Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase II/III, Multicenter, Randomized, Placebo-controlled Study of Gemcitabine Plus Cisplatin With or Without Bintrafusp alfa (M7824) as First-line Treatment of Biliary Tract Cancer
Study Number:	MS200647_0055
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Study Phase:	Phase II/III
Short Title:	1L BTC Phase II/III Gemcitabine Plus Cisplatin With or Without Bintrafusp alfa (M7824)
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Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	15 May 2019
1.1	Region-specific amendment (EU countries participating in the Voluntary Harmonisation Procedure)	19 September 2019
2.0	Global Amendment	11 October 2019
2.1	Region-specific amendment (Taiwan and Korea)	3 December 2019
3.0	Global Amendment	27 July 2020
4.0	Global Amendment	20 April 2021
5.0	Global Amendment	14 July 2021

Protocol Version 5.0 (14 July 2021)

Overall Rationale for the Amendment

The primary driver for this nonsubstantial amendment is to include additional information to be taken into consideration by the Independent Data Monitoring Committee (IDMC) for expansion into Phase III.

Section # and Name	Description of Change	Brief Rationale
Title Page	Removed rows for Medical Monitor and Approval Date.	Text has been updated for consistency with Merck protocol standards.
Synopsis, Overall Design Synopsis, Number of Participants Synopsis, Involvement of Special Committee(s) 4.1 Overall Design 4.1.2 Randomized, Double-blind Part Figure 2 Outline of Randomized, Double-blind Study Design	Text has been revised to include a summary of the additional criterion for expansion into Phase III.	An expansion criterion was added to increase confidence in a sufficiently large beneficial effect of bintrafusp alfa under the evolving treatment landscape before expanding treatment to additional participants.

Section # and Name	Description of Change	Brief Rationale
4.2 Scientific Rationale for Study Design [redacted]		
2.3 Risk/Benefit Assessment	Text has been revised to include the most up-to-date assessment.	Revisions are made for consistency with other program documents.
4.2 Scientific Rationale for Study Design	Text has been revised to include additional rationale for the study expansion criteria.	An expansion criterion was added to increase confidence in a sufficiently large beneficial effect of bintrafusp alfa under the evolving treatment landscape before expanding treatment to additional participants.
5.2 Exclusion Criteria	Exclusion criterion 10 has been split into 2 separate bullets without change in content.	The criterion was split at the request of the VHP.
6.6.1 Dosing Instructions	Text related to local requirements for dosing of gemcitabine and cisplatin has been revised. Links to Sections 6.6.3 and 6.6.4 referring to dose modification instructions for gemcitabine and cisplatin were added.	Revisions were made to improve clarity.
6.6.4 Dose Modification of Gemcitabine, Cisplatin, and Bintrafusp alfa/Placebo for Renal Impairment	Text was added to clarify no other CrCl formula should be used.	The text was added to clarify a study procedure.
6.9.5 Bleeding Events	Text was restructured (without changing content).	The text was revised for clarity and consistency with other program documents.
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/III, Multicenter, Randomized, Placebo-controlled Study of Gemcitabine Plus Cisplatin With or Without Bintrafusp alfa (M7824) as First-line Treatment of Biliary Tract Cancer

Short Title: 1L BTC Phase II/III Gemcitabine Plus Cisplatin With or Without Bintrafusp alfa (M7824)

Rationale: The global standard of care (SoC) for first-line (1L) chemotherapy for locally advanced or metastatic biliary tract cancer (BTC) is a combination of gemcitabine and cisplatin (National Comprehensive Cancer Network [NCCN] and European Society for Medical Oncology [ESMO] guidelines), however, the prognosis of patients with advanced BTC remains limited. Bintrafusp alfa (M7824), a first-in-class, bifunctional fusion protein, targets the programmed death-ligand 1 (PD-L1) and human transforming growth factor beta (TGFβ), both major mechanisms of immunosuppression in the tumor microenvironment. Moreover, combination chemotherapy regimens that include a PD-L1 inhibitor may maximize the chance of tumor response to cytotoxic chemotherapy, leading to prolonged survival. Clinically, bintrafusp alfa monotherapy has shown promising clinical efficacy signals in second-line (2L) treatment of BTC, suggesting that bintrafusp alfa immunotherapy in combination with chemotherapy could be a reasonable approach to improve standard 1L treatment. The current study aims to evaluate whether bintrafusp alfa in combination with gemcitabine plus cisplatin improves overall survival (OS) in advanced BTC compared with SoC (gemcitabine plus cisplatin) alone. This approach is supported by scientific evidence and promising clinical efficacy data with the goal of fulfilling an unmet medical need and bringing clinical benefit to patients.

Objectives and Endpoints:

Objectives	Endpoints (Outcome Measures)
Open-label, Safety Run-in	
To assess the following items with bintrafusp alfa 2400 mg once every 3 weeks in combination with gemcitabine and cisplatin in locally advanced or metastatic biliary tract cancer (BTC)	
Primary	
To assess if bintrafusp alfa 2400 mg once every 3 weeks is safe and tolerable and to confirm this dose as the recommended Phase II dose for the randomized, double-blind part of the study	Occurrence of dose-limiting toxicities (DLTs) during the DLT evaluation period
Secondary	
To assess the safety profile of bintrafusp alfa in combination with gemcitabine and cisplatin	• Occurrence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (AEs) • Occurrence of abnormalities (Grade ≥ 3) in laboratory tests

Objectives	Endpoints (Outcome Measures)
Randomized, Double-blind Part	
To assess the following items with bintrafusp alfa in combination with gemcitabine plus cisplatin versus placebo with gemcitabine plus cisplatin in participants with advanced or metastatic BTC who have not received chemotherapy/immunotherapy in the advanced/metastatic setting	
Primary	
To assess overall survival (OS)	OS
Secondary	
To assess progression-free survival (PFS)	PFS according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as assessed by the Investigator[a]
To assess objective response rate (ORR)	Confirmed objective response according to RECIST 1.1 as assessed by the Investigator[a]
To assess duration of response (DOR)	DOR assessed by confirmed complete response or partial response until death or progression of disease according to RECIST 1.1 as assessed by the Investigator[a]
To assess durable response rate (DRR)	Durable confirmed response of at least 6 months according to RECIST 1.1 as assessed by the Investigator[a]
To assess the safety profile of bintrafusp alfa or placebo in combination with gemcitabine plus cisplatin	Occurrence of TEAEs and treatment-related AEs, including adverse events of special interest (AESI)
To characterize the pharmacokinetic (PK) profile of bintrafusp alfa	• PK profile of bintrafusp alfa in terms of C_{eoi} and C_{trough} for participants in the bintrafusp alfa arm • PK profile of bintrafusp alfa in terms of AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{½}$ for participants in the safety run-in part of the study only
To evaluate the immunogenicity of bintrafusp alfa and to correlate it to exposure	Immunogenicity as measured by antidrug antibody assays at baseline and on-treatment for participants in the bintrafusp alfa arm

AUC_{0-t}=area under the concentration-time curve (AUC) from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification, $AUC_{0-\infty}$=AUC from time zero extrapolated to infinity, based on the predicted value for the concentration at the last sampling time, C_{eoi}=concentration observed immediately at the end of infusion, C_{max}=maximum observed concentration, C_{trough}=concentration observed immediately before next dosing, IRC=Independent Review Committee, $t_{½}$=apparent terminal half-life, t_{max}=time to reach the maximum observed concentration collected during a dosing interval.

a If the study is not expanded to Phase III, tumor-based efficacy endpoints will also be assessed as per the IRC.

Overall Design: This is a multicenter study consisting of an open-label, safety run-in part followed by a randomized, double-blind, placebo-controlled Phase II/III part.

- The open-label, safety run-in part will confirm the safety and tolerability of 1L bintrafusp alfa in combination with gemcitabine and cisplatin in chemotherapy and immunotherapy-naive participants with locally advanced or metastatic BTC. Dose-limiting toxicity (DLT) will be evaluated in 2 separate regional cohorts (Asian sites and non-Asian sites) in the first 21 days following the first dose of bintrafusp alfa. Six DLT-evaluable participants will be recruited sequentially in each cohort, with an additional 6 participants recruited if DLT is observed in 2

or 3 participants. If DLT is observed in ≤ 1 (of 6) or ≤ 3 (of 12) participants, the region may start to enroll participants into the randomized, double-blind part of the study.

- The randomized, double-blind, placebo-controlled Phase II/III part will evaluate whether bintrafusp alfa in combination with the current SoC (gemcitabine plus cisplatin) improves OS in chemotherapy and immunotherapy-naive participants with locally advanced or metastatic BTC compared with placebo, gemcitabine, and cisplatin. Initial 150 participants recruited in Phase II who have no documentation (electronic case report form (eCRF)) of any systemic antibiotic treatment within 30 days prior to randomization (antibiotics-naive) will be analyzed for efficacy for an expansion decision for full Phase III sample size. If the prespecified criteria are met, the study will be expanded into Phase III. If the study is not expanded to Phase III, it will be completed as a Phase II study.

Unless otherwise specified, all study assessments apply to both the open-label, safety run-in and the randomized, double-blind parts of the study.

Number of Participants: The planned number of participants in the study is a maximum of 524:

- 12 to 24 participants in the open-label, safety run-in part of the study
- Up to 300 participants or 500 participants in Phase II/III, if expanded.

The randomized, double-blind, placebo-controlled part has an adaptive design that allows for expansion of Phase II into Phase III through the enrollment of additional participants. The analysis for the adaptation decision will be conducted in the first 150 antibiotics-naive participants, when 80 PFS events have occurred and once at least 19 weeks of follow-up for the first 150 antibiotics-naive participants randomized is reached.

Expansion into Phase III will take place if:

If the study will not be expanded to full Phase III sample size, the Independent Data Monitoring Committee (IDMC) will consider to make a recommendation to stop the study early for futility if the observed PFS HR is > 1 and taking into account the totality of available data including available OS data at this point.

The sample size calculation for the randomized, double-blind part is based on the following assumptions:

- 1:1 randomization
- Alpha of 0.025 (1-sided)
- Exponential distribution of OS

- OS HR of 0.70 corresponding to an increase in median OS from 11.7 months in the control arm to 16.7 months in the bintrafusp alfa arm, expected dropout rate of 5% at 40 months
- Assumptions for the adaptation decision analysis:
  - ORR odds ratio of 2.0 corresponding to 25% ORR in the control arm and 40% ORR in the bintrafusp alfa arm
  - PFS HR of 0.65 corresponding to an increase in median PFS from 5.8 months in the control arm to 8.9 months in the bintrafusp alfa arm; expected dropout rate of 15%.
  - Exponential distribution of PFS.

Study Intervention Groups and Duration:

In the open-label, safety run-in part, participants will receive bintrafusp alfa (2400 mg every 3 weeks) in combination with gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) administered on Day 1 and Day 8 for 8 cycles every 3 weeks, followed by bintrafusp alfa (2400 mg every 3 weeks) until 1 of the criteria for discontinuation is met.

In the randomized, double-blind part, participants will be randomized in a 1:1 ratio to receive either bintrafusp alfa (2400 mg) or matching placebo once every 3 weeks. Participants in both the bintrafusp alfa and placebo arms will also receive gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) on Day 1 and Day 8 for 8 cycles every 3 weeks. Treatment with bintrafusp alfa or placebo will continue until 1 of the criteria for discontinuation is met (see below). Randomization will be stratified according to the following factors:

- Type of BTC (based on 3 anatomical locations, i.e., intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma including ampulla of Vater's cancer, and gallbladder cancer)
- Metastatic at diagnosis versus others, where "others" includes participants with unresectable, locally advanced disease at diagnosis and participants with resectable disease at diagnosis who have undergone prior surgical resection with curative intent
- Asia sites versus non-Asia sites

In participants with complete response (CR), bintrafusp alfa/placebo should continue for 2 years after the first onset of CR or until 1 of the criteria for discontinuation is met, whichever occurs first. In all other cases, bintrafusp alfa/placebo should continue until 1 of the criteria for discontinuation is met. All participants should receive 8 cycles of gemcitabine and cisplatin. Any missed dose(s) of chemotherapy may be made up at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination) provided the participant does not meet any of the criteria for discontinuation.

Two Safety Follow-up Visits will be performed: at 28 days (± 7 days) and 12 weeks (± 2 weeks) after the last dose of treatment.

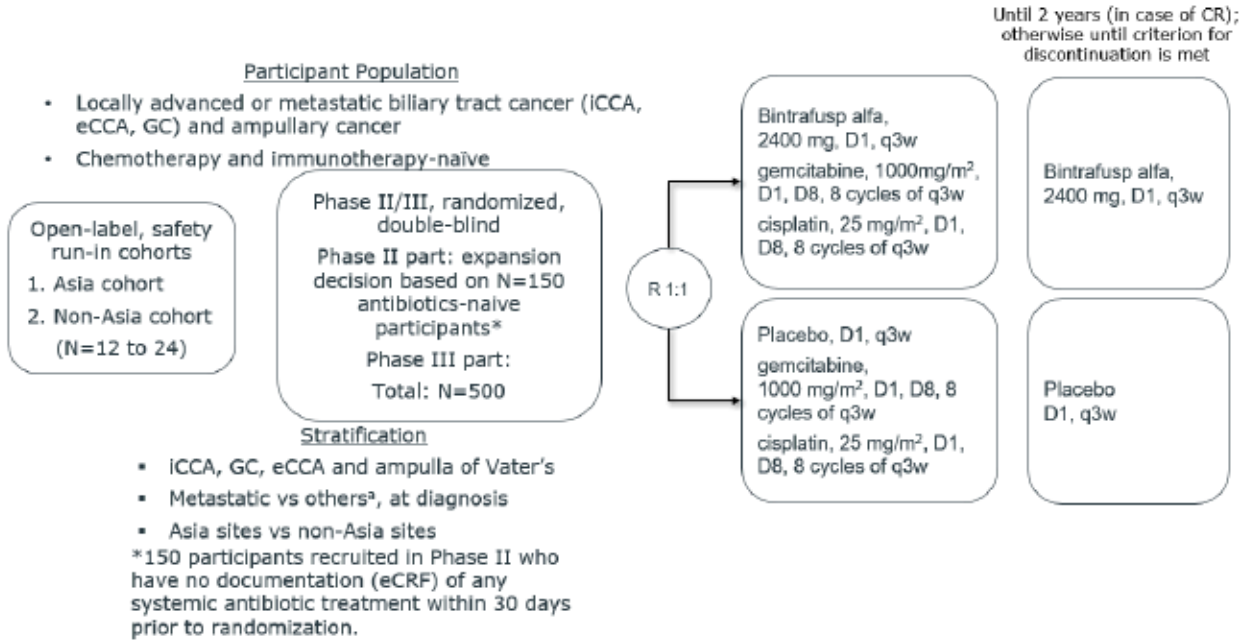
Long-term follow-up, including survival follow-up, will be performed every 3 months (± 2 weeks) (or every 6 weeks [± 1 week] if the participant has initiated and continuing 2L treatment) after the 12-week Safety Follow-up Visit, unless the participant is reported as lost to follow-up, dead, or after study termination.

Involvement of Special Committee(s): Yes

- A Safety Monitoring Committee (SMC) will assess safety of participants in the open-label, safety run-in part
- An IDMC will undertake periodic review of safety data throughout the randomized, double-blind part of the study. In order to make a recommendation regarding the expansion of the study into Phase III, the IDMC will review efficacy data from the first 150 antibiotics-naive participants enrolled in Phase II and safety data for all participants treated in the study until the data cutoff of this analysis. In the event that the study is expanded to 500 participants as a Phase III (further to the analysis for adaptation decision), the IDMC will be requested to review participants' efficacy and safety data and could recommend that the study be stopped earlier for efficacy or futility.
- An Independent Review Committee (IRC) will review radiographic image findings for the determination of objective response and date of disease progression for the Phase II part of the study, and may be requested to do this also for the Phase III part of the study.

1.2 Schema

Figure 1 Overall Study Design Schema



eCRF=electronic case report form, CR=complete response, D=day, eCCA=extrahepatic cholangiocarcinoma, GC=gallbladder cancer, iCCA=intrahepatic cholangiocarcinoma, N=number of participants, q3w=every 3 weeks, R=randomization.

a "Others" includes participants with unresected, locally advanced disease at diagnosis and participants with resectable disease at diagnosis who have undergone prior surgical resection with curative intent.

1.3 Schedule of Activities

The Schedule of Activities, as described in Table 1 and Table 2, is the same for both parts of the study, i.e., for participants in the open-label, safety run-in part and those in the randomized, double-blind part, except where indicated. See Table 3 and Table 4 for the Schedule of Activities with respect to sampling for CCI pharmacokinetics (PK), and CCI for the open-label, safety run-in part and the randomized, double-blind part, respectively.

Note: all activities/procedures should be scheduled from Week 1, Day 1 (W1D1).

