. If consultation with or transfer to a hemophilia center is not immediately possible, then investigation and treatment should be initiated while a liaison is being established. All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

AE=adverse event, ANC=absolute neutrophil count, ANCA=antineutrophil cytoplasmic antibodies; ATG=antithymocyte globulin, CMV=cytomegalovirus, CT=computed tomography, DIC=disseminated intravascular coagulation, EBV=Epstein-Barr virus, G=grade, GPI=glycosylphosphatidylinositol, Hgb=hemoglobin, HHV6=human herpesvirus 6, ICPi=immune checkpoint inhibitor, INR=international normalized ratio, irAE=immune-related adverse event, IV=intravenous, IVIG=intravenous immunoglobulin, LDH=lactate dehydrogenase, LLN=lower limit of normal, MRI=magnetic resonance imaging, NSAID=nonsteroidal anti-inflammatory drug, PB=peripheral blood, PEX=plasma ex-change, PNH=paroxysmal nocturnal hemoglobinuria, PT=prothrombin time, PTT=partial thromboplastin time, Q2W=every 2 weeks, RBC=red blood cell, TTP= thrombotic thrombocytopenic purpura.

Table A9 Management of Cardiovascular irAEs in Patients Treated With ICPis

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

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

BNP=brain natriuretic peptide, CT=computed tomography, CTPA=computed tomography pulmonary angiography, CXR=chest x-ray, DVT=deep vein thrombosis, ICPi=immune checkpoint inhibitor, irAE=immune-related adverse event, IV=intravenous, LMWH=low-molecular-weight heparin, MRI=magnetic resonance imaging, PE=pulmonary embolism, 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 20/40	Permanently discontinue ICPi Urgent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents
G4: 20/200 or worse	Permanently discontinue ICPi Emergent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents
Additional considerations: Consider use of infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment.	
10.3 Blepharitis	
Definition: Inflammation of the eyelid that affects the eyelashes or tear production Diagnostic work-up: As per 10.0	
Grading	**Management**
No formal grading system	Warm compresses and lubrication drops Continue therapy unless persistent and serious
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

ICPi=immune checkpoint inhibitor, irAE=immune-related adverse event, IV=intravenous, TNF=tumor necrosis factor.


CCI

Appendix 8 Protocol Amendment History

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

Note: changes incorporated into protocol version 4.1 CHN are not included in the current document.

Protocol Version 4.1-CHN (21 October 2020)

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

Overall Rationale for the Amendment

The key change to the protocol is to align the China-specific protocol with the changes made in Version 4.0 (global protocol amendment; 20 October 2020) which were to update the definitions for end of study and Survival Follow-up period, as described in the table below.

Section # and Name	Description of Change	Brief Rationale
Title Page Appendix 9 Sponsor Signature Page Appendix 10 Coordinating Investigator Signature Page Appendix 11 Principal Investigator Signature Page	Added the ClinicalTrials.gov number	For transparency and easy tracking
Title Page 6.1 Study Intervention 7.2 Participant Discontinuation/Withdrawal from the Study 8 Study Assessments and Procedures 8.2.3 Clinical Safety Laboratory Assessments 8.5 Pharmacokinetics CCI 8.10 Immunogenicity Assessments 9.4.3 Other Analyses Appendix 2 Study Governance	Added additional text or modified the previous text	To update wording to be consistent with current Sponsor protocol template
Title page	Updated Medical Monitor Name and Contact Information	Administrative change
1.1 Synopsis 8.2.4 Review Committees	Removed Contract Research Organization from Review Committees	To correct an error (Contract Research Organization is not a review committee)
1.1 Synopsis 1.3 Table 1 Schedule of Activities 4.1 Overall Design	Updated Survival Follow-up period and end of study definition	Provide sufficient survival follow up data collection for participants with long-term benefit

Section # and Name	Description of Change	Brief Rationale
4.4 End of Study Definition 7.2 Participant Discontinuation/Withdrawal from the Study Appendix 2 Study Governance		
1.3 Table 1 Schedule of Activities	Updated T4 and TSH Assessments & Procedures	To specify in Table 1 that Free T4 should be measured
CCI		
Throughout the document	Minor editorial, typographic, grammatical or administrative changes	Minor text revisions are made for clarity, readability, consistency of language across the development program, and compliance with current Sponsor guidelines

Protocol Version 4.0 (20 October 2020)

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

Overall Rationale for the Amendment

The key changes to the protocol are to update the definitions for end of study and Survival Follow-up period.