Table 1 Schedule of Activities – Day 1 to Day 168 (Bintrafusp alfa/Placebo Plus Chemotherapy)

Activities	Screening/ Baseline	Treatment Phase (± 3 Days)[a]																Notes
		Week																[a]If a participant discontinues treatment, see Table 2 for next steps
	Day -28 up to Day 1	1	2	4	5	7	8	10	11	13	14	16	17	19	20	22	23	
		Day																
		1	8	22	29	43	50	64	71	85	92	106	113	127	134	148	155	
Administrative Procedures																		
Written informed consent	X																	
Inclusion/exclusion criteria	X	X																Day 1, specified items only in Sections 5.1 and 5.2
Demographic data	X																	
Medical history	X																	Include: history of BTC with stage at diagnosis, environmental/occupational exposure to chemicals, baseline medical conditions
Prior anticancer drug/radiotherapy/ procedures	X																	
Documentation of concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every visit
Enrollment/ randomization	X	X																Enrollment requires prior confirmation that participant fulfills all inclusion criteria and no exclusion criteria. Randomization on Day 1 via IXRS. Administration of the first dose of study intervention should be initiated within 3 days after randomization.

Activities	Screening/ Baseline	Treatment Phase (± 3 Days)[a]																Notes
		Week																[a]If a participant discontinues treatment, see Table 2 for next steps
	Day -28 up to Day 1	1	2	4	5	7	8	10	11	13	14	16	17	19	20	22	23	
		Day																
		1	8	22	29	43	50	64	71	85	92	106	113	127	134	148	155	
Documentation of non-protocol related hospitalizations, emergency room visits, and outpatient hospital visits		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every visit
[redacted]																		

Activities	Screening/ Baseline	Treatment Phase (± 3 Days)[a]															Notes
		Week															[a]If a participant discontinues treatment, see Table 2 for next steps
	Day -28 up to Day 1	1	2	4	5	7	8	10	11	13	14	16	17	19	20	22	23
		Day															
		1	8	22	29	43	50	64	71	85	92	106	113	127	134	148	155
Study Intervention Administration																	

Activities	Screening/ Baseline	Treatment Phase (± 3 Days)[a]																Notes
		Week																[a]If a participant discontinues treatment, see Table 2 for next steps
	Day -28 up to Day 1	1	2	4	5	7	8	10	11	13	14	16	17	19	20	22	23	
		Day																
		1	8	22	29	43	50	64	71	85	92	106	113	127	134	148	155	
Premedication and bintrafusp alfa/placebo administration		X[c]		X[c]		X		X		X		X		X		X		Bintrafusp alfa/placebo: W1D1, Q3W. [c]Premedication with an antihistamine and paracetamol (acetaminophen) approximately 30-60 minutes prior to each dose is mandatory for the first 2 infusions only (e.g., 25-50 mg diphenhydramine and 500-650 mg paracetamol IV or oral equivalent). All premedication must be reported in the eCRF. If bintrafusp alfa/placebo cannot be administered on D1 ± 3 days of a given cycle (for safety, tolerability or other unavoidable reasons), the dosing can be postponed for up to +18 days (except for W1D1), after which the dose will be considered omitted. If bintrafusp alfa/placebo dosing schedule is shifted, other activities scheduled on D1 which have not been done before the decision will be shifted accordingly. The safety assessment must be done on the day of dosing and the blood samples for full chemistry and hematology must be drawn a day before or on the day prior to dosing. The next cycle of bintrafusp alfa/placebo will get back to the original schedule but should be administered at least 15 days (= minimal interval calculated with Q3W ± 3 days window) apart from the previous cycle. If the minimal interval is not maintained, the next cycle should be skipped. Contact Medical Monitor for any questions on dosing schedule. If further schedule change is needed, an approval from the Medical Monitor is required.

Activities	Screening/ Baseline	Treatment Phase (± 3 Days)[a]																Notes
		Week																[a]If a participant discontinues treatment, see Table 2 for next steps
	Day -28 up to Day 1	1	2	4	5	7	8	10	11	13	14	16	17	19	20	22	23	
		Day																
		1	8	22	29	43	50	64	71	85	92	106	113	127	134	148	155	
Premedication/ hydration and gemcitabine/cisplatin		X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	D1 and D8, Q3W for 8 cycles. [d]Administer cisplatin premedication, anti-emetic drugs (excluding steroids, see Section 6.6.1), and IV hydration (during cisplatin infusion to prevent nephrotoxicity) as per standard practice. All premedication, including hydration (drugs and fluids) must be reported in the eCRF.
		If chemotherapy cannot be administered on D1 or D8 of a given cycle (for safety, tolerability or other unavoidable reasons), it may be administered on D15 of that cycle. In addition, any missed dose(s) of chemotherapy may be made up at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination) provided the participant does not meet any of the criteria for discontinuation from study intervention or study participation (Section 7). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision. See Table 2 for further information. If a missed dose of chemotherapy is administered at an additional visit, the safety assessments detailed in Table 1 for W1D8 should be completed, i.e., documentation of concomitant medications and procedures; documentation of non-protocol related hospitalizations, emergency room visits, and outpatient hospital visits; documentation of AEs, physical examination, vital signs, SpO_2, and core chemistry and hematology.																	
Physical Assessment																		
Documentation of AEs and SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every visit
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every visit. Complete PE at Screening and brief PE at all other visits.
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every visit, including height (at Screening only), weight, temperature, pulse rate, respiratory rate, and blood pressure.

Activities	Screening/ Baseline	Treatment Phase (± 3 Days)[a]															Notes
		Week															[a]If a participant discontinues treatment, see Table 2 for next steps
	Day -28 up to Day 1	1	2	4	5	7	8	10	11	13	14	16	17	19	20	22	23
		Day															
		1	8	22	29	43	50	64	71	85	92	106	113	127	134	148	155
ECOG PS	X	X		X		X		X		X		X		X		X		ECOG PS of 0 or 1 required at W1D1 prior to dosing
Skin assessment	X	X				X				X				X				Q6W
12-lead ECG	X																	
SpO_2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every visit, using pulse oximeter
Laboratory Assessments																		
Full chemistry and hematology	X	X		X		X		X		X		X		X		X		See Appendix 6 (Table- A) for full chemistry and hematology/coagulation parameters. Blood samples must be drawn a day before or on the day prior to dosing. Results of asterisked parameters (*) must be reviewed by Investigator before dosing. Review results of other parameters within 5 working days of visit.
Core chemistry and hematology			X		X		X		X		X		X		X		X	See Appendix 6 (Table- B) for core chemistry and hematology parameters to be evaluated at visits where full panel is not required. Blood samples must be drawn a day before or on the day prior to dosing. Results of asterisked parameters (*) must be reviewed by Investigator before dosing. Review results of other parameters within 5 working days of visit.
Anemia	As clinically indicated																	See Appendix 6 (Table- C) for parameters to be assessed
CA19-9	X					X				X				X				Q6W. See Appendix 6 (Table- F)

Activities	Screening/ Baseline	Treatment Phase (± 3 Days)[a]															Notes
		Week															[a]If a participant discontinues treatment, see Table 2 for next steps
	Day -28 up to Day 1	1	2	4	5	7	8	10	11	13	14	16	17	19	20	22	23
		Day															
		1	8	22	29	43	50	64	71	85	92	106	113	127	134	148	155
Urinalysis	X	X				X				X				X				Q6W. Full urinalysis (dipstick plus microscopy) at Screening and EoT Visits; basic urinalysis (only dipstick is required but not microscopy) at other indicated visits prior to dosing. Results of basic urinalysis must be reviewed before dosing. If basic urinalysis is abnormal, a full urinalysis plus culture should be performed. See Appendix 6 (Table- D) for parameters to be assessed.
Pregnancy test	X	X		X		X		X		X		X		X		X		Q3W. Serum or highly sensitive urine hCG pregnancy test (for women of childbearing potential). Note: Local urine testing is standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
ACTH, ANA, ANCA, and RF		As clinically indicated																See Appendix 6 (Table- F)
Hepatitis	X					X				X				X				HBV and HCV serology at baseline. If one or more of the following, HB-surface antigen, HB-core antibody /or HB-surface antibody are positive at baseline, examine HBV DNA at screening and Q6W during the study. If baseline HCV antibody is positive, examine HCV RNA. If HCV RNA is positive, monitor HCV RNA Q6W. See Appendix 6 (Table- E). Review results within 5 working days of visit.
Free T4 and TSH	X					X				X				X				Q6W. See Appendix 6 (Table- F). Review results within 5 working days of visit.
KL-6, SP-A, and SP-D	X			X		X		X		X		X		X		X		**Japanese sites only**. Q3W. See Appendix 6 (Table- F). Review results within 5 working days of visit.

Activities	Screening/ Baseline	Treatment Phase (± 3 Days)[a]															Notes
		Week															[a]If a participant discontinues treatment, see Table 2 for next steps
	Day -28 up to Day 1	1	2	4	5	7	8	10	11	13	14	16	17	19	20	22	23
		Day															
		1	8	22	29	43	50	64	71	85	92	106	113	127	134	148	155
CCI [redacted]																	

Document No. CCI [redacted]
Object No. CCI [redacted]

Document No. CCI [redacted]
Object No. CCI [redacted]

CCI

ACTH=adrenocorticotropic hormone, CCI , AEs=adverse events, CCI ,
BTC=biliary tract cancer, CA19-9=carbohydrate antigen 19-9, CT=computed tomography, D=day, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group performance status, eCRF=electronic Case Report Form, CCI EoT=End of Treatment, CCI , EU=European Union,
HB=hepatitis B, HBV=hepatitis B virus, hCG=human chorionic gonadotropin, HCV=hepatitis C virus, IL=Item Library, IRB/IEC=Institutional Review Board/Independent Ethics Committee, IV=intravenous, IXRS=interactive response system, KL-6=Krebs von den Lungen-6, MRI=magnetic resonance imaging, PD=progressive disease, PE=physical examination, CCI , CCI ,
PK=pharmacokinetics, CCI , Q3W=every 3 weeks, Q6W=every 6 weeks, Q12W=every 12 weeks, CCI
RF=rheumatoid factor, RNA=ribonucleic acid, SAEs=serious adverse events, SP-A/D=surfactant protein A/D, SpO_2=blood oxygen saturation, T4=thyroxine, TSH=thyroid-stimulating hormone, W=week, US=United States

Table 2 **Schedule of Activities – Day 169 Onwards (Bintrafusp alfa/Placebo Monotherapy) and Activities Following Study Intervention Discontinuation**

Activities	Treatment Phase (± 3 days)[a]								End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Week												[a]If treatment continues beyond Week 43/Day 295, continue assessments until EoT, as indicated in the table [b]Decision to stop study intervention
	25	28	31	34	37	40	43[a]						
	Day												
	169	190	211	232	253	274	295[a]	Until EoT	On Day of or Within 7 Days of Decision[b]	28 (± 7) Days After Last Treatment	12 (± 2) Weeks After Last Treatment	Every 3 Months (± 2 Weeks)	
Administrative Procedures – Documentation of:													
Subsequent anticancer therapy										X	X	X	
Concomitant medications and procedures	X	X	X	X	X	X	X	Q3W	X	X			
Non-protocol-related hospitalization, emergency room visits, outpatient hospital visits	X	X	X	X	X	X	X	Q3W	X	X			
CCI [redacted]													
Study Intervention Administration													
Premedication and bintrafusp alfa / placebo administration	X	X	X	X	X	X	X	Q3W					Bintrafusp alfa/placebo: W1D1, Q3W Premedication is mandatory for first 2 infusions only (see Table 1)

Activities	Treatment Phase (± 3 days)[a]								End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Week												[a]If treatment continues beyond Week 43/Day 295, continue assessments until EoT, as indicated in the table [b]Decision to stop study intervention
	25	28	31	34	37	40	43[a]			28 (± 7) Days After Last Treatment	12 (± 2) Weeks After Last Treatment	Every 3 Months (± 2 Weeks)	
	Day												
	169	190	211	232	253	274	295[a]	Until EoT	On Day of or Within 7 Days of Decision[b]				
Premedication /hydration, and gemcitabine/ cisplatin	If chemotherapy cannot be administered on D1 or D8 of a given cycle (for safety, tolerability or other unavoidable reasons), it may be administered on D15 of that cycle. In addition, any missed dose(s) of chemotherapy may be made up at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination) provided the participant does not meet any of the criteria for discontinuation from study intervention or study participation (Section 7). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision. Resuming chemotherapy after an interruption of more than 12 weeks should be discussed with the Medical Monitor (see Section 6.6.3) Missed doses of chemotherapy should be made up as follows: • Administer Day 1 of an any missed dose of chemotherapy on D1 W1 of the next appropriate scheduled dosing with bintrafusp alfa/placebo, i.e., Week 25, 28, 31, 34, 37, 40, 43, etc • To enable administration of chemotherapy on Day 8, schedule an additional visit 7 days later, i.e., at Weeks 26, 29, 32, 35, 38, 41, and/or 44, etc, as appropriate If a missed dose of chemotherapy is administered at an additional visit, the safety assessments detailed in Table 1 for W1D8 should be completed, i.e., documentation of concomitant medications and procedures, documentation of non-protocol related hospitalizations, emergency room visits, and outpatient hospital visits, documentation of AEs, physical examination, vital signs, SpO_2, and core chemistry and hematology												D1 and D8, Q3W for 8 cycles. Administer cisplatin premedication, anti-emetic drugs (excluding steroids, see Section 6.6.1), and IV hydration (during cisplatin infusion to prevent nephrotoxicity) as per standard practice. All premedication, including hydration (drugs and fluids) must be reported in the eCRF.
Physical Assessments													
Documentation of AEs and SAEs	X	X	X	X	X	X	X	Q3W	X	X	X[c]	X	At every visit. [c]According to the definition of AE reporting period and follow-up of AEs/SAEs. Conduct 12-week Safety Follow-up Visit and Long-term Follow-up Visit via telephone calls or patient chart reviews unless there is medical necessity for a clinical visit.
Physical examination	X	X	X	X	X	X	X	Q3W	X	X			Brief physical examination
Vital signs	X	X	X	X	X	X	X	Q3W	X	X			Including weight, temperature, pulse rate, respiratory rate, and blood pressure
ECOG PS	X		X		X		X	Q6W	X	X			

Activities	Treatment Phase (± 3 days)[a]								End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Week									28 (± 7) Days After Last Treatment	12 (± 2) Weeks After Last Treatment	Every 3 Months (± 2 Weeks)	[a]If treatment continues beyond Week 43/Day 295, continue assessments until EoT, as indicated in the table [b]Decision to stop study intervention
	25	28	31	34	37	40	43[a]						
	Day												
	169	190	211	232	253	274	295[a]	Until EoT	On Day of or Within 7 Days of Decision[b]				
Skin assessment	X		X		X		X	Q6W	X	X	X		Conduct 12-week Safety Follow-up Visit via telephone calls or patient chart reviews unless there is medical necessity for a clinical visit
12-lead ECG									X				
SpO_2	X	X	X	X	X	X	X	X	X	X			Using pulse oximeter
Laboratory Assessments													
Full chemistry and hematology	X	X	X	X	X	X	X	Q3W	X	X			See Appendix 6 (Table- A) for full chemistry and hematology/ coagulation. Blood samples must be drawn a day before or on the day prior to dosing. Results of asterisked parameters (*) must be reviewed by Investigator before dosing. Review results of other parameters within 5 working days of visit.
Anemia	As clinically indicated												See Appendix 6 (Table- C) for parameters to be assessed.
CA19-9	X		X		X		X	Q6W	X				Q6W. See Appendix 6 (Table- F)
Urinalysis	X		X		X		X	Q6W	X	X			Full urinalysis (dipstick plus microscopy) at EoT visit. Basic urinalysis (only dipstick is required but not microscopy) at each visit indicated prior to dosing. Review results of basic urinalysis before dosing. If basic urinalysis is abnormal, perform a full urinalysis plus culture. See Appendix 6 (Table- D) for parameters to be assessed.
Pregnancy test	X	X	X	X	X	X	X	Q3W		X			Serum or highly sensitive urine hCG pregnancy test (for women of childbearing potential). Note: Local urine testing is standard for the protocol unless serum testing is required by local regulation or the IRB/IEC.
ACTH, ANA, ANCA, and RF	As clinically indicated												See Appendix 6 (Table- F)

Activities	Treatment Phase (± 3 days)[a]								End-of-Treatment Visit	Safety Follow-up Visit		Long-term Follow-up	Notes
	Week												[a]If treatment continues beyond Week 43/Day 295, continue assessments until EoT, as indicated in the table [b]Decision to stop study intervention
	25	28	31	34	37	40	43[a]						
	Day												
	169	190	211	232	253	274	295[a]	Until EoT	On Day of or Within 7 Days of Decision[b]	28 (± 7) Days After Last Treatment	12 (± 2) Weeks After Last Treatment	Every 3 Months (± 2 Weeks)	
Hepatitis	X		X		X		X	Q6W					If one or more of the following, HB-surface antigen, HB-core antibody, or HB-surface antibody are positive at baseline, examine HBV DNA at screening and Q6W during the study. If HCV antibody and HCV RNA were positive at baseline, examine HCV RNA Q6W. See Appendix 6 (Table- E). Review results within 5 working days of visit.
Free T4 and TSH	X		X		X		X	Q6W		X			See Appendix 6 (Table- F). Review results within 5 working days of visit.
KL-6, SP-A, and SP-D	X		X		X		X	Q6W					**Japanese sites only**. See Appendix 6 (Table- F). Review results within 5 working days of visit.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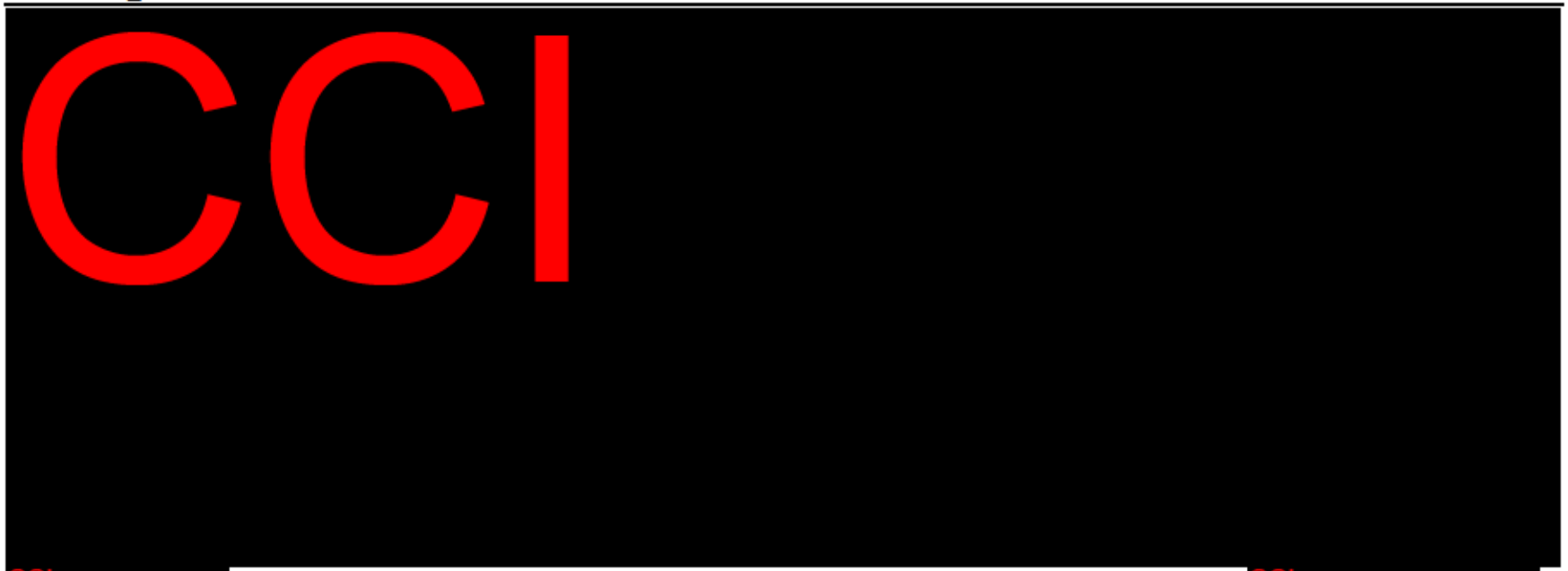
2L=second-line, 3L=third-line, ACTH=adrenocorticotropic hormone, CCI , AEs=adverse events, ANA=antinuclear antibody, ANCA=antineutrophil cytoplasmic antibodies, CA19-9=carbohydrate antigen 19-9, CR=complete response, CT=computed tomography, D=day, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group performance status, eCRF=electronic Case Report Form, CCI , EoT=End of Treatment, CCI EU= European Union, HB=hepatitis B, HBV=hepatitis B virus, hCG=human chorionic gonadotropin, HCV=hepatitis C virus, IL=Item Library, IRB/IEC=Institutional Review Board/Independent Ethics Committee, IV=intravenous, KL-6= Krebs von den Lungen-6, MRI=magnetic resonance imaging, PD=progressive disease, CCI PK=pharmacokinetics, CCI PR=partial

response, Q3W=every 3 weeks, Q6W=every 6 weeks, Q12W=every 12 weeks, [redacted] RF=rheumatoid factor, RNA=ribonucleic acid, SAEs=serious adverse events, SD=stable disease, SP-A/D=surfactant protein-A/D, SpO_2=blood oxygen saturation, T4=thyroxine, TSH=thyroid-stimulating hormone, W=week, US=United States


CCI

Screening/ Baseline	Treatment Phase (± 3 Days)[a]											EoT Visit	Safety Follow-up Visit	Notes
Day -28 up to Day 1	W1		W2	W3	W4	W5	W7	W13	W19	W25[a]	Until EoT	On Day of or within 7 Days of Decision[b]	28 (± 7) Days After Last Treatment	[a]If treatment continues beyond Week 25/Day 169, continue assessments until EoT, as indicated in the table. [b]Decision to stop study intervention
	D1	D2	D8	D15	D22	D29	D43	D85	D127	D169[a]				
PK sampling (pre-infusion/post-infusion)														
	X/X[e]	X[f]	X	X	X/-		X/X	X/-	X/-	X[g]/-	X/- Q12W from W25	X	X	During treatment, collect PK samples before (pre-infusion: as close to the start of infusion as possible) and immediately after completion of infusion (post-infusion: as close to completion as possible and no later than 30 minutes post-end of infusion). Predose samples should be drawn even if dosing is ultimately deferred at the visit. If participant missed a visit altogether, no PK sample will be collected. Record exact time of each draw. A protocol deviation will be defined if a sample is not drawn, or time of draw is not recorded. [e]On W1D1 only, collect additional PK sample 4 hours after start of bintrafusp alfa/placebo infusion. [f]On W1D2 only, collect a PK sample 24 hours after start of D1 bintrafusp alfa/placebo infusion. [g]Collect PK samples pre-infusion W25, then Q12W.



CCI , D=day, EoT=End of Treatment, PK=pharmacokinetics, PD=progressive disease, Q12W=every 12 weeks, CCI , W=week.

Table 4 Schedule of Activities for CCI , PK, and CCI Sampling: Randomized, Double-blind Part

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PK sampling (pre-infusion/post-infusion)												
	X/X		X/-		X/X	X/-	X/-	X[e]/-	X/- Q12W from W25	X	X	During treatment, collect PK samples before (pre-infusion: as close to the start of infusion as possible) and immediately after completion of infusion (post-infusion: as close to completion as possible and no later than 30 minutes post-end of infusion). Predose samples should be drawn even if dosing is ultimately deferred at the visit. Record exact time of each draw. If participant missed a visit altogether, no PK sample will be collected. A protocol deviation will be defined if a sample is not drawn or time of draw is not recorded. [e]Collect PK samples pre-infusion W25, then Q12W.

CCI , D=day, EoT=End of Treatment, PK=pharmacokinetics, Q12W=every 12 weeks, CCI , W=week.

2 Introduction

Bintrafusp alfa (M7824, MSB0011359C) is a first-in-class, bifunctional fusion protein that combines an anti-programmed death-ligand 1 (anti-PD-L1) antibody and the soluble extracellular domain of the human transforming growth factor beta (TGFβ) receptor as a TGFβ neutralizing "trap", into a single molecule. Bintrafusp alfa is being developed for the treatment of patients with biliary tract cancer (BTC), including intrahepatic and extrahepatic cholangiocarcinoma (CCA), gallbladder cancer (GC), and ampullary cancer. Bintrafusp alfa is the recommended international nonproprietary name for M7824.

The current study will evaluate whether bintrafusp alfa in combination with the current standard of care (SoC), gemcitabine plus cisplatin, improves overall survival (OS) in advanced BTC compared with SoC alone.

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

2.2 Background

Biliary tract cancer is a collective term used to describe a heterogeneous group of tumors that includes intrahepatic and extrahepatic CCA and GC, and usually includes ampulla of Vater's cancer depending on the guidelines or study design (Valle 2016, Valle 2010, Miyazaki 2015). More than 90% of BTCs are adenocarcinomas (Hezel 2008). Most patients have advanced disease at presentation and relapse despite surgery. BTC patients have a poor prognosis, with an estimated 5-year OS of about 17.5% (Lepage 2015). The recurrence rate is about 67% at 24 months among patients who undergo curative resection (Jarnagin 2003). Unresectable BTC is treated with chemotherapy, but the median survival time is < 1 year (Valle 2010).

In the last few years, the clinical development of immune checkpoint inhibitors represents the main step forward in the treatment of various cancers. Bintrafusp alfa is a first-in-class bifunctional fusion protein designed to target PD-L1 and TGFβ, 2 mechanisms of immunosuppression in the tumor microenvironment.

Bintrafusp alfa has shown promising clinical efficacy signal in a cohort of Asian participants whose BTC had progressed after platinum-based 1L treatment (Study MS200647_0008). Thirty Asian participants with advanced/metastatic BTC who had progressed after receiving platinum-based 1L therapy were treated with bintrafusp alfa 1200 mg every 2 weeks. As of 23 July 2018, 30 participants with pretreated BTC had received bintrafusp alfa for a median duration of 8.9 weeks (range: 2.0-75.6 weeks), with 4 participants remaining on treatment. Six participants had a confirmed objective response by Independent Review Committee (IRC) (objective response rate [ORR]: 20.0%). Per anatomical location, the ORR was 0% (0/7) for extrahepatic and 30% (3/10) for intrahepatic CCA, 25.0% (3/12) for GC, and 0% (0/1) for ampulla of Vater's cancer. The ORR as assessed by the Investigator was 23.3% (95% CI: 9.9, 42.3); with 1 additional participant with initial pseudoprogression and subsequent long-lasting response, the overall clinical response rate was 26.7%. With a minimum follow-up of 8 months, the duration of response (DOR) ranged from 8.3 to 13.9 months, and median OS was 12.7 months, with 4/6 responses

ongoing at the data cutoff. Besides the confirmed 20.0% ORR, 1 participant with ampulla of Vater's cancer had shrinkage of lung and liver target and nontarget lesions after having stopped bintrafusp alfa treatment and receiving radiotherapy (Gamma Knife® radiosurgery) for a brain lesion. The efficacy results obtained in the BTC cohort are better than the historical data reported by Lamarca et al (Lamarca 2014), in a systematic review of 2L studies, including 761 patients which showed a mean OS of 7.2 months and a weighted mean ORR of 7.7%, as well as a pembrolizumab study in 2L BTC which had a median OS of 9.1 months and an ORR of 5.8% (KEYNOTE-158 study, Ueno 2018). Recently, a nivolumab study exhibited an ORR of 3.3% (n = 30) and a median OS of 5.2 months in 2L treatment of Japanese patients (Ikeda 2019). However, there was no correlation between response and PD-L1 expression observed in this cohort of 30 participants with BTC, of whom 53.3% were PD-L1 positive (Study MS200647_0008).

The SoC for the 1L treatment of locally advanced or metastatic BTC is a combination of gemcitabine and cisplatin, as established in the ABC-02 study (Valle 2016), which achieved a response rate of 26.1% (n = 161) (95% confidence interval [CI]: 19.3-32.8), a median PFS of 8.0 months (95% CI: 6.6, 8.6), and a median OS of 11.8 months (95% CI: 9.5, 14.3). Treatment with nivolumab in conjunction with gemcitabine plus cisplatin demonstrated a median OS of 15.4 months, a median PFS of 4.2 months and an ORR of 36.7% (n = 30) in treatment-naive BTC patients (Ikeda 2019).

2.3 Benefit/Risk Assessment

At the time of study initiation, in Study MS200647-0008, a Phase Ib study of 2L BTC, bintrafusp alfa (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 bintrafusp alfa: 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 bintrafusp alfa 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 bintrafusp alfa related IRRs were 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 bintrafusp alfa studies and aligned with the known safety profile of approved anti-PD-(L)1 agents.

Dermatologic adverse events (AEs) related to TGFβ-inhibition (including keratoacanthomas [KA] and cutaneous squamous cell cancers) are an important identified risk with bintrafusp alfa. These

lesions were previously observed in individuals with genetic mutations in the TGFβ receptor (i.e., Ferguson-Smith syndrome), and patients treated with the TGFβ-targeting agent, fresolimumab (Goudie 2011, Morris 2014). Overall, in the EMR200647_001/MS200647_0008 studies, treatment-emergent TGFβ inhibition mediated skin reactions were reported in 69/630 (11.0%) participants. They were well managed with simple excision or resolved spontaneously and did not require any participant to discontinue treatment. The risk of these lesions with bintrafusp alfa was considered manageable in these studies, particularly in the context of encouraging clinical activity against an advanced cancer. Note: fresolimumab is not approved in Japan.

An analysis of observed treatment-emergent adverse events (TEAEs) of bintrafusp alfa and the known safety profile of gemcitabine/cisplatin did not reveal prominent overlapping toxicity for special consideration in the study design; however, as generally seen with chemotherapy, low blood counts, fatigue, nausea, vomiting, and infusion reaction (mainly due to cisplatin) are common side effects, and interstitial lung disease (ILD), diarrhea, and oral sores are less common but require diligent monitoring while investigating bintrafusp alfa in combination with chemotherapy. Considering bintrafusp alfa's observed efficacy in BTC, and manageable safety profile, as observed in 2 Phase I studies (EMR200647_001 and MS200647_0008), the benefit/risk assessment appears favorable to conduct this Phase II/III global study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of bintrafusp alfa may be found in Section 4.2 and the 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 study comprises an open-label, safety run-in part, and a randomized, double-blind part for the evaluation of efficacy and safety. Primary objectives and endpoints are presented separately for the 2 parts in Table 5.

Table 5 Study Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)
Open-label, Safety Run-in	
To assess the following items with bintrafusp alfa 2400 mg Q3W in combination with gemcitabine and cisplatin in locally advanced or metastatic BTC	
Primary	
To assess if bintrafusp alfa 2400 mg Q3W is safe and tolerable and to confirm this dose as the recommended Phase II dose for the randomized, double-blind part of the study	Occurrence of DLTs during the DLT evaluation period
Secondary	
To assess the safety profile of bintrafusp alfa in combination with gemcitabine and cisplatin	• Occurrence of TEAEs and treatment-related AEs • Occurrence of abnormalities (Grade ≥ 3) in laboratory tests
Randomized, Double-blind Part	

Objectives	Endpoints (Outcome Measures)
To assess the following items with bintrafusp alfa in combination with gemcitabine plus cisplatin versus placebo with gemcitabine plus cisplatin in participants with advanced or metastatic BTC who have not received chemotherapy/immunotherapy in the advanced/metastatic setting	
Primary	
To assess OS	OS
Secondary	
To assess PFS	PFS according to RECIST 1.1 as assessed by the Investigator[a]
To assess ORR	Confirmed objective response according to RECIST 1.1 as assessed by the Investigator[a]
To assess DOR	DOR assessed by confirmed complete response or partial response until death or progression of disease according to RECIST 1.1 as assessed by the Investigator[a]
To assess DRR	Durable confirmed response of at least 6 months according to RECIST 1.1 as assessed by the Investigator[a]
To assess the safety profile of bintrafusp alfa or placebo in combination with gemcitabine plus cisplatin	Occurrence of TEAEs and treatment-related AEs, including adverse events of special interest
To characterize the PK profile of bintrafusp alfa	• PK profile of bintrafusp alfa in terms of C_{eoI} and C_{trough} for participants in the bintrafusp alfa arm • PK profile of bintrafusp alfa in terms of AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{½}$ for participants in the safety run-in part of the study only

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time at which the concentration is at or above the lower limit of quantification, $AUC_{0-\infty}$=AUC from time zero extrapolated to infinity, based on the predicted value for the concentration at the last sampling time, BTC=biliary tract cancer, C_{eoi}=concentration observed immediately at the end of infusion, C_{max}=maximum observed concentration, C_{trough}=concentration observed immediately before next dosing, DLT=dose-limiting toxicity, DOR=duration of response, DRR=durable response rate, CCI , IL=Item Library, IRC=Independent Review Committee, CCI ORR=objective response rate, OS=overall survival, PFS=progression-free survival, PK=pharmacokinetics, CCI , Q3W=once every 3 weeks, CCI , RECIST 1.1=Response Evaluation Criteria in Solid Tumors Version 1.1, $t_{½}$=apparent terminal half-life, TEAEs=treatment-emergent adverse events, t_{max}=time to reach the maximum observed concentration collected during a dosing interval.

a If the study is not expanded to Phase III, tumor-based efficacy endpoints will also be assessed as per the IRC.