Section # and Name	Description of Change	Brief Rationale
Title Page Appendix 9 Sponsor Signature Page Appendix 10 Coordinating Investigator Signature Page Appendix 11 Principal Investigator Signature Page	Added the ClinicalTrials.gov number	For transparency and easy tracking
Title Page 6.1 Study Intervention 7.2 Participant Discontinuation/Withdrawal from the Study 8 Study Assessments and Procedures 8.2.3 Clinical Safety Laboratory Assessments 8.5 Pharmacokinetics CCI 8.10 Immunogenicity Assessments 9.4.3 Other Analyses Appendix 2 Study Governance	Added additional text or modified the previous text	To update wording to be consistent with current Sponsor protocol template

Section # and Name	Description of Change	Brief Rationale
Title page	Updated Medical Monitor Name and Contact Information	Administrative change
1.1 Synopsis 8.2.4 Review Committees	Removed Contract Research Organization from Review Committees	To correct an error (Contract Research Organization is not a review committee)
1.1 Synopsis 1.3 Table 1 Schedule of Activities 4.1 Overall Design 4.4 End of Study Definition 7.2 Participant Discontinuation/Withdrawal from the Study Appendix 2 Study Governance	Updated Survival Follow-up period and end of study definition	Provide sufficient survival follow up data collection for participants with long-term benefit
1.3 Table 1 Schedule of Activities	Updated T4 and TSH Assessments & Procedures	To specify in Table 1 that Free T4 should be measured
CCI [redacted]		
Throughout the document	Minor editorial, typographic, grammatical or administrative changes	Minor text revisions are made for clarity, readability, consistency of language across the development program, and compliance with current Sponsor guidelines

Protocol Version 3.1-CHN (14 March 2020)

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

Overall Rationale for the Amendment

The key change to the protocol is the addition of a China extension cohort to the study.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis (Overall Design, Number of Participants), 4.1 Overall Design, 5 Study Population	Details of the addition of a China extension cohort, into which participants will continue to be enrolled once global enrollment has been closed, were added.	The China extension cohort was added to satisfy a China regulatory request.
4.4 End of Study Definition	Text was added to accommodate the China extension cohort in the definition of end of study.	To describe the definition of the end of study for the China extension cohort.
1.3 Schedule of Activities, 7.2 Participant Discontinuation/Withdrawal from the Study, Appendix 2 Study Governance	Text was added defining the survival follow-up for participants enrolled in China.	To describe the extent of survival follow-up for participants in the China extension cohort.
9.2 Sample Size Determination	A justification for the sample size of the China extension cohort was added.	To explain the size decided for the China extension cohort.

Section # and Name	Description of Change	Brief Rationale
9.3 Populations for Analyses	Text was added stating that the Chinese participants enrolled in the China extension cohort after global enrollment is closed will not be included in the analysis sets specified in Table 9, and that China participants (including those enrolled both in global study and extension cohort) will be analyzed separately.	Per regulatory requirements.
1.1 Synopsis (Statistical Analyses), 9.4.4 Sequence of Analyses	The details of when the separate analyses of China participants will be performed were added.	To describe when the separate analyses of China participants will be performed.