4 Study Design

4.1 Overall Design

This multicenter, international study consists of an open-label, safety run-in part and a randomized, double-blind, placebo-controlled Phase II/III part. In Phase II/III part, the study will evaluate whether bintrafusp alfa in combination with the current SoC (gemcitabine plus cisplatin) improves OS in chemotherapy and immunotherapy-naive participants with locally advanced or metastatic BTC compared to placebo, gemcitabine and cisplatin (see Figure 1):

- A multicenter, open-label, safety run-in to confirm the safety and tolerability of 1L bintrafusp alfa in combination with gemcitabine and cisplatin. Safety will be assessed by a Safety Monitoring Committee (SMC). The safety run-in part of the study will enroll 6 to 12 dosed participants in Asia and in non-Asia, with competitive enrollment within each region
- A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of bintrafusp alfa with gemcitabine plus cisplatin as 1L treatment. A total of maximum 300 participants will be recruited in Phase II and the analysis for the adaptation decision will be conducted in the first 150 participants in Phase II who have no documentation (eCRF) of any systemic antibiotic treatment within 30 days prior to randomization (referred to as antibiotics-naive from here on for simplicity).

  Expansion into Phase III will take place if:

  - The odds ratio of a confirmed ORR is ≥ 1.6 or PFS HR is < 0.75, and
  - the probability of success exceeds a prespecified threshold (success is defined as projected OS HR below a prespecified threshold at the primary analysis). Details will be specified in an appendix to the IDMC charter and IDMC statistical analysis plan.

If the prespecified criteria are met, the study will expand into Phase III adding up to 500 participants in total. If the study is not expanded into Phase III, it will be completed as a Phase II study.

The study plans to enroll a maximum of 524 eligible participants from countries in Asia, Europe, South America, and the US. Enrollment in the randomized, double-blind part will be competitive.

The Sponsor will monitor enrollment in the study and may make determinations to limit enrollment in certain countries and/or regions in order to obtain a study population representative across the participating global regions (for e.g., Asian versus non-Asian countries).

Unless otherwise specified, all study assessments apply to both the open-label, safety run-in and the randomized, double-blind parts of the study.

Study intervention in this protocol refers to bintrafusp alfa/placebo, gemcitabine, and/or cisplatin.

4.1.1 Open-label, Safety Run-in Part

Prior to the randomization phase, the safety of bintrafusp alfa in combination with gemcitabine and cisplatin will be confirmed in an open-label, safety run-in. In the safety run-in part, participants will be treated with bintrafusp alfa at a dose of 2400 mg once every 3 weeks in combination with gemcitabine at 1000 mg/m^2 and cisplatin at 25 mg/m^2 dosed on Day 1 and Day 8 for 8 cycles every 3 weeks.

Dose-limiting toxicity (DLT) will be evaluated in the first 21 days following the first dose of bintrafusp alfa (see Section 6.6.2 for the definition of DLT). Safety will be evaluated independently in 2 separate cohorts:

- In the Asian sites' cohort
- In the non-Asian sites' cohort.

Six DLT-evaluable participants will be recruited sequentially in each cohort (as detailed in the SMC Charter). If DLT is observed in 2 or 3 of the 6 participants, an additional 6 evaluable participants will be added to the cohort. Depending on the decision of the SMC, the number of participants in the safety run-in part may be expanded further. If DLT is observed in ≤ 1 (of 6) or ≤ 3 (of 12) participants, the region may start to enroll participants into the randomized, double-blind part of the study. If DLT is observed in ≥ 4 out of 6 or 12 participants in the regional cohort, recruitment in that region will be temporarily halted. The SMC will review the safety findings with ethnicity and an appropriate measure will be added to this study protocol, if applicable.

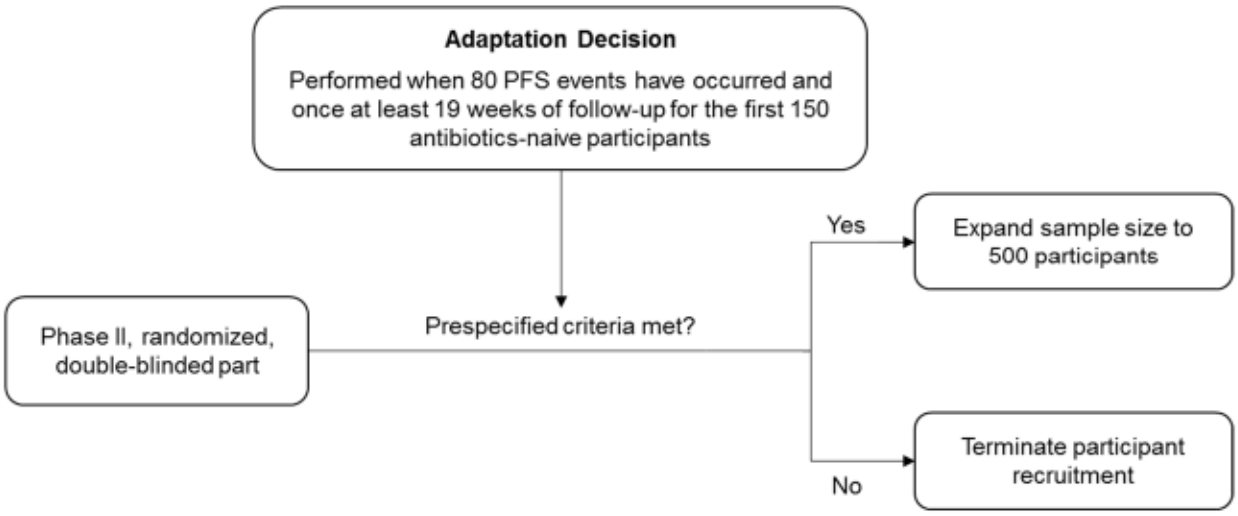
Treatment duration and criteria for dose and schedule modifications are described in Sections 4.1.2, 6.6.1, and 7.

4.1.2 Randomized, Double-blind Part

The randomized, double-blind part is comprised of Phase II and Phase III. A total of maximum 300 participants will be recruited in Phase II and the analysis for the adaptation decision will be conducted in the first 150 antibiotics-naive participants for efficacy data and for safety data from all treated participants. Study enrollment will be expanded into Phase III to reach 500 participants if the prespecified criteria are met (see Section 4.1). The Independent Data Monitoring Committee (IDMC) will review PFS, ORR, OS, and safety data in Phase II regardless of whether the expansion criteria are met, in order to consider the overall benefit-risk, and will recommend to the study team whether to continue the study as Phase II or Phase III.

The primary analysis (PA) of the study will be conducted on data from all participants in the randomized, double-blind part of the study but will not include data from participants in the safety run-in part. If neither of the criteria for study expansion into Phase III are met, no further participants will be enrolled, and the study will be completed as a Phase II study. The design of the randomized, double-blind part of the study is outlined in Figure 2.

Figure 2 Outline of Randomized, Double-blind Study Design



PFS=progression-free survival.

Participants will be randomized in a 1:1 ratio to receive either bintrafusp alfa (2400 mg) or matching placebo once every 3 weeks. In both the bintrafusp alfa and placebo arms, participants will be dosed with gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) on Day 1 and Day 8 for 8 cycles every 3 weeks. Treatment allocation/randomization will be stratified according to the following factors:

1. Type of BTC (on the basis that anatomical location may reflect a different tumor origin as well as a different etiology):

- intrahepatic CCA
- extrahepatic CCA including ampulla of Vater's cancer
- gallbladder cancer (GC).

2. Metastatic at diagnosis versus others, where "others" includes participants with unresectable, locally advanced disease at diagnosis and participants with resectable disease at diagnosis who have undergone prior surgical resection with curative intent

3. Asia sites versus non-Asia sites

In participants with complete response (CR), treatment with bintrafusp alfa/placebo will continue for 2 years after the first onset of CR or until 1 of the criteria for discontinuation in Section 7 is met, whichever occurs first. Participants with CR may be able to continue treatment beyond 2 years, subject to discussion between the Investigator and the Medical Monitor. In all other cases, treatment with bintrafusp alfa /placebo will continue until 1 of the criteria for discontinuation in Section 7 is met. All participants will receive 8 cycles of gemcitabine and cisplatin. Any missed dose(s) of chemotherapy may be made up at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination) provided the participant does not meet any of the criteria for discontinuation. Refer to the Schedule of Activities for details of assessments to be performed (see Section 1.3).

Two Safety Follow-up Visits will be performed: at 28 days (± 7 days) and 12 weeks (± 2 weeks) after the last dose of treatment.

Long-term follow-up, including survival follow-up, will be performed every 3 months (± 2 weeks) (or every 6 weeks [± 1 week] if the participant has initiated and continuing 2L treatment) after the 12-week Safety Follow-up Visit, unless the participant is reported as lost to follow-up, dead, or after study termination.

Long-term follow-up can be performed using chart reviews or telephone calls.

4.2 Scientific Rationale for Study Design

Overall Study Design

In general, following the observation of bintrafusp alfa antitumor activity in the Phase I expansion study MS200647_0008, based on a small sample size, randomized follow-up studies would be conducted either as a Phase II-like proof of concept study or a confirmatory Phase III study. Moving directly from Phase I to a full Phase III study has the potential to reduce development time, but such an aggressive approach may be very risky without proof of concept data. To mitigate this risk, while also optimizing development time, an adaptive Phase II/III design will be employed in this study. A similar approach has been described previously to expedite oncology drug development, such that if an interim analysis (IA) has a definitively positive outcome, the study

expands into a planned Phase III population (Chen 2018). In this study, expansion of Phase II into Phase III requires either a PFS HR < 0.75 or a confirmed ORR odds ratio ≥ 1.6 between the treatment and control arms. The ORR odds ratio is included in the expansion criteria to complement the limitation of predictability of the OS HR with the PFS HR to correctly expand the study, since the correlation between PFS HR and OS HR is influenced by many factors, including the synergistic effect of combinations and later lines of treatment. Thus, an additional criterion, i.e., assessment of probability of success to reach the projected OS HR at the primary analysis, will be provided to the IDMC to be taken into consideration for their recommendation. However, the actual threshold for the probability of success criterion is not documented in the protocol and, therefore, not apparent to the Investigators and participants to minimize bias in terms of recruiting a different patient population for after the decision to expand.

For example, in the case of NSCLC, the only indication where chemotherapy and immunotherapy combination data are available, there is a good correlation between OS HR and PFS HR in the subset analysis of different PD-L1 expression groups, such as PD-L1 high, positive, and negative in the 1L nonsquamous NSCLC study (KEYNOTE-189, Gandhi 2018). However, less correlation was observed in the 1L squamous NSCLC study (KEYNOTE-407, Paz-Ares 2018). The response rate of gemcitabine and cisplatin combination in the available Phase III studies is variable, ranging from 15% (KHBO1401-MITSUBA study, Sakai 2018) to 32% (JCOG 1113 FUGA-BT study, Morizane 2018). An odds ratio of 1.6 corresponds to a 10% increase in ORR, assuming ORR in the gemcitabine and cisplatin arm is 25%.

Choice of Comparator

The 1L SoC treatment for patients with advanced-stage or unresectable BTC is a combination of gemcitabine and cisplatin (Valle 2016, Miyazaki 2015, refer to NCCN 2018) based on the results of the Phase III ABC-02 study conducted in the UK (Valle 2010), where the combination of gemcitabine/cisplatin exhibited a response rate of 26.1% (42 out of 161 participants; 95% CI: 19.3, 32.8), median PFS of 8.0 months (95% CI: 6.6, 8.6) with every 3 months of radiological assessment, and median OS of 11.7 months (95% CI: 9.5, 14.3) in 1L treatment of locally advanced or metastatic BTC. A similar benefit was seen in the randomized, Phase II BT-22 Japanese study, with a median OS of 11.2 months (95% CI: 9.1, 12.5), PFS of 5.8 months with every 6 weeks of radiological assessment, and 19.5% ORR (95% CI: 8.8, 34.9) in the cisplatin plus gemcitabine combination group (Okusaka 2010).

Since the NCCN guidelines recommend gemcitabine with cisplatin for 1L treatment as category 1 evidence level and gemcitabine/cisplatin is the SoC in 1L BTC, the control arm of the randomized, double-blind part of this study is justified.

Recently, in the KHBO1401-MITSUBA study, the triplet regimen of gemcitabine, cisplatin, and S1 (GCS), demonstrated an OS benefit compared to gemcitabine and cisplatin (Gem-Cis) in Japanese patients (Sakai 2018). The median OS was 13.5 months in the GCS arm and 12.6 months in the Gem-Cis arm, with a HR of 0.791 (CI: 0.628, 0.996) (p = 0.046). Although the OS benefit was statistically significant, the benefit in median OS was only 0.9 months. During both the 1L study period and the subsequent 2L treatment, only 25% of patients in the Gem-Cis arm received S1 compared to 100% of patients in the GCS arm. In addition, the dose intensity of gemcitabine and cisplatin in the GCS arm was 25% lower than in the Gem-Cis arm. These findings may indicate

the clinical benefit of sequential treatment with gemcitabine and cisplatin as 1L followed by S1 as 2L rather than the triplet of GCS regimen. Taken together, the gemcitabine plus cisplatin regimen remains a SoC in 1L even in countries where S1 is available.

Target Disease

Gallbladder cancer, intrahepatic CCA and extrahepatic CCA, including ampullary cancer were included as target indications in the ABC-02 study (Valle 2010). In this protocol, perihilar and distal bile duct cancers are handled as an extrahepatic CCA since extrahepatic CCA was separated traditionally into perihilar, mid-duct, and distal CCA, although it may be difficult to distinguish clinically central intrahepatic CCA from hilar CCA, particularly in the presence of a periductal infiltrating growth pattern (Amin 2017).

Antibiotics-naive patients for the expansion decision

Accumulating evidence shows that antibiotics used before checkpoint inhibitors are associated with poor prognosis (Pinato 2019, Chalabi 2020). Some of the studies exhibited even deteriorated efficacy of checkpoint inhibitor treatment in conjunction with antibiotics compared to the comparator arm. In Study Protocol Version 3.0 (dated 27 July 2020), participants who used systemic antibiotics during the screening period are not eligible for the study; therefore, the full Phase III sample size is expected to be largely antibiotics-naive participants. The antibiotics-naive population will be the basis of the analysis for the expansion decision from Phase II to Phase III in order to have a population more representative of the anticipated population in the full Phase III sample size.

Efficacy Endpoints

In this study, the primary endpoint is OS.

The assumed median OS of the control arm of this study is being set as 11.7 months based on the ABC-02 study (Valle 2010).

Crossover between treatment arms (i.e., from placebo to bintrafusp alfa after confirmation of progressive disease [PD]) is not allowed, to avoid any impact on OS outcomes.

There have been reports that the response rate of a salvage line of chemotherapy after immunotherapy is better than the response rate of the last chemotherapy before immunotherapy (Park 2018). In view of the suggestion that immunotherapy may increase a tumor's sensitivity to chemotherapy, the association of bintrafusp alfa treatment and objective response of 2L treatment will be assessed in this study to describe the influence of bintrafusp alfa on subsequent therapy.

Duration of Treatment

The number of cycles and duration of gemcitabine and cisplatin treatment to be used in this study was determined based on the ABC-02 study (Valle 2010) and is defined as 8 cycles, given every 3 weeks. This treatment schedule is consistent with current SoC and reflects both the toxicity of chemotherapy and the observation that there is currently no prospective study that demonstrates a

clinical benefit of continued gemcitabine and cisplatin combination treatment beyond 8 cycles. To ensure participants are able to receive 8 cycles of chemotherapy, any missed doses may be made up after the 8 scheduled cycles (up to 16 administrations of gemcitabine and cisplatin combination) provided the participant does not meet any of the criteria for discontinuation.

Due to the lack of prospective studies, the optimal duration of immunotherapy is not yet clear, particularly whether it should continue until disease progression or be terminated after a fixed number of administrations. To date, CheckMate-153 is the only study of a PD-1 inhibitor that prospectively examined the benefit of nivolumab treatment duration, with 1 arm continuing treatment until PD and the other arm discontinuing treatment at 1 year (re-treatment was permissible in the event of disease progression). Both PFS and OS were superior in the continuous treatment arm compared to the 1-year treatment arm (Spigel 2017). In this study, bintrafusp alfa/placebo treatment will continue for 2 years in participants with CR or until 1 of the criteria for discontinuation is met (Section 7); continuation of treatment with bintrafusp alfa /placebo beyond 2 years after the first onset of CR may be possible subject to discussion between the Investigator and the Medical Monitor. In all other cases, treatment with bintrafusp alfa/placebo will continue until 1 of the criteria for discontinuation in Section 7 is met.

Immune-related response patterns, such as an initial increase in tumor burden or the appearance of new lesions, termed 'pseudoprogression', may lead to misinterpretation of patient status, and, as a result, lead to suboptimal clinical decisions. Conventional Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) (Eisenhauer 2009) evaluation is reported to underestimate the benefit of immune checkpoint inhibitors in 11% of progressive patients with NSCLC (Tazdait 2018). In the case of NSCLC, a retrospective analysis of a subset of patients in the OAK study demonstrated prolonged clinical benefit beyond PD treatment with the PD-L1 antibody atezolizumab in the 2L setting (Rittmeyer 2017). In the BTC cohort of the bintrafusp alfa Phase I study, 2 atypical responses (1 pseudoprogression and 1 delayed response or abscopal effect case, out of 30 participants) were observed by Investigator assessment after PD according to RECIST 1.1. Although the evidence to continue PD-1/PD-L1 treatment beyond PD is limited, this study will encourage Investigators to continue bintrafusp alfa/placebo treatment until confirmed PD.

Prognostic Factors

Several predictive/prognostic factors influence OS. According to a univariate analysis (Suzuki 2019), the following factors influence OS for gemcitabine plus cisplatin treatment:

- Eastern Cooperative Oncology Group performance status (ECOG PS) 0 versus 1-2 (HR: 2.38 [1.70-3.33])
- Locally advanced disease versus metastatic disease (HR: 1.51 [1.02-2.30])
- Absence versus presence of peritoneal dissemination (HR: 1.56 [1.07-2.22])
- Presence versus absence of prior surgical resection (HR: 1.72 [1.15-2.66]).

A Korean group (Kim 2017) reported factors as:

- Locally advanced disease versus initially metastatic disease (HR: 1.92 [1.38-2.67])
- Normal versus elevated baseline carbohydrate antigen 19-9 (HR: 1.31 [1.0-1.58])

- Measurable disease by RECIST 1.1: no versus yes (HR: 1.40 [1.15-1.70]).

To date, no predictive factors have been identified for the efficacy of bintrafusp alfa in BTC from the Phase I study. Mismatch repair–deficient tumors are more responsive to PD-1/PD-L1 blockade than mismatch repair–proficient tumors (Le 2015). However, microsatellite instability (MSI)-high was reported in only 1% of 102 CCA patients (Winkelmann 2018). Given the design, eligibility criteria, and practical considerations of the current study, and the fact that the relevance of PD-L1 expression in the tumor or tumor microenvironment in BTC to predict treatment response to PD-1/PD-L1 antibodies is not yet understood (in Study MS200647_0008, no correlation between response and PD-L1 expression was observed in 30 participants with BTC, of whom 53.3% were PD-L1 positive), the 3 factors outlined in Section 4.1.2 were selected as randomization stratification factors in this study.

CCI

Study Blinding

A randomized, double-blind, placebo-controlled design was selected for this study to reduce bias in the evaluation of the efficacy, safety, and patient-reported outcomes (PROs). Blinding is important since knowledge of treatment assignment could potentially bias the participant's related outcomes or Investigator assessment of tumor imaging. The use of placebo in combination with chemotherapy will ensure the objectivity of Investigator-assessed progression as well as any decisions to interrupt/discontinue therapy. The double-blind, placebo-controlled nature of the study also allows objective assessment of the relatedness of AEs, while PROs can be interpreted more reliably in double-blind studies.

The safety assessments to be performed are standard for oncology studies and will be used to assess the benefit-risk balance of combination therapy with bintrafusp alfa and gemcitabine plus cisplatin. It is acknowledged that even in a double-blind setting, AEs that are unique to active treatment, e.g., skin-related toxicity, may reveal assignment to bintrafusp alfa treatment. However, as most participants will not experience these toxicities, the risk of reported AEs leading to unblinding is limited. Moreover, the blinded design will allow a better characterization of the safety profile of bintrafusp alfa by clarifying the relative percentage of related AEs reported for the 2 treatment arms.

Detection of Interstitial Lung Disease (Japanese Sites)

For proper and early detection of events of ILD/pneumonitis in Japanese participants, serum Krebs von den Lungen-6 (KL-6), surfactant protein (SP)-A and SP-D levels will be measured in study sites in Japan. Inclusion of these markers will potentially help to identify treatment-emergent lung toxicity at the earliest opportunity and allow for further investigations to be initiated promptly, e.g., chest computed tomography (CT) for confirmatory diagnosis (Kubo 2013). In a Phase I study

of bintrafusp alfa in Asia, treatment-related Grade 5 ILD events were reported in 2 Japanese participants post-chemotherapy in a 2L+ BTC cohort of 30 participants. One participant experienced ILD on treatment after 3 doses of bintrafusp alfa. The second had Grade 3 ILD after 3 doses. The patient initially recovered but subsequently worsened with fatal outcome 6 months after the initial diagnosis of ILD and last bintrafusp alfa dose. These 2 cases of treatment-related Grade 5 interstitial pneumonitis represent an incidence of approximately 3% in Japanese participants (out of 66 Japanese participants) and of 0.3% overall in bintrafusp alfa studies (i.e., 2 AEs in more than 670 treated participants). According to the literature, a higher incidence of ILD is observed in the Japanese population (Takada 2014, Azuma 2007). Therefore, consistent with guidelines for drug-induced lung injury in Japan, serum KL-6, SP-A, and SP-D levels will be measured in Japanese participants.

4.3 Justification for Dose

4.3.1 Chemotherapy

The doses of gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) selected for this study are the doses routinely used as SoC in the 1L treatment of BTC. Chemotherapy will be administered on Days 1 and 8 of each 3-week cycle.

4.3.2 Bintrafusp alfa with Chemotherapy

Since gemcitabine and cisplatin are administered every 3 weeks, the same dosing interval for bintrafusp alfa is preferred for convenience and compliance. The recommended Phase II dose (RP2D) for bintrafusp alfa in combination with chemotherapies is 2400 mg, administered as an intravenous infusion once every 3 weeks, and was selected as follows:

- The RP2D for dosing every 2 weeks with bintrafusp alfa in monotherapy studies (1200 mg) was selected based on Phase I data, PK-pharmacodynamic analysis, and population PK (popPK) and exposure-response modeling and simulations. These data were also used to estimate the target steady-state C_{trough} ($C_{trough-ss}$); refer to the IB for further information
- For the selection of the once every 3 weeks dose, it was assumed that to achieve efficacy, the $C_{trough-ss}$ would need to be similar to that achieved with 1200 mg once every 2 weeks (monotherapy RP2D) dosing, and that the majority of participants should achieve the target $C_{trough-ss}$. The bintrafusp alfa 2400 mg every 3 weeks dosing regimen was selected based on these assumptions and population PK-based prediction of $C_{trough-ss}$. The safety of 2400 mg once every 3 weeks in monotherapy settings is supported by preliminary assessment of safety and exposures achieved in the Phase I study (Study EMR200647_001), which included 0.3 to 30 mg/kg dose escalation cohorts (including 3 participants who received at least bintrafusp alfa 2400 mg every 2 weeks) and exposure-safety modeling; refer to the IB for further information
- Based on the known clearance mechanism, the transient mild cytokine profile change with bintrafusp alfa dosing, and the observed safety profile of bintrafusp alfa monotherapy, and standard dose chemotherapy regimens, PK interactions or overlapping toxicities of bintrafusp alfa and chemotherapy are considered unlikely, except for bleeding and anemia. Given this hypothesis, no adjustment in dose selection for chemotherapies is required, and the bintrafusp

alfa 2400 mg once every 3 weeks dose is considered optimal for combination studies. However, in the cases of bleeding events, a dose modification might be required. 1200 mg Q3W bintrafusp alfa dose is recommended for the dose reduction in a participant with a suspected bleeding event, since this dose is expected to reduce the risk of bleeding (based on a recent exposure-safety analysis for bleeding AEs conducted with preliminary data from Phase I and Phase II studies), while maintaining pharmacologically relevant exposures associated with PD-L-1 inhibition. For further details on dose modifications for management of bleeding see Section 6.9.5.

In conclusion, the population PK-based estimation of efficacious target trough concentration for dosing once every 3 weeks, evaluation of potential overlapping toxicities, PK interactions of the combination, and planned mitigation measures (including dose interruptions and reductions) in the study support the safety evaluation of bintrafusp alfa at 2400 mg once every 3 weeks in combination with chemotherapy in this study.

4.4 End of Study Definition

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

The end of the study is defined as the date of the data cutoff for the primary OS analysis when 334 participants have died. However, if the study does not expand into Phase III but continues as a Phase II study, the end of study is defined accordingly, as the data cutoff date for the primary OS analysis when 60% of participants have died.

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

5 Study Population

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

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

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

5.1 Inclusion Criteria

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

Age

1. Are ≥ 18 (or ≥ 20 in Japan and Taiwan or age legally considered to be an adult) years of age at the time of signing the informed consent. In Japan, a participant aged < 20 years of age but ≥ 18 years of age may participate if written informed consent from his/her parent or guardian is provided in addition to the participant's written informed consent.

Type of Participant and Disease Characteristics

2. Are participants with histologically or cytologically confirmed locally advanced or metastatic BTC, including intrahepatic CCA, extrahepatic CCA, gallbladder cancer, and ampulla of Vater's cancer. The histological origin of ampullary carcinomas (intestinal, pancreaticobiliary, or other) will be collected. Histological subtypes such as a sarcomatoid tumor or HCC mixed subtype, for which- gemcitabine and cisplatin treatment are not considered as the standard of care should be excluded. Contact Medical Monitor for rare subtypes.

3. Naive to chemotherapy, immunotherapy, and interventional radiological treatment (transarterial chemo-embolization, transarterial embolization, transarterial infusion) for locally advanced or metastatic BTC. Participants whose disease has recurred ≥ 6 months after completion of neoadjuvant or adjuvant treatments will be considered eligible.

4. Availability of tumor tissue (primary or metastatic) (fresh or archival biopsies) before the first administration of study intervention. Availability of tumor tissue is mandatory except for the safety run-in part. Brush cytology and cell blocks are not acceptable. Tumor tissue (fresh or archival) must be suitable for biomarker assessment as described in the Laboratory Manual.

5. At least 1 measurable lesion according to RECIST 1.1. Participants in the safety run-in part do not require a measurable lesion at baseline.

6. ECOG PS of 0 or 1 at study entry and at Week 1, Day 1 prior to dosing.

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

8. Adequate hematological function defined by white blood cell count ≥ 2.0×10^9/L with absolute neutrophil count ≥ 1.5×10^9/L, lymphocyte count ≥ 0.5×10^9/L, platelet count ≥ 100×10^9/L, and hemoglobin (Hgb) ≥ 9 g/dL (participants may have been transfused) at study entry and at Week 1 Day 1 prior to dosing.
   - Previously transfused participants are allowed in the study with a stable Hgb of ≥ 9 g/dL at the time of study entry.

9. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × upper limit of normal (ULN), an aspartate aminotransferase level ≤ 3.0 × ULN, and an alanine aminotransferase level ≤ 3.0 × ULN. For participants with liver involvement, aspartate aminotransferase ≤ 5.0 × ULN and alanine aminotransferase ≤ 5.0 × ULN are acceptable.

10. Adequate renal function defined by an estimated creatinine clearance (CrCl) > 50 mL/min according to the Cockcroft-Gault formula or by measure of CrCl from 24-hour urine collection.

- CrCl (mL/min) = (140-age) × weight (kg) / (72 × serum creatinine [Cr_{jaffe}])
- If female, × 0.85
- If creatinine is measured by the enzymatic method, add 0.2 and use as $Cr_{jaffe} = 0.2 + Cr_{enzyme}$.

11 Albumin ≥ 2.8 g/dL.

12 Adequate coagulation function defined as prothrombin time or international normalized ratio ≤ 1.5 × ULN unless the participant is receiving anticoagulant therapy.

13 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 is 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 approved antiviral.

Sex

14 Are male or female:

- Male Participants

  Agree to the following during the intervention period and for at least 4 months after the last dose of study intervention (35 days corresponding to the time needed to eliminate any study interventions, e.g., 5 terminal half-lives plus 90 days for spermatogenic cycle):

- Refrain from donating sperm

  PLUS, either:

- Abstain from any activity that allows for exposure to ejaculate

  OR

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

- Female Participants

  Are not pregnant or breastfeeding, and at least 1 of the following conditions applies:

  - **Not** a woman of childbearing potential

OR

- If a woman of childbearing potential, agree to 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 study intervention(s), if using hormonal contraception:
  - Has completed at least one 4-week cycle of an oral contraceptive pill and has either had or has begun her menses

    OR
  - Has used a depot contraceptive or extended-cycle contraceptive for at 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 65 days (time needed to eliminate any study interventions, e.g., 5 terminal half-lives plus 30 days for a menstrual cycle), and as indicated in the respective label (Summary of Product Characteristics [SmPC]) for gemcitabine and cisplatin. Participants have to agree to the followings:
  - Women of childbearing potential should refrain from donating eggs from the start of dosing until 2 months after discontinuing 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 provided 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

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Previous and/or intercurrent cancers. With the exception of: curatively-treated cancers with no recurrence in > 3 years or early cancers treated with curative intent, including but not limited

to cervical carcinoma in situ, superficial, noninvasive bladder cancer, basal cell carcinoma, squamous cell carcinoma in situ, or endoscopically resected gastrointestinal cancers limited in mucosal layer.

2. Rapid clinical deterioration not related to malignancy which, in the opinion of the Investigator, may predispose to inability to tolerate treatment or study procedures at study entry and at Week 1 Day 1 prior to dosing.

3. Participants with symptomatic central nervous system (CNS) metastases are excluded. Participants with a history of treated CNS metastases (by surgery or radiation therapy) are not eligible unless they are judged to have fully recovered from treatment.

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. Significant acute or chronic infections including:

- Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (testing at Screening is not required). If an Investigator has a strong suspicion of HIV infection without known history for a participant in screening, but the participant refuses testing, discuss with 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 (presence of clinical symptoms, physical or radiographic findings of active tuberculosis).
- Uncontrolled biliary infection. Biliary tract obstruction should be released by stenting or percutaneous transhepatic biliary drainage (PTBD). Participants with biliary obstruction should have adequate biliary drainage with no evidence of ongoing infection without antibiotics treatment during the screening period.
- Active bacterial, fungal, or viral infection (with the exception of hepatitis B and hepatitis C) requiring systemic therapy during the screening period.

6. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:

- Participants with type 1 diabetes, 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 $\leq$ 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, intra-ocular, or inhalation) is acceptable.

7. History of, or concurrent, interstitial lung disease.

8. Known history of hypersensitivity reactions to bintrafusp alfa or its products or known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 National Cancer Institute [NCI]-Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0), any history of anaphylaxis, or recent (within 5 months) history of uncontrolled asthma.

9. 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.

10. a. Other severe, acute, or chronic medical conditions, including immune colitis, inflammatory bowel disease, immune pneumonitis, or psychiatric conditions, including recent (within the past year) or active suicidal ideation or behavior.

    b. Participants with history of bleeding diathesis or recent major bleeding events considered by the Investigator as high risk for study intervention are also excluded.

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

12. Participants who are candidates for liver transplantation and who can receive the transplantation within a medically acceptable period.

Prior/Concomitant Therapy

13. Concurrent treatment with nonpermitted drugs. Participants who have completed prior adjuvant therapy ≥ 6 months prior to randomization are eligible.

14. Prior therapy with any antibody/drug targeting T-cell coregulatory proteins (immune checkpoints), including but not limited to anti-PD-1, anti-PD-L1, anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody, or anti-4-1BB antibody is not allowed, inclusive of localized administration of such agents.

15. Prior therapy with any antibody/drug targeting TGFβ/TGFβ receptor.

16. Radiation within 28 days other than focal palliative bone-directed radiotherapy.

17. 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.

18. Live vaccine administration within 4 weeks of study intervention administration.

Prior/Concurrent Clinical Study Experience

19. Participation in any concurrent interventional clinical study.

Diagnostic Assessments

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

Other Exclusions

21. Major surgery within 28 days before the start of study intervention (excluding prior diagnostic biopsy and stenting/PTBD for the purpose of releasing biliary tract obstruction).

22. Pregnancy or breastfeeding.

23. Known alcohol or drug abuse.

24. Legal incapacity or limited legal capacity.

5.3 Lifestyle Considerations

No specific lifestyle or dietary restrictions are required during 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.

Participants who have an abnormal liver function test at Screening, that may normalize with biliary drainage or stenting, can be rescreened. It is recommended that participants with other laboratory abnormalities that may resolve, concomitant medication that will be discontinued, requirement of re-biopsy, or undergoing a prohibited procedure that will be completed, are discussed with the Medical Monitor with regard to whether the screening window can be extended, rather than screen-failing the participant.

In other situations, when a participant is a screen failure, 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(s) Administration

Details of the study interventions administered are provided in Table 6.