Protocol Version 3.0 (10 October 2019)

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

Overall Rationale for the Amendment

The key changes of the protocol are:

- To clarify exclusion criteria of the study population and the management of immune-related adverse event and bleeding events during study intervention.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Clarified the exclusion criterion #13	To exclude participants with history of bleeding diathesis or recent major bleeding events
6.6.1 Adverse Drug Reactions Requiring Treatment Modification 6.9.5.1 Management of Bleeding Events	Added text to describe management of bleeding events	To provide guidelines for the management of bleeding events and indications for when participants should have study intervention held or discontinued
6.9.2 Immune-Related Adverse Events	Added text regarding Grade 4 events requiring permanent treatment discontinuation	For consistency with current risk information.
Appendix 6 Management of irAEs	Revised the recommendations for immune related adverse events (irAE) management	To update irAE management guidelines. Instructions include the requirement that treatment must be permanently discontinued for certain Grade 4 irAE toxicities.
Throughout the document	Minor editorial, typographic, grammatical or, administrative changes.	Minor text revisions are made for clarity, readability, consistency of language across the development program, and compliance with current Sponsor guidelines.

Protocol Version 2.0 (26 August 2019)

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

Overall Rationale for the Amendment

The key changes of the protocol are:

- To clarify eligibility criteria of the study population
- To modify non-serious adverse event of special interest (AESI) reporting
- To include separate consent forms for treatment after initial and confirmed progressive disease
- To revise the laboratory assessments
- To include CCI [redacted] per biliary tract cancer (BTC) subtype.

Section # and Name	Description of Change	Brief Rationale
Title Page	Updated the Sponsor name in Japan	To be consistent with current information
Title Page Appendix 9	Updated the Medical Responsible name and contact information	To be consistent with current information
1.1 Synopsis 1.2 Schema 4.1 Overall Designs and throughout the document as applicable	Sections updated	• To clarify that treatment up to 24 months will be applicable only for participants with confirmed complete response and that treatment beyond 24 months, it may be permissible after discussion with the Medical Monitor and the Sponsor Medical Responsible. • To correct an error about when tumor response evaluation will be performed.
Section 1.3 Table 1: Schedule of Activities	Removed mention of an abbreviated checklist for Day 1 for confirmation of eligibility	Abbreviated checklist will not be used to confirm the participant eligibility
	Updated note regarding tumor archival (deleted the following sentence: If no archival material is available and only 1 lesion is amenable for biopsy and it is the only target lesion, the Medical Monitor should be consulted for participant eligibility)	To remove the information about participant eligibility based on a discussion with Medical Monitor.
Section 1.3 Table 1 Schedule of Activities and throughout the document as applicable	CCI [redacted]	
	Updated note for premedication and M7824 administration	• To specify 'related' for the Grade 2 infusion reactions • To remove the specific time window for premedication

Section # and Name	Description of Change	Brief Rationale
	Updated note for laboratory assessment (hematology, serum chemistry and coagulation parameters)	• To clarify which laboratory tests must be reviewed before dosing and for consistency with Appendix 5. • To specify time points for the assessment of coagulation parameters. • To remove the information about participant eligibility based on a discussion with Medical Monitor.
	Updated note for β-HCG pregnancy test	For clarity and consistency
	Updated note for PRO assessments	Clarify the timing and the procedure of PRO questionnaires
	Updated note for patient interview	To clarify the countries who will follow this procedure in protocol
	Updated the tumor evaluation/staging assessment and notes	• Clarify the timing of tumor evaluation with confirm CR or PR • Tumor assessment should continue in any case until confirmed PD, regardless of subsequent anticancer therapy
Section 1.3 Table 2: M7824 Pharmacokinetic, Immunogenicity Sampling and throughout the document as applicable	Clarified the protocol deviation for PK blood sample when the time of collection is not recorded	To add clarity on protocol deviation definition regarding PK sampling
2. Introduction and throughout the document as applicable	Bintrafusp alfa was included as the international nonproprietary name for M7824	For consistency across the development program
3 Objectives and Endpoints	CCI [redacted]	
4.2 Scientific Rationale for Study Design	Addition of the following text: In this study participants who benefit from treatment will stay on treatment with frequent safety monitoring visits until unacceptable toxicity or loss of clinical benefit. Participants with confirmed CR will continue treatment for up to 24 months since confirmation of CR. In the M7824 program, participants have been exposed to M7824 beyond 12 months and the treatment was well tolerated. In Study MS200647-0008, some participants with objective responses had long lasting reduction in tumor size beyond 12 months under ongoing treatment. Treatment up to 24 months was also used with other checkpoint inhibitors published in 2L BTC (Ueno 2018). In addition, recent data showed continuous treatment beyond 12 months of nivolumab significantly	A scientific rationale for treatment up to 24 months was provided based on the published literature.