Table 6 Study Intervention Administration

Study Intervention Name	Bintrafusp alfa (M7824)	Placebo	Gemcitabine[a]	Cisplatin[a]
Dose Formulation	Sterile concentrate solution for infusion	Sterile concentrate solution for infusion. The composition of the placebo is identical to the composition of bintrafusp alfa drug product, except for the presence of bintrafusp alfa	Concentrate for Solution for Infusion or Powder	Concentrate for Solution for Infusion or Powder
Unit Dose Strength/Dosage Level	CCI [redacted]	Not applicable	Depends on commercial product	Depends on commercial product
Route of Administration	Intravenous	Intravenous	Intravenous	Intravenous
Dose Frequency	Q3W	Q3W	On Day 1 and Day 8, Q3W[a]	On Day 1 and Day 8, Q3W[a]
Dosing Instructions (see Section 6.6.1)	Flat dose of 2400 mg administered over a minimum of 1 hour and up to 2 hours	Administered over a minimum of 1 hour and up to 2 hours	1000 mg/m^2	25 mg/m^2
Supplier/Manufacturer	Merck Healthcare KGaA/ CCI [redacted]	Merck Healthcare KGaA/ CCI [redacted]	Merck Healthcare KGaA/ commercial manufacturer	Merck Healthcare KGaA/ commercial manufacturer
Packaging and Labeling	Study intervention: Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.			
	Packaging and labeling will be prepared to protect the blinded nature of study.	Packaging and labeling will be prepared to protect the blinded nature of study.	If provided as commercial product, prefer to SmPC for gemcitabine or package insert for more information	If provided as commercial product, prefer to SmPC for cisplatin or package insert for more information

Q3W=every 3 weeks, SmPC=Summary of Product Characteristics.

a. Chemotherapy should be administered over 8 cycles. If chemotherapy cannot be administered on Day 1 or Day 8 of a given cycle (for safety, tolerability or other unavoidable reasons), the missed dose may be administered on Day 15 of that cycle or may be made up at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.

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

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

- Upon receipt of the study intervention(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the Pharmacy Manual.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused study intervention(s).
  - Dates, quantities, batch numbers, vial numbers, expiry dates, and the participant numbers.
- The Investigator site will maintain records, which adequately document that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.

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

Further guidance and information for the final disposition of unused study intervention(s) are provided in the Pharmacy Manual.

Bintrafusp alfa/placebo should be stored CCI CCI until use. Bintrafusp alfa/placebo CCI and should be stored in the original packaging.

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

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

For both parts of the study, the interactive response system (IXRS) will be used to assign unique participant numbers and to assign study intervention to participants at each study intervention visit.

During the randomized, double-blind part, following confirmation of a participant's eligibility and at the last practical moment prior to administration of the study intervention, each participant will be centrally allocated to either bintrafusp alfa or placebo in a 1:1 ratio using the IXRS, as per a computer-generated randomization list.

Before the study is initiated, the telephone number and call-in directions and/or the log-in information and directions for using the IXRS will be provided to each site. The site will contact the IXRS prior to starting the administration of study intervention for each participant.

Treatment allocation/randomization will be stratified according to the following 3 factors:

- Type of BTC: intrahepatic CCA versus extrahepatic CCA including ampulla of Vater's cancer versus GC
- Metastatic at diagnosis versus others, where "others" includes participants with unresectable, locally advanced disease at diagnosis and participants with resectable disease at diagnosis who have undergone prior surgical resection with curative intent
- Asia sites versus non-Asia sites

6.3.2 Blinding

Blinding Method

Following the open-label, safety run-in part, the second part of this study will be double-blind. Therefore, the participant, Investigator, contract research organization (CRO), and Sponsor personnel involved in the treatment administration or clinical evaluation of participants, will be unaware of the group assignments and will not know whether the study intervention administered contains bintrafusp alfa or placebo. The chemotherapy agents, gemcitabine and cisplatin, will be open-label.

The study team will remain blinded throughout the study, i.e., blinding will be maintained during the entire study period, except in the event that emergency unblinding by the Sponsor's drug safety department is necessary for participant safety as described in Section 6.3.3. IDMC is not part of the study team and will be unblinded (see Section 8.2.4.2)

Assignment Method Retention

The Bioanalyst will have access to the randomization list to facilitate analysis of the PK/CCI samples (i.e., to avoid the unnecessary analysis of placebo samples). The Bioanalyst will not share

the randomization details or results of the analysis to prevent the study team from being unblinded prematurely. Details will be specified in a Firewall Charter, as appropriate.

Unblinding Clinical Studies for Sample Analysis of Special Data

The bioanalytical monitors and analytical laboratory for measurement of bintrafusp alfa concentrations will be unblinded since obtaining the result reveals the study intervention arm for the participant. Bintrafusp alfa concentration information that may unblind the study will not be reported with participant identifiers to investigative sites or blinded personnel until the study has been unblinded.

6.3.3 Emergency Unblinding

In an emergency, the Investigator is solely responsible for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in this decision. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to the unblinding, unless this could delay emergency treatment. The Sponsor must be notified within 24 hours after unblinding. The Investigator must provide the Sponsor the reason for unblinding without revealing the study intervention, except to the designated drug safety representative via the Emergency Unblinding Notification Form. The date of and reason for unblinding must be recorded in the source documents and electronic Case Report Form (eCRF). Contact information for unblinding in an emergency is given on the participant emergency card provided to each participant, as noted in Appendix 2.

The Sponsor's drug safety department will submit any Suspected Unexpected Serious Adverse Reaction (SUSAR) reports to regulatory authorities and ethics committees with unblinded information, per applicable regulations. Only blinded information will be provided to the study team.

6.4 Study Intervention Compliance

All study participants will receive study intervention at the investigational 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 (chemotherapy only)/total volume infused (bintrafusp alfa/placebo) will be recorded on the eCRF. In case of dose reduction of bintrafusp alfa/placebo, the date, time, administered dose, total volume infused, and reason for dose reduction will be recorded on the 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 cycle of study intervention (i.e., bintrafusp alfa/placebo, gemcitabine, and/or cisplatin) for nonmedical reasons and barring any extenuating circumstances in the opinion of the Investigator. Extenuating circumstances should be documented and discussed with the Sponsor in advance.

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.

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

6.5.1 Rescue Medicines

Not applicable.

6.5.2 Permitted Medicines

The only permitted medications are the following: the study medications, i.e., bintrafusp alfa, placebo, gemcitabine, and cisplatin.

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.

Any medications (other than those excluded by the clinical study protocol; see Section 6.5.3) that are considered necessary for the participants' welfare and will not interfere with the study intervention may be given at the Investigator's discretion.

Medications may be administered for the management of symptoms associated with the administration of bintrafusp alfa/placebo, as required. These might include analgesics, antinausea medications, antihistamines, diuretics, antianxiety medications, and medication for pain management, including narcotic agents.

6.5.3 Prohibited Medicines

As stated in the exclusion criteria (see Section 5.2), participants must not have had any prior therapy with any antibody/drug targeting T-cell coregulatory proteins (immune checkpoints), such as anti-PD-1, anti-PD-L1, anti-CTLA-4 antibody, or anti-4-1BB antibody, or concurrent anticancer treatment (e.g., cytoreductive therapy, immune therapy, or cytokine therapy, except for erythropoietin and granulocyte-colony stimulating factor), concurrent systemic therapy with steroids or other immunosuppressive agents, or use of any investigational drug within 28 days before the start of study intervention. Steroids as premedication (see Section 6.5.4.1) are not acceptable.

In addition, the following treatments must not be administered during the study:

- Immunotherapy, immunosuppressive drugs (i.e., systemic corticosteroids), or other experimental pharmaceutical products

- Short-term administration of systemic steroid (i.e., for allergic reactions or the management of irAEs and other AEs) is allowed. Prophylactic use of steroid for contrast agents should follow the local guidance.
- Steroids with no or minimal systemic effect (topical, intranasal, intra-ocular, inhalation) are allowed
- Hormone replacement with corticosteroids for adrenal insufficiency is allowed if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg prednisone or equivalent per day.

- Vaccination with live vaccines while on study is prohibited. Administration of inactivated vaccines (i.e., inactivated influenza vaccines) or approved SARS-COV-2 vaccines is allowed.

If the administration of a non-permitted concomitant drug becomes necessary during the study, the participant should be withdrawn from study intervention (the Sponsor may be contacted to discuss whether the study intervention must be discontinued); see Section 7.1.

The following treatments are permitted, but should be used with caution during the study:

- Those with potential to cause drug interactions with cisplatin:
  - Allopurinol, colchicine, probenecid, sulfinpyrazone*: increase in serum uric acid concentration
  - Cephalosporins, aminoglycosides, amphotericin B: increase nephrotoxic and ototoxic effects of cisplatin in these organs
  - Cyclosporine: excessive immunosuppression, with risk of lymphoproliferation
  - Cyclizine*, phenothiazines: may mask ototoxicity symptoms
  - Furosemide (high doses), hydralazine, diazoxide, and propranolol: intensify nephrotoxicity
  - Oral anticoagulants: require an increased frequency of international normalized ratio monitoring
  - Penicillamine: may diminish the effectiveness of cisplatin
  - Phenytoin: reduced epilepsy control.
- Other anticonvulsants (possible interactions that have been described with cisplatin)
- Nephrotoxic drugs (concomitant use should be avoided in participants treated with cisplatin).

*Not approved in Japan.

6.5.4 Other Interventions

The following nondrug interventions must not be administered during the study (within 28 days before randomization):

- Major surgery, except for urgent palliative surgery, prior diagnostic biopsies and stenting/PTBD for the purpose of releasing biliary tract obstruction. Discuss with the Medical

Monitor if unplanned major surgery is required during the study to plan for timing of re-treatment

- Radiotherapy, except for palliative bone-directed radiotherapy.

The following nondrug interventions must not be administered during the study (and within 28 days before randomization):

- Herbal remedies with immune-stimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin).
- 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. A nonexhaustive list of prohibited Chinese medications are provided in Appendix 10.

6.5.4.1 Premedication

To mitigate potential IRRs, premedication with an antihistamine and with paracetamol (e.g., 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] intravenous or oral equivalent) approximately 30 to 60 minutes prior to each dose of bintrafusp alfa (in the open-label, safety run-in part) or bintrafusp alfa/placebo (in the randomized, double-blind part) is mandatory for the first 2 infusions.

Premedication is optional and at the discretion of the Investigator after the second infusion. However, if Grade 2 infusion reactions are seen during the first 2 infusions, premedication should not be stopped (see Section 6.9.1). Steroids as premedication are not permitted, except for anti-emesis. See also Section 6.6.1 for guidance on the prophylactic use of steroids for anti-emesis.

6.6 Dose Selection and Modification

6.6.1 Dosing Instructions

Bintrafusp alfa or placebo should be administered prior to gemcitabine and cisplatin dosing when given on the same day. Premedication is mandatory prior to the first 2 infusions of bintrafusp alfa (open-label, safety run-in part) or bintrafusp alfa/placebo (randomized, double-blind part) but is optional thereafter (see Section 6.5.4.1).

Participants assigned to the open-label, safety run-in part or to the bintrafusp alfa arm in the randomized, double-blind part will receive an intravenous infusion of bintrafusp alfa as a flat dose of 2400 mg over a minimum of 1 hour CCI [redacted] and up to 2 hours CCI [redacted] once every 3 weeks until confirmed disease progression, unacceptable toxicity, or until any criterion for discontinuation of the study intervention (Section 7.1) or discontinuation/withdrawal from the study (Section 7.2) is met. In order to manage specific AEs (as specified in Section 6.9.5), a bintrafusp alfa dose of 1200 mg may be administered within 1 hour CCI [redacted] Participants with CR should continue study

intervention for 2 years after the first onset of CR or until 1 of the criteria for discontinuation is met, whichever occurs first.

Participants assigned to the placebo arm of the randomized, double-blind part will receive an intravenous infusion of placebo over a minimum of 1 hour [redacted] and up to 2 hours [redacted]) every 3 weeks until confirmed disease progression, unacceptable toxicity, or until any criterion for discontinuation of the study intervention (Section 7.1) or discontinuation/withdrawal from the study (Section 7.2) is met. In order to manage specific AEs (as specified in Section 6.9.5), an intravenous infusion of placebo corresponding to a bintrafusp alfa dose of 1200 mg may be administered within 1 hour [redacted] Participants with CR should continue study intervention for 2 years after the first onset of CR or until 1 of the criteria for discontinuation is met, whichever occurs first.

To keep the dose intensity of bintrafusp alfa/placebo, follow the dosing schedule instruction in Table 1. Modification of the infusion rate due to IRRs is described in Section 6.9.1. Modification of the dose of bintrafusp alfa/placebo due to bleeding events is described in Section 6.9.5.

Participants who experience a CR should be treated with bintrafusp alfa/placebo for 2 years after the first onset of CR. However, the Investigator may temporarily withhold the treatment after the CR for 12 months in the absence of progression after entering CR depending on the clinical decision. The Investigator may resume bintrafusp alfa/placebo after the interruption if it is considered clinically beneficial, after consultation with the Medical Monitor.

In cases of CR, continuation of bintrafusp alfa/placebo may be allowed beyond 2 years after the first onset of CR, subject to discussion between the Investigator and Medical Monitor taking both clinical benefit and safety into consideration.

For both the bintrafusp alfa arm and the placebo arm in the randomized, double-blind part or for the bintrafusp alfa arm in the open-label, safety run-in part, gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) will be administered intravenously on Days 1 and 8 of every 21-day cycle for 8 cycles in accordance with the local label (SmPC), package insert, or NHS-approved practice (in the UK only) for gemcitabine and cisplatin. If chemotherapy cannot be administered on Day 1 or Day 8 of a given cycle (for safety, tolerability or other unavoidable reasons), the missed dose may be administered on Day 15 of that cycle. In addition, any missed dose(s) of chemotherapy may be made up at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination) provided the participant does not meet any of the criteria for discontinuation of study intervention or discontinuation of study (Section 7). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision. The Investigator should try to keep the dose intensity of gemcitabine and cisplatin as high as possible, with dosing scheduled on Days 1 and 8 during the 8 treatment cycles, and dose of gemcitabine and/or cisplatin modified, as appropriate. For dose modifications, see Section 6.6.3 Section 6.6.4, and Table 13.

Intravenous hydration (given during cisplatin infusion to prevent nephrotoxicity) should be administered as per standard practice. A corticosteroid-sparing approach for anti-emetic prophylaxis should be considered since concurrent use of corticosteroid may negatively impact the efficacy of immune checkpoint inhibitor therapy. Thus, in this study, a 5-HT$_3$ antagonist and/or a

neurokinin-1 (NK1) inhibitor should be used for anti-emesis. If nausea and/or vomiting are not clinically manageable by 5-HT_3 antagonist and/or neurokinin-1 inhibitor, prophylactic use of steroid is allowed.

Tumor measurements to determine response will be performed as indicated in the Schedule of Activities (see Section 1.3).

6.6.2 Definition of Dose-limiting Toxicity

A DLT is a toxicity related to the study intervention that meets the following criteria as evaluated in the open-label, safety run-in:

1. Grade 3 or 4 irAE that needs permanent discontinuation of bintrafusp alfa treatment. A malignant skin lesion induced by bintrafusp alfa that is local and can be resected with a negative resection margin is not a DLT.

2. Grade 3 or 4 nonhematologic toxicity other than irAE, except for the following:
   - Grade 3 IRRs resolving within 6 hours from the end of infusion and controlled with medical management
   - Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever that are controlled with medical management
   - Transient (≤ 48 hours) Grade 3 nausea or vomiting despite optimal supportive care
   - Transient (≤ 72 hours) Grade 3 fatigue, local reactions, or headache
   - Toxicities that do not require medical intervention as treatment.

3. A life-threatening hematological toxicity (unless clearly attributable to chemotherapy alone), which is hardly medically manageable, including a bleeding event resulting in urgent intervention and admission to an intensive care unit.

4. Grade 5 toxicity.

The DLT criteria are selected based on toxicity that necessitates permanent discontinuation of the study intervention.

The DLT evaluation period is the first 21 days following the first dose of bintrafusp alfa.

6.6.3 Treatment Modification

An Investigator may attribute each toxicity event to bintrafusp alfa/placebo, gemcitabine and/or cisplatin alone, or to the combination, and use the appropriate treatment modification as per the matrix shown in Table 7.

Toxicity needs to resolve to Grade ≤ 1 or baseline prior to resuming the study intervention to which the toxicity was attributed. However, the study intervention can be resumed even if the toxicity does not resolve to Grade ≤ 1 or baseline if the toxicity is manageable and/or asymptomatic. If a

participant experiences several toxicities and there are conflicting recommendations, the most conservative dose and/or treatment modification recommended should be followed (chemotherapy dose reduction appropriate to the most severe toxicity). Other AEs (e.g., infections) should be handled in a similar manner, if clinically indicated.

Bintrafusp alfa/placebo treatment may be interrupted, modified, or discontinued due to toxicity (Table 7).

Chemotherapy and bintrafusp alfa/placebo may be interrupted for a maximum of 12 weeks. Beyond 12 weeks, discuss further treatment plans with the Medical Monitor. If a toxicity is incorrectly attributed to the study intervention and the treatment is modified, the drug may go back to the premodified condition.

Any questions or concerns should be discussed with the Medical Monitor.

Table 7 Treatment Modification for Bintrafusp alfa/Placebo, Gemcitabine, and Cisplatin

Attributed Drug as a Cause of Adverse Drug Reaction	Treatment Modification	
	Bintrafusp alfa/Placebo	Chemotherapy
Bintrafusp alfa/Placebo	• For irAEs, follow ASCO guideline in Appendix 8 • Adverse events related to bintrafusp alfa/placebo which are not covered in the ASCO guideline, see the guidance in this section. • For bleeding and rapid progressing anemia, follow the modification guidance in Sections 6.9.4 and 6.9.5.	• Consider to dose if the toxicity does not meet the DLT criteria in Section 6.6.2 on the day of dosing • Withhold the dose if medically indicated. • In the case of hematological and renal impairment, follow the modifications in Table 10 and Table 11, respectively.
Chemotherapy	• Consider to dose if the toxicity does not meet the DLT criteria in Section 6.6.2 on the day of dosing • Withhold the dose if medically indicated. • For bleeding and rapid progressing anemia, follow the modification guidance in Sections 6.9.4 and 6.9.5.	• Follow Table 8, Table 9, Table 10, and Table 11, as appropriate to the reaction • Resume gemcitabine and/or cisplatin after improving to Grade 1 or lower

ASCO=American Society of Clinical Oncology, DLT=dose-limiting toxicity, irAEs=immune-related adverse events.

6.6.3.1 Bintrafusp alfa/Placebo-related Adverse Drug Reactions

Any adverse drug reaction (ADR) assessed as related to bintrafusp alfa or placebo may require permanent or transient discontinuation of bintrafusp alfa/placebo treatment. For the management of certain ADRs assessed to be irAEs, follow the American Society of Clinical Oncology (ASCO) guideline with modification in Appendix 8. The ASCO guidance does not necessarily supersede the clinical decision of the Investigator. If the Investigator considers that it is medically more appropriate for the participant to continue in the study or to terminate the study, even if deviating

from the guidance, the Investigator should consult the Medical Monitor. Single laboratory values out of the normal range that do not have any clinical correlate do not necessarily need treatment interruption. Questions or concerns regarding the management and/or follow-up of ADRs should also be discussed with the Medical Monitor.

Infusion-related reactions, irAEs, TGFβ inhibition mediated skin reactions, anemia, and bleeding events should be managed and followed-up as described in the subsequent protocol sections. Permanent discontinuation of study intervention may be recommended, so the relevant protocol section must be reviewed:

- Guidance on IRRs and hypersensitivity is presented in Section 6.9.1
- Management and guidance of suspected irAEs is provided in Section 6.9.2 and Appendix 8
- Guidance and management of TGFβ inhibition mediated skin reactions is discussed in Section 6.9.3
- Guidance on anemia is presented in Section 6.9.4.
- Guidance and management of bleeding events are discussed in Section 6.9.5

In general, the following applies for ADRs related to bintrafusp alfa/placebo 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 (≤ 6 hours) Grade 3 flu-like symptoms or fever that is controlled with medical management
- Transient (≤ 24 hours) 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 (see Sections 6.9.4 and 6.9.5 for further details)
- KA and cutaneous squamous cell carcinoma (cSCC). Any suspicious skin lesion should be biopsied and surgically removed
- Increases in ECOG PS to ≥ 3 that resolve to ≤ 2 by Day 1 of the next infusion (i.e., infusion should not be given if the ECOG PS is ≥ 3 on the day of treatment, and should be delayed until ECOG PS is ≤ 2)
- Endocrinopathies controlled with hormone replacement therapy

Any Grade 2 ADRs should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue
- If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle but 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 8). Toxicity grading is assigned based on NCI-CTCAE Version 5.0. The ASCO guideline should be used only for the management of immune-related toxicity due to bintrafusp alfa/placebo.

6.6.3.2 Gemcitabine and/or Cisplatin-related Adverse Drug Reactions

If a dose reduction for chemotherapy-related toxicity other than neutropenia and thrombocytopenia occurs with gemcitabine or cisplatin, the dose may not be re-escalated. Participants can have a maximum of 2 dose reductions (if applicable) to each of the components throughout the course of the study for toxicities. If participants require a third dose modification, that agent will be discontinued.

Reduction of 1 chemotherapy agent and not the other agent is appropriate if the toxicity is related to 1 of the treatments but not to the other. If the toxicity is related to the combination of both chemotherapy agents, either gemcitabine or cisplatin, or both drugs depending on the Investigator's clinical decision should be reduced according to the recommended dose modifications in Table 8 (gemcitabine and cisplatin), Table 9 (nonhematological toxicity), Table 10 (neutropenia and thrombocytopenia), and Table 11 (renal impairment).

Table 8 Dose Modification for Gemcitabine and Cisplatin

Toxicity	Gemcitabine	Cisplatin
-1 level First occurrence	Give 75%	Give 75%
-2 level Second occurrence	Give 50%	Give 50%
-3 level Third occurrence	Permanent cessation	Permanent cessation

Nonhematological Toxicity Related to Gemcitabine and/or Cisplatin

Table 9 Nonhematological Toxicity

Toxicity Grade	Gemcitabine Dose	Cisplatin Dose
Nausea/vomiting	No reduction	No reduction
Other nonhematological toxicity Grade 3[a]	1 level reduction	1 level reduction
Other nonhematological toxicity Grade 4[a]	1 level reduction or permanent discontinuation[b]	1 level reduction or permanent discontinuation[b]

a Other than hypersensitivity, infusion-related reaction, and nonhematological toxicity that does not require medical intervention including, but not limited to, alopecia and fatigue.

b Clinical judgment.

Resume gemcitabine and/or cisplatin after improvement to Grade ≤ 1 with dose modification for chemotherapy-related toxicity. For Grade 4 toxicity, the Investigator will make a clinical decision whether to discontinue treatment or to resume with dose modification. The use of anti-emetics other than prophylactic steroids should follow the guidance provided in Section 6.6.1.

Hematological Toxicity Related to Gemcitabine and/or Cisplatin

Table 10 Dose Modification for Neutropenia and Thrombocytopenia

Toxicity Grade on the Day of Dosing	Gemcitabine Dose	Cisplatin Dose
Neutrophils 0.5×10^9/L to $< 1.0 \times 10^9$/L	1 level reduction	No reduction
Neutrophils $< 0.5 \times 10^9$/L	Skip dose	Skip dose
Platelets 50×10^9/L to $< 100 \times 10^9$/L	1 level reduction	No reduction
Platelets $< 50 \times 10^9$/L	Skip dose	Skip dose

In the case of chemotherapy-related anemia (Hgb < 8 g/dL), febrile neutropenia, neutrophils $< 0.5 \times 10^9$/L, or platelets $< 50 \times 10^9$/L for longer than 7 days, resume gemcitabine and cisplatin with 1 level reduction after improving to Grade 1 or less. Other than these reductions, the dose can be re-escalated to baseline. The Investigator may reduce the dose of gemcitabine and/or cisplatin further to that indicated in Table 10 (i.e., dose reduction up to -2 level either/both gemcitabine or/and cisplatin, or gemcitabine monotherapy) to keep dose intensity as high as possible on Days 1 and 8 of every 21-day cycle dosing if the participant needs or anticipates to skip dosing more frequently due to chemotherapy-related hematological toxicities.

If a Grade 2 anemia does not resolve to Grade ≤ 1 by the last day of the current cycle but 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.

Otherwise, adjust gemcitabine and cisplatin dose according to Table 10 based on the blood count on the day of or a day before dosing. Administration of granulocyte-colony stimulating factor should follow local guidelines or NCCN guidelines. The use of erythropoietin should follow local guidelines.

6.6.4 Dose Modification of Gemcitabine, Cisplatin, and Bintrafusp alfa/Placebo for Renal Impairment

In the case of renal toxicity, dose modification of gemcitabine and cisplatin will be applied as per Table 11, regardless of the cause. If baseline CrCl is < 60 mL/min, modify the starting dose of cisplatin accordingly.

Cisplatin-induced renal impairment must be recovered to Grade 1 or baseline value in order to resume cisplatin treatment.

Table 11 Dose Modification for Renal Impairment

Creatinine Clearance (mL/min)	Gemcitabine	Cisplatin
≥ 60 (Grade 1 or better)	Give 100%	Give 100%
50-59	Give 100%	-1 reduction[a]
40-49	Give 100%	-2 reductions
30-39	Give 100%	Permanent discontinuation
< 30 (Grade 3)	Permanent discontinuation	Permanent discontinuation

CrCL=creatinine clearance.

a Eligibility criteria require a CrCL > 50 mL/min; if baseline CrCL is < 60 mL/min, modify the starting dose of cisplatin accordingly.

The CrCl will be estimated by the Cockcroft-Gault formula or calculated from 24-hour urine collection. No other formula should be used for the CrCl calculation. If an enzymatic method is used for serum creatinine measurement, add 0.2 ($Cr_{jaffe} = 0.2 + Cr_{enzyme}$) to calculate.

Treatment of bintrafusp alfa/placebo should be modified according to the ASCO guideline (Appendix 8) if the cause of renal impairment is attributed to an irAE. If renal impairment is related to chemotherapy, follow Table 8. If renal impairment is related to bintrafusp alfa/placebo, follow Table 7.

6.6.5 Disease Specific Risk: Hepatic Impairment

BTC can cause cholestasis that could induce 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. Participants with acute cholangitis may develop septic shock and thus require frequent monitoring for signs of shock.

Diagnostic criteria for acute cholangitis are summarized in Table 12 (Kiriyama 2013). If biliary infection is suspected, the study intervention must be withheld. The Investigator should consider biliary drainage as well as treatment with antibiotics. Biliary tract obstruction should be relieved by PTBD, percutaneous transhepatic gallbladder drainage, endoscopic stenting, stenting via PTBD tube, or bypass surgery, and must be free of infection prior to dosing. For stenting, a covered, expandable metallic stent should be used if anatomically and technically applicable rather than a small diameter plastic tube stent. Neutropenia caused by gemcitabine and cisplatin, as well as immunomodulation with bintrafusp alfa, could worsen with biliary tract infection. If biliary tract

infection is clinically deniable or improved, the study intervention can be resumed. Immune-related cholangitis should be differentiated if medically indicated.

Hepatitis B virus (HBV) DNA positive participants must be treated and on a stable dose of antivirals (e.g., entecavir, tenofovir, or lamivudine; adefovir or interferon is not allowed) at study entry and for the duration of the study, in addition to planned monitoring and management including HBV-DNA quantity according to appropriate labeling guidance. HCV ribonucleic acid (RNA) should be monitored during the study if HCV RNA is positive at baseline. If a liver function test is elevated in an HBV- or HCV-positive participant, HBV DNA or HCV RNA must be monitored to exclude the possibility of reactivation of viral hepatitis. In case of viral reactivation, follow the local HBV and HCV management guideline.

If an Investigator can attribute the cause of hepatic impairment to bintrafusp alfa and/or chemotherapy, follow the irAE guideline in Appendix 8 or the nonhematological dose modification in Table 8 and Table 9.

Table 12 Diagnostic Criteria for Acute Cholangitis

A. Systemic Inflammation	A-1. Fever and/or shaking chills	Body temperature > 38°C
	A-2. Laboratory data: evidence of inflammatory response	WBC < 4 × 10^9/L, or > 10 × 10^9/L CRP ≥ 1 mg/dL (190 nmol/L)
B. Cholestasis	B-1. Jaundice	T-Bil ≥ 2 mg/dL
	B-2. Laboratory data: abnormal liver function tests	ALP > 1.5 × ULN γGTP > 1.5 × ULN AST > 1.5 × ULN ALT > 1.5 × ULN
C. Imaging	C-1. Biliary dilatation	
	C-2. Evidence of the etiology on imaging (stricture, stone, stent, etc)	

ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CRP=C-reactive protein, γGTP=gamma-glutamyl transpeptidase, T-Bil=total bilirubin, ULN=upper limit of normal, WBC=white blood cell.

Suspected diagnosis: One item in A and 1 item in either B or C.

Definite diagnosis: One item in A, 1 item in B, and 1 item in C.

Other factors that are helpful in the diagnosis of acute cholangitis include abdominal pain (right upper quadrant or upper abdominal).

6.7 Study Intervention After the End of the Study

Participants will be followed for survival and AEs as specified in the Schedule of Activities (see Section 1.3).

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

6.8 Special Precautions

As a part of safety-related precautionary measures, a standardized risk management approach is planned for bintrafusp alfa for IRRs, irAEs, TGFβ inhibition mediated skin reactions, anemia, and bleeding AEs. This approach is mainly based on the monoclonal antibody mechanism of PD-L1 inhibition and TGFβ inhibition.

- As a routine precaution, for the first 2 infusions, all participants enrolled in this study must be observed for 2 hours following the end of infusion in an area with resuscitation equipment and emergency agents. If no IRRs are observed during the first 2 infusions, the mandated 2-hour post-infusion observation time may be reduced to 60 minutes. The subsequent gemcitabine and/or cisplatin infusion can be initiated during the 1- to 2-hour observation period
- At all times during bintrafusp alfa/placebo treatment, immediate emergency treatment of an IRR or a severe hypersensitivity reaction according to institutional standards must be assured
- To treat possible hypersensitivity reactions like anaphylactic reactions, dexamethasone 10 mg and epinephrine in a 1:1000 dilution (or equivalents) should always be available along with equipment for assisted ventilation.

See Section 6.9 for further details.

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

Adverse events of special interest (AESI) are serious or nonserious AEs that are of clinical interest and should be closely followed.

For this study, AESIs include the following:

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

6.9.1 Infusion-related Reactions Including Immediate Hypersensitivity

Infusion-related reactions (including immediate hypersensitivity) are common ADRs with monoclonal antibodies, related to drug administration. They are AESI and identified risks for bintrafusp alfa; IRRs are also likely caused by cisplatin.

Infusion-related Reactions

IRRs 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 drug 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.

See Table 13 for instructions on-treatment modification of bintrafusp alfa/placebo for IRRs.

Table 13 Treatment Modification of Bintrafusp alfa/Placebo for Symptoms of Infusion-Related Reactions Including Immediate Hypersensitivity

NCI-CTCAE Grade (Description)	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
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 bintrafusp alfa/placebo infusion • Increase monitoring of vital signs as medically indicated • If symptoms resolve quickly or decrease to Grade 1, resume infusion at 50% of original rate with close monitoring of any worsening, otherwise hold dosing until resolution of symptoms with mandated premedication for the next scheduled visit • Consider treatment with corticosteroids if symptoms persist • At the next infusion, consider H_2-blockers (e.g., famotidine or ranitidine) as clinically indicated. If participants have a second Grade ≥ 2 IRR on the reduced-rate infusion with the suggested medication, stop the infusion and remove the participant from treatment • 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 bintrafusp alfa/placebo infusion immediately and disconnect infusion tubing from the participant with additional appropriate medical measures and close monitoring until deemed medically stable by attending Investigator. Hospitalization and/or close monitoring is recommended • Administration of glucocorticoids may be required • Permanently withdraw participant from bintrafusp alfa/placebo treatment and do not administer any further bintrafusp alfa/placebo treatment

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

If the bintrafusp alfa infusion is interrupted or the rate reduced to 50% of the previous infusion rate, it is recommended that the rate remains reduced for all subsequent infusions. The speed may be adjusted depending on the presentation of IRRs during subsequent infusions.

For Grade 3 or 4 infusion-related reactions, bintrafusp alfa/placebo discontinuation is mandated.

For Grade 3 infusion-related reactions, "prolonged" is defined in this protocol as lasting > 6 hours.

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

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 (UK) can be found at

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 monitor 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.

Cisplatin-related Hypersensitivity

IRRs due to intravenous chemotherapy can be minimized with close monitoring for any early development of any signs and symptoms (mainly hypersensitivity induced by platinum-containing chemotherapy, known to occur more with subsequent cycles) (Makrilia 2010). The incidence of cisplatin-induced hypersensitivity ranges from 5% to 20% and occurs within minutes of infusion mostly commonly between the 4th and 8th treatment courses. Once cisplatin-induced IRR/hypersensitivity occurs, cisplatin should be permanently withdrawn.

Since corticosteroid use as premedication is prohibited, close participant vigilance and prompt recognition of hypersensitivity symptoms are advised. Moderate to severe IRR symptoms will require infusion interruption and prompt symptomatic management. Refer to the product label for IRR/immediate hypersensitivity management guidelines.

If the responsible drug for IRRs/hypersensitivity is not identified, see Table 14 for instructions on which drug(s) to modify.

Table 14 Modification of Combination Treatment for Infusion-related Reactions/Hypersensitivity

Timing of IRR Occurrence	Cause of IRR	First Occurrence			
		On Day of Bintrafusp alfa/Placebo /Gemcitabine/Cisplatin Infusion		On Day of Gemcitabine/Cisplatin Infusion	
		Apply Modification to:	No Modification[a]	Apply Modification to:	No Modification[a]
Before cisplatin infusion	Bintrafusp alfa/ placebo	Bintrafusp alfa/placebo	Gemcitabine and cisplatin	NA	NA
A few minutes after starting cisplatin infusion	Likely cisplatin[b]	Cisplatin[b]	Bintrafusp alfa/placebo and gemcitabine	Cisplatin	Bintrafusp alfa/placebo and gemcitabine
After cisplatin infusion	Bintrafusp alfa/ placebo or cisplatin	Bintrafusp alfa/placebo and/or cisplatin	Gemcitabine	Cisplatin	Bintrafusp alfa/placebo and gemcitabine

IRR=infusion-related reaction, NA=not applicable.
Follow Table 13 for dose modification of bintrafusp alfa/placebo.
Cisplatin will be permanently terminated in case of cisplatin-related hypersensitivity.
Sequence of infusion: 1. Bintrafusp alfa/placebo, 2. Gemcitabine or Cisplatin, 3. The rest of Gemcitabine or Cisplatin.
a When resumed.
b Carefully observe the next dosing, as the possibility of IRRs related to bintrafusp alfa remains.