Section # and Name	Description of Change	Brief Rationale
	improved progression-free survival (PFS) in non-small cell lung cancer compared to 12-month treatment duration (Spigel 2017).	
4.3 Justification for dose	Reduced the section content and referred to the information provided in the Investigator's Brochure	To summarize the key information while providing source for detailed information, if needed
4.4 End of Study Definition	Added the following information: "The Sponsor may terminate the study at any time once access to study intervention for participants still benefitting is provided via a rollover study, expanded access, marketed product or another mechanism of access as appropriate."	To provide further clarification about end of study definition
5.1 Inclusion Criteria and throughout the document as applicable	Updated inclusion criterion 3	To clarify that no time window is needed for availability of tumor archival material or fresh biopsies
	Updated inclusion criterion 4	To clarify eligibility criteria for 2L participants
	Updated inclusion criterion 9 to delete "transfusion" (inclusion criterion 8 in the current protocol)	Transfusion is standard of care procedure in cancer patients
	Updated inclusion criterion 10 (inclusion criterion 9 in the current protocol)	To clarify inclusion criteria for subjects with biliary obstruction
	Updated inclusion criterion 16 (inclusion criterion 15 in the current protocol)	For consistency across the development program
5.1 Inclusion Criteria 5.2 Exclusion Criteria	Removed inclusion criterion 8 regarding curative cancer and added it as the exclusion criterion 5 with updated language	For clarity in the protocol
5.2 Exclusion Criteria and throughout the document as applicable	Updated exclusion criterion 7 (exclusion criterion 8 in the current protocol)	To revise this criterion to cover only specific disease situations
	Added exclusion criterion 16	To clarify eligibility criteria for 2L participants
	Updated exclusion criterion 25 (inclusion criterion 27 in the current protocol)	To add stenting/ percutaneous transhepatic biliary drainage procedures as an exception of exclusion criteria
5.4 Screen Failure	Section updated to avoid waiver and to provide clarification about rescreening.	To allow rescreening instead of extending the Screening window and to provide specific information about rescreening to the sites.
6.5.3 Prohibited Medicines	Section updated to: • exclude information already mentioned in the exclusion criteria • include prohibited procedures	• For clarity and to avoid repetition • To indicate that procedures as radio/chemo-embolization are prohibited since they can confound the efficacy results.
6.6.1 Adverse Drug Reactions Requiring Treatment Modification	Updated the definition and management of adverse drug reaction	For consistency across the development program
6.9 Management of Adverse Events of Special Interest	Updated non-serious AESI reporting	To discontinue expedited reporting of non-serious AESI

Section # and Name	Description of Change	Brief Rationale
and throughout the document as applicable		
6.9.1 Infusion-related Reactions Including Immediate Hypersensitivity	Addition of the following text: If IRR is observed at the first or second infusion, premedication should be used for subsequent infusions at the discretion of the Investigator.	To clarify as some sites had concerns that premedication is prohibited.
6.9.3. Skin Adverse Events	Updated the skin adverse events and the management of potential TGF-β mediated skin adverse events	For consistency across the development program and to provide guidelines on the management of potential TGF-β mediated skin adverse events
6.9.4 Treatment-related Anemia Appendix 4	Section updated to add information for new anemia events.	For consistency across the development program
6.9.5.3 Mild to moderate mucosal bleeding events	Included low grade mucosal bleeding events as additional potential risks	To be aligned with newly identified potential risk as per current Investigator's Brochure (Version 5)
7.1 Discontinuation of Study Intervention	• Inclusion of occurrence of exclusion criteria as a reason for participant withdrawn. • Deletion that nonpermitted concomitant drug can be approved by Sponsor and Medical Responsible	To clarify study discontinuation
7.1.2 Rechallenge	Section updated	To specify the rechallenge only after treatment discontinuation for PD. All other cases (discontinuation due to AEs, should be covered in the dose modifications section).
7.1.2.1 Treatment Beyond Initial Progression 7.1.2.2 Treatment Beyond Confirmed Progression	Updated criteria and treatment discontinuation information.	To include a separate informed consent if a participant wants to continue to receive treatment after disease progression as per the United States FDA request.
7.1.2.3 Continuation of Study Intervention After Local Treatment of Disease Progression	Included radiotherapy	To broaden the treatment options
8.1.1 Tumor Response	Added a note that measurable disease at Baseline will be made by IRC	For clarity
8.2.1 Physical Examinations and Vital Signs	Removed the following information: Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF.	To correct the text to be aligned with standard vital signs measurement
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious	Updated the timing for collecting Adverse Event and Serious Adverse Event Information	For consistency across the development program