6.9.2 Immune-related Adverse Events

An irAE is defined as an off-target side effect associated with exposure of immunogenic drug and is consistent with an immune mechanism. In the process of identification of irAEs, any possible etiology of neoplastic, infectious, metabolic, toxin, or any other factor should be ruled out. Serological, histological (biopsy), and immunological data should be obtained to support immune mediation of the occurrence of an AE.

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

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

- Immune-related hepatitis
- Immune-related pneumonitis
- Immune-related colitis
- Immune-related nephritis and renal dysfunction
- Immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorders)
- Immune related rash

- Other immune-related events (myositis, myocarditis, encephalitis)

The following irAEs are important potential risks for bintrafusp alfa:

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

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

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

For reporting irAE severity/toxicity grading, refer to the CTCAE Version 5.0 toxicity grading system. The recommendations for irAE management are guided by the joint ASCO Clinical Practice Guidelines and NCCN guidelines, listed in Appendix 8.

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 study intervention may be considered.

For additional organ/system specific management guidelines, see the guideline tables in Appendix 8.

6.9.3 TGFβ Inhibition Mediated Skin Reactions

TGFβ inhibition mediated skin reactions, including hyperkeratosis, KA and/or cSCCs, are important identified risks and AESI for bintrafusp alfa.

Skin assessments are performed at baseline and every 6 weeks for all participants as specified in the Schedule of Activities (Section 1.3). 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 ultraviolet exposure/sun damage of skin, and occupational or environmental exposure to radiation or chemicals.

Management guidelines for potential TGFβ 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
- A diagnostic and treatment plan should be developed in collaboration between the Investigator and dermatologist. In general, treatment of TGFβ inhibition mediated skin lesions such as hyperkeratosis, KA and cSCC should be based on local guidelines/SoC. Lesion evaluation should include excision biopsy of 1 representative lesion to confirm diagnosis
- Treatment and follow-up for KA and cSCC will depend on the number and localization of lesions:
  - For single lesions:
    - Full excision may be recommended.
  - In case of multiple lesions or a 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 the dermatologist, may be considered after discussion with the Medical Monitor.

- Close clinical follow-up for re-evaluation, resolution, or potential recurrence should be implemented
- Spontaneous resolution of KA lesions without surgical intervention has been observed, typically occurring within weeks after discontinuing bintrafusp alfa
- The number and localization of lesions, diagnosis (including histopathological diagnosis), treatment, and outcome should be appropriately documented in the eCRF.

Consult with the Medical Monitor as needed for the management of TGFβ inhibition mediated skin lesions.

6.9.4 Anemia

Nonclinical testing of bintrafusp alfa led to the classification of anemia as an AESI and important identified risk (refer to the IB for further information).

Notably there are many reasons for anemia in advanced cancer patients, including anemia caused by gemcitabine and cisplatin chemotherapy. Also, given that participants with a Hgb level of 9 g/dL may enter the study, a thorough investigation of new cases of anemia with unspecified etiology is requested.

Safety laboratory testing of relevant blood parameters should be conducted per the Schedule of Activities (see Section 1.3).

Since the study intervention will be administered in combination with chemotherapy, distinguishing anemia induced by bintrafusp alfa/placebo from that by chemotherapy may not be possible. However, if the events are assessed as bintrafusp alfa/placebo-related, items queried may include but are not limited to: detailed relevant past medical and treatment history, bruising tendency, history of blood transfusions and/or dependency, and a request for an updated eCRF (including details such as concomitant medications, all laboratory data, updated dosing information, and recent tumor evaluation scans). See also Section 6.9.5 for management of rapid Hgb decrease.

General guidance for anemia management and evaluation include the following:

- Participants must enter the study with an Hgb value of at least 9 g/dL and baseline anemia evaluation as conducted per Table 15
- All relevant hematologic testing for anemia should be performed 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, so that this work-up is not confounded. If participant recovers to Grade 1 anemia with a blood transfusion, suspend the next dosing until confirming anemia is stably controlled, and the underlying cause of anemia is resolved. As guidance, the Investigator should wait for at least 1 week post-transfusion to confirm stabilization. If anemia is stabilized and the dosing criteria (Hgb Grade 1 or baseline) are met 1 week after the transfusion, the Investigator can proceed to the next dosing.

- Guidance for the evaluation of suspected anemias is provided in Table 15. Discuss further management with the Medical Monitor for clinically significant anemias.

Table 15 Evaluation Guidance for Suspected Anemia

Anemia Evaluation (Prior to Transfusion, if Feasible)	
Hgb and CBC with differential (e.g., MCV, RDW, ANC, hematocrit, reticulocytes counts) Peripheral blood smear for cell morphological assessment Complete metabolic panel including liver panel-LFTs, bilirubin, LDH, renal function, serum folate, B12, and other chemistries: • Coagulation factors (PT, PTT, INR) • Urinalysis, including culture • Iron panel (TIBC[a], ferritin, Fe) • TSH/hormonal panel • Fecal-occult blood testing • 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

CCI [redacted], 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, PTT=partial thromboplastin time, RDW=red cell distribution width, TIBC=total iron binding capacity, TSH=thyroid-stimulating hormone.

a If TIBC cannot be evaluated locally, replace with transferrin.

6.9.5 Bleeding Events

Bleeding events are AESIs and an important identified risk for bintrafusp alfa (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 bintrafusp alfa in ongoing studies. Events may include epistaxis, hemoptysis, gingival bleeding, or hematuria, among others. In general, these reactions resolve without discontinuation of treatment.

For all participants:

For Grade 2 non-tumor bleeding, see Section 6.6.3.1 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. Upon resumption of the study intervention, bintrafusp alfa dose should be reduced to 1200 mg Q3W or relevant volume of matching placebo.

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

In case of rapid decrease of hemoglobin (Hgb), such as a decrease greater than 3.0 g/dL across a 3 weeks period, withhold the subsequent cycles of study intervention until Hgb is stabilized and do a thorough assessment of bleeding (for example, upper and lower GI endoscopy, enhancement CT etc.); if Grade 1 or greater bleeding is observed or suspected, withhold the bintrafusp alfa/placebo until the bleeding is resolved/controlled and resume the dose of bintrafusp alfa reduced to 1200 mg Q3W or corresponding volume of matching placebo. Gemcitabine and cisplatin may be resumed earlier after consultation with the Medical Monitor. The dose of bintrafusp alfa/placebo may be re-escalated to full dose (bintrafusp alfa 2400 mg or corresponding volume for placebo) once Hgb is stabilized without further need for blood transfusion in the subsequent cycles. The timing of re-escalation may need a case-by-case decision. Once Hgb decrease is recovered to $\leq$ Grade 1 or baseline and stably controlled, the Investigator is encouraged to communicate with Medical Monitor to re-escalate the dose (see Section 6.9.4 regarding stabilization of anemia).

6.9.5.2 Tumor Bleeding

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

If Grade 3 or severe bleeding event had been observed regardless of causality with the study intervention, upon resumption of the study intervention, bintrafusp alfa dose should be reduced to 1200 mg Q3W or relevant volume of matching placebo. Study intervention should be permanently discontinued if the Investigator considers the participant to be at risk for additional severe bleeding.

In case of rapid decrease of Hgb, see Section 6.9.5.1.

6.9.6 Other Potential Risks

6.9.6.1 Impaired Wound Healing

Impaired wound healing is considered an important potential risk (a theoretical risk-based on literature findings) for bintrafusp alfa given the role of TGFβ in wound healing. Management of wound healing or tissue damage repair should be discussed with the Medical Monitor for participants requiring surgery on study. It is recommended to hold treatment 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 therefore considered an important potential risk for bintrafusp alfa. Refer to the IB for further information.

An appropriate contraception warning is provided as part of the inclusion criteria (see Section 5.1). Participants with pregnancies or breastfeeding are prohibited from being enrolled in clinical studies. Pregnant women are not allowed in the bintrafusp alfa study and adequate contraceptive measures are recommended during the study to minimize or eliminate the potential risk to the developing fetus.

Respective safety measures comprise inclusion/exclusion criteria for participation in clinical studies with bintrafusp alfa, guidance for prevention, monitoring, and medical management of potential risks, as well as guidance on study intervention interruption or discontinuation. See also Appendix 3.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

7.1.1 Permanent Treatment Discontinuation

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

1. Participants with PD as initially determined by the site based on RECIST 1.1 while on treatment, with the exceptions detailed in Section 7.1.2.
2. Significant clinical deterioration (clinical progression), defined as new symptoms that are deemed by the Investigator to be clinically significant or significant worsening of existing symptoms.
3. Unacceptable toxicity; see Sections 6.6 and 6.9.
4. Therapeutic failure requiring urgent additional or alternative anticancer treatment.
5. Occurrence of AEs resulting in the permanent discontinuation of the study intervention being desired or considered necessary by the Investigator and/or the participant.
6. Occurrence of pregnancy in the participant.
7. Use of a prohibited concomitant drug, as defined in Section 6.5.3, where the predefined consequence is withdrawal from the study intervention if considered necessary by the Investigator or the Sponsor.
8. Noncompliance: see Section 6.4.

After initiation of study intervention, participants with obstructive jaundice and/or biliary tract infection without concomitant radiological PD should undergo prompt biliary drainage and be retained in the study.

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. See Section 1.3.

7.1.2 Treatment Beyond Initial Progression

See Figure 3 for treatment continuation beyond radiological PD.

Once the site detects PD by RECIST 1.1, PD (as defined below) should be confirmed by the Investigator on a further scan performed at least 28 days after the initial Investigator detection of PD or at the next scheduled scan. The Investigator is encouraged to continue bintrafusp alfa/placebo treatment during this time, i.e., from the initial detection of PD by the Investigator according to RECIST 1.1, until confirmed PD if all following criteria (criteria 1 to 6) are met:

1. Study intervention is ongoing
2. No new unacceptable treatment or disease-related toxicity is observed
3. Tolerance of study interventions
4. Stable or improving ECOG PS
5. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)
6. Participant has signed a separate informed consent to ensure and to document that they are aware of being treated beyond initial disease progression.

The continuation of gemcitabine and cisplatin until confirmed PD (or up to 8 cycles, whichever occurs first) is at the discretion of the Investigator if all the stated conditions (criteria 1-6) are met.

Confirmed PD is defined as a further progression of any detectable increase in tumor burden, with no lower limit to the magnitude of the increase. Any enlargement of existing target lesions, or of nontarget lesion burden, of existing new lesions, or appearance of any further new lesion will constitute further progression. Further definitions are provided in Table 16.

If radiographic assessment does not confirm PD, the assessment should continue according to the Schedule of Activities (see Section 1.3) until further progression or any other criterion for withdrawal is met.

A Decision Tree for continuation of treatment until confirmed PD is provided in Figure 3.

Table 16 Definitions of Progressive Disease

Term	Definition
Confirmed PD	Site has detected disease progression and has performed a second scan at least 28 days later that shows further progression of disease Note: Confirmation is made 28+ days later by the Investigator
Further progression	Further progression is defined as any detectable increase in tumor burden as compared to onset of PD, with no lower limit to the magnitude of the increase. Any enlargement of existing target lesions, or of nontarget lesion burden, of existing new lesions, or any further new lesion will constitute further progression

PD=progressive disease.

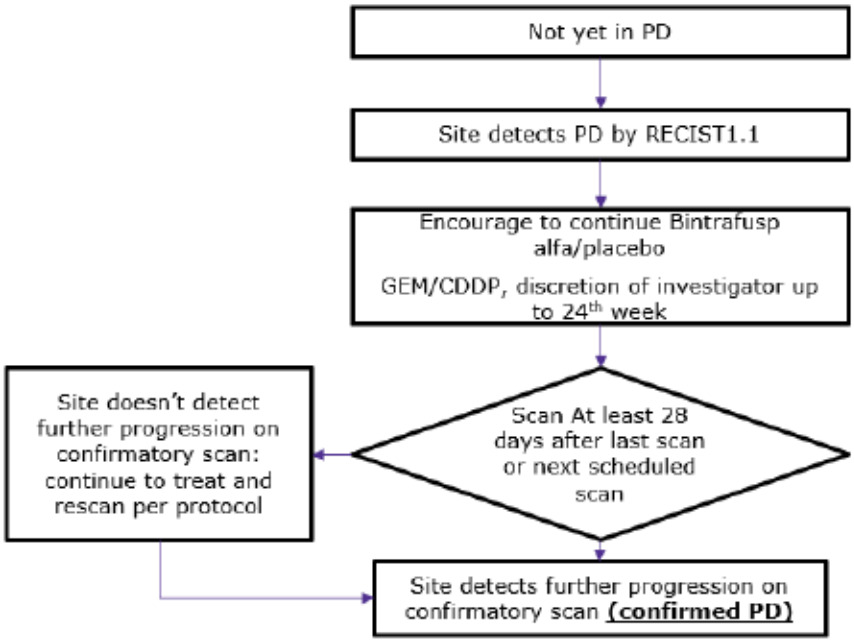
Documented Date of Progressive Disease

The date that the site first detects PD for a study participant will be referred to as the "site date of progression for RECIST 1.1."

For the participants in scope of the adaptative decision analysis, the IRC will determine the date of PD under RECIST 1.1 separately through the IRC processes, and will also determine the date of final immune PD under immune-related Response Evaluation Criteria in Solid Tumors

(irRECIST) (Bohnsack 2014). The Sponsor or delegate will collect radiological images for all participants and these will be assessed by the IRC if required.

Figure 3 Decision Tree for Continuation of Treatment Beyond Progressive Disease



GEM/CDDP=gemcitabine/cisplatin, PD=progressive disease, RECIST 1.1=Response Evaluation Criteria in Solid Tumors Version 1.1.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants can be withdrawn from the study and/or treatment for any of the following reasons:

- 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
- If the participant withdraws consent for future involvement in the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed
- A participant has the right at any time to request destruction of any biological samples taken. The Investigator must document this in the site study records.

At the time of discontinuing from the study, if possible, a discontinuation visit (End-of-Treatment Visit) will be conducted, as listed in the Schedule of Activities (Section 1.3). The Schedule of

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

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

In case of withdrawal from study intervention:

- 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-up, which includes the collection of data on survival, PRO questionnaires, and subsequent anticancer therapy. After completion of the long-term 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 the 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.

Replacement of Participants

- If a participant in the open-label, safety run-in part of the study is withdrawn from study intervention or from the study during the DLT evaluation period for any reason other than DLT, he/she will be replaced.
- If a participant in the safety run-in part of the study does not receive at least 1 dose of bintrafusp alfa and of both gemcitabine and cisplatin during the DLT evaluation period, he/she will be replaced.
- If a participant in the randomized, double-blind part of the study is withdrawn from study intervention or from the study for any reason, he/she will not be replaced.

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 clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee will make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known

mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner or caretaker (where allowed by local regulations) for information. These contact attempts will be documented in the participant's medical record.

- If the participant continues to be unreachable, he/she will be deemed as "lost to follow-up".

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the Schedule of Activities. See Section 1.3.
- No protocol waivers or exemptions are allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2.
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (Section 1.3).
- A maximum of 127 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 the 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, an MRI of the abdomen and pelvis, 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.

Baseline and on-study brain CT/MRI scan should be performed if clinically indicated by development of new specific symptoms.

Tumor responses to treatment will be assigned based on the evaluation of the response of target, nontarget, and new lesions according to RECIST 1.1.

Baseline scans will be taken within 28 days prior to treatment. Disease must be measurable, with at least 1 unidimensionally measurable lesion per RECIST 1.1 (except for participants in the open-label, safety run-in part). 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. All on-treatment scans are to be repeated using the same method at the subsequent assessment time points.

Participants will be evaluated with radiographic imaging to assess response every 6 weeks up to Week 37 and then every 12 weeks until PD (see Schedule of Activities, Section 1.3).

Treatment decisions will be made by the assessment of the treating Investigator (see Figure 3). 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); irRECIST will not be assessed by the Investigator. An IRC, blinded for treatment, will review radiographic image findings for the determination of objective response and date of PD for each of the first 150 antibiotics-naive participants according to RECIST 1.1 and irRECIST (Bohnsack 2014). All radiological images for the remaining participants must also be submitted.

Confirmation of CR or partial response (PR) should be performed preferably at the regularly scheduled assessment intervals, but no sooner than 4 weeks after the initial documentation. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR provided PD has not occurred between the 2 time points.

Participants who start 2L treatment should be monitored for response to that treatment. Objective response according to RECIST 1.1 to this 2L treatment for metastatic disease should be reported. A participant's progression may involve the following: objective radiological, symptomatic progression, or death due to advancing disease. Details of RECIST 1.1 methodology are supplied as Appendix 11.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