Section # and Name	Description of Change	Brief Rationale
Adverse Event Information 8.3.3 Follow-up of Adverse Events and Serious Adverse Events		
8.5 Pharmacokinetics 9.4.3 Other Analyses	Section updated to delete detailed information about PK that will be included in the IAP	Information will be described in the IAP as indicated in Section 9.4.3
CCI		
9.3 Population for Analyses	Changes the analysis population from "Antidrug Antibody" to Immunogenicity Analysis Set"	For consistency across the development program
CCI		
9.4.4 Sequence of Analyses	• Deletion of the following text: Additional Interim Analyses Interim analyses at time points that are not specified in the protocol may be performed for internal planning purposes	Text related to the interim analyses was removed based on VHP feedback
Appendix 5	Appendix 5 (Liver Safety: Suggested Actions and Follow-up Assessments) was deleted	For consistency across the development program
Appendix 5 (previous Appendix 6)	• Deletion of bicarbonate • Addition of amylase • Incorrect cross-reference to footnote 'a' removed from the term 'Lipase' • Specified which laboratory tests must be reviewed before dosing.	To revise the laboratory assessments
Throughout the document	Minor editorial, typographic, grammatical or administrative changes.	Minor text revisions are made for clarity, readability, consistency of language across the development program, and compliance with current Sponsor guidelines.

Protocol Version 1.3 (31 May 2019)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

This protocol is being amended based on Chinese authorities request.

Section # and Name	Description of Change	Brief Rationale
Title Page Appendix 11	Update the Medical Responsible name and contact information	To be consistent with current information
1.3 Table 1: Schedule of Activities and throughout the document as applicable	CCI	
	Update laboratory assessment (coagulation)	To specify time points for the assessment of coagulation parameters
	CCI	
	Update the tumor evaluation/staging assessment and notes	Clarify the timing of tumor evaluation with confirm CR or PR
CCI		
5.1 Inclusion Criteria	Update inclusion criterion 4	To clarify eligibility criteria for second-line (2L) participants
5.2 Exclusion Criteria	Add exclusion criterion 15	To clarify eligibility criteria for 2L participants
CCI		
Appendix 6	Incorrect cross-reference to footnote ‘a’ removed from the term ‘Lipase’	To revise the laboratory assessments
Throughout the document	Minor editorial, typographic, grammatical or administrative changes.	Minor text revisions are made for clarity, readability, consistency of language across the development program, and compliance with current Sponsor guidelines.

Protocol Version 1.2 (01 February 2019)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The protocol is being amended based on a United States Food and Drug Administration request.

Section # and Name	Description of Change	Brief Rationale
Title Page; Appendix 11	Medical responsible amended to Motonobu Osada	To update medical responsible person.
7.1.2.1Treatment Beyond Initial Progression	Addition of the following text: • Participants must sign a separate informed consent to ensure that they are aware of being treated beyond initial progression.	To include a separate informed consent if a participant wants to continue to receive treatment after disease progression as per the USA FDA's request.
7.1.2.2Treatment Beyond Confirmed Progression	Addition of following text: To qualify for treatment beyond confirmed progression: • Participants must sign a separate informed consent to ensure that they are aware of being treated beyond confirmed progression. • Investigators must document clinical judgment to justify the continuation of study drug rather than other possible alternative treatments. Treatment should be discontinued permanently in case of any overall, meaningful and unequivocal further increase in tumor burden after confirmation of PD. As a general guidance, a meaningful increase, for example, may represent an approximately 10% increase in tumor burden, considering the totality of all existing target lesions, non-target lesion burden, existing new lesions, and any further new lesions. Note: This 10% increase is provided as a general guide to be interpreted considering the clinical condition of the participant and any other considerations which the Investigator feels relevant, such as the availability of alternative treatments. In unclear situations, the Investigator should consult with the Medical Monitor, and the wellbeing of the individual participant should be the key consideration in determining the continuation of study drug after confirmed progression.	To include a separate informed consent if a participant wants to continue to receive treatment after disease progression as per the USA FDA's request.

Protocol Version 1.1 (15 January 2019)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The protocol is being amended based on VHP request.

Section # and Name	Description of Change	Brief Rationale
4.2 Scientific Rationale for Study Design	Addition of the following text: Treatment in this study is limited to 24 months. Only participants who benefit from treatment (either stable disease, PR, or CR) will stay on treatment with frequent safety monitoring visits. In the M7824 program, participants have been exposed to M7824 beyond 12 months and the treatment was tolerated. In study MS200647_0008, some participants with objective responses had long lasting tumor shrinkages beyond 12 months under ongoing treatment. Treatment up to 24 months was also used with other checkpoint inhibitors published in 2L BTC (Ueno 2018). In addition, recent data showed continuous treatment beyond 12 months of nivolumab significantly improved progression-free survival (PFS) in non-small cell lung cancer (NSCLC) compared to 12-month treatment duration (Spigel 2017).	A scientific rationale for treatment up to 24 months was provided based on the published literature.
6.5.3 Prohibited Medicines	Addition of the following text: Concomitant local or regional treatment (radio/chemo-embolization) are not permitted.	To provide direction to sites that radio/chemo-embolization are not allowed as they can confound the efficacy results of M7824 monotherapy.
9.4.4 Sequence of Analyses	Deletion of the following text: Additional Analyses Interim analyses at time points that are not specified in the protocol may be performed for internal planning purposes.	Text related to the interim analyses was removed based on VHP feedback.

Appendix 9 Sponsor Signature Page

Study Title:	A Phase II, Multicenter, Open-label Study to Investigate the Clinical Efficacy of M7824 Monotherapy in Participants With Locally Advanced or Metastatic Biliary Tract Cancer Who Fail or are Intolerant to First-line Platinum-Based Chemotherapy
Regulatory Agency Identifying Numbers:	IND: CCI EudraCT: 2018-003707-19 ClinicalTrials.gov: NCT03833661
Clinical Study Protocol Version:	22 June 2021/Version 5.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	Protocol Lead
Institution:	EMD Serono Research & Development Institute, Inc. (Affiliate of Merck KGaA, Darmstadt, Germany)
Address:	45A Middlesex Turnpike, Billerica, MA 01821, USA
Telephone number:	PPD
Fax number:	Not applicable
E-mail address:	PPD

Appendix 10 Coordinating Investigator Signature Page

Study Title:	A Phase II, Multicenter, Open-label Study to Investigate the Clinical Efficacy of M7824 Monotherapy in Participants With Locally Advanced or Metastatic Biliary Tract Cancer Who Fail or are Intolerant to First-line Platinum-Based Chemotherapy
Regulatory Agency Identifying Numbers:	IND: CCI EudraCT: 2018-003707-19 ClinicalTrials.gov: NCT03833661
Clinical Study Protocol Version:	22 June 2021/Version 5.0
Site Number:	101

I approve the design of the clinical study, am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

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

Appendix 11 Principal Investigator Signature Page

Study Title:	A Phase II, Multicenter, Open-label Study to Investigate the Clinical Efficacy of M7824 Monotherapy in Participants With Locally Advanced or Metastatic Biliary Tract Cancer Who Fail or are Intolerant to First-line Platinum-Based Chemotherapy
Regulatory Agency Identifying Numbers:	IND: CCI EudraCT: 2018-003707-19 ClinicalTrials.gov: NCT03833661
Clinical Study Protocol Version:	22 June 2021/Version 5.0
Site Number:	

I am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

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

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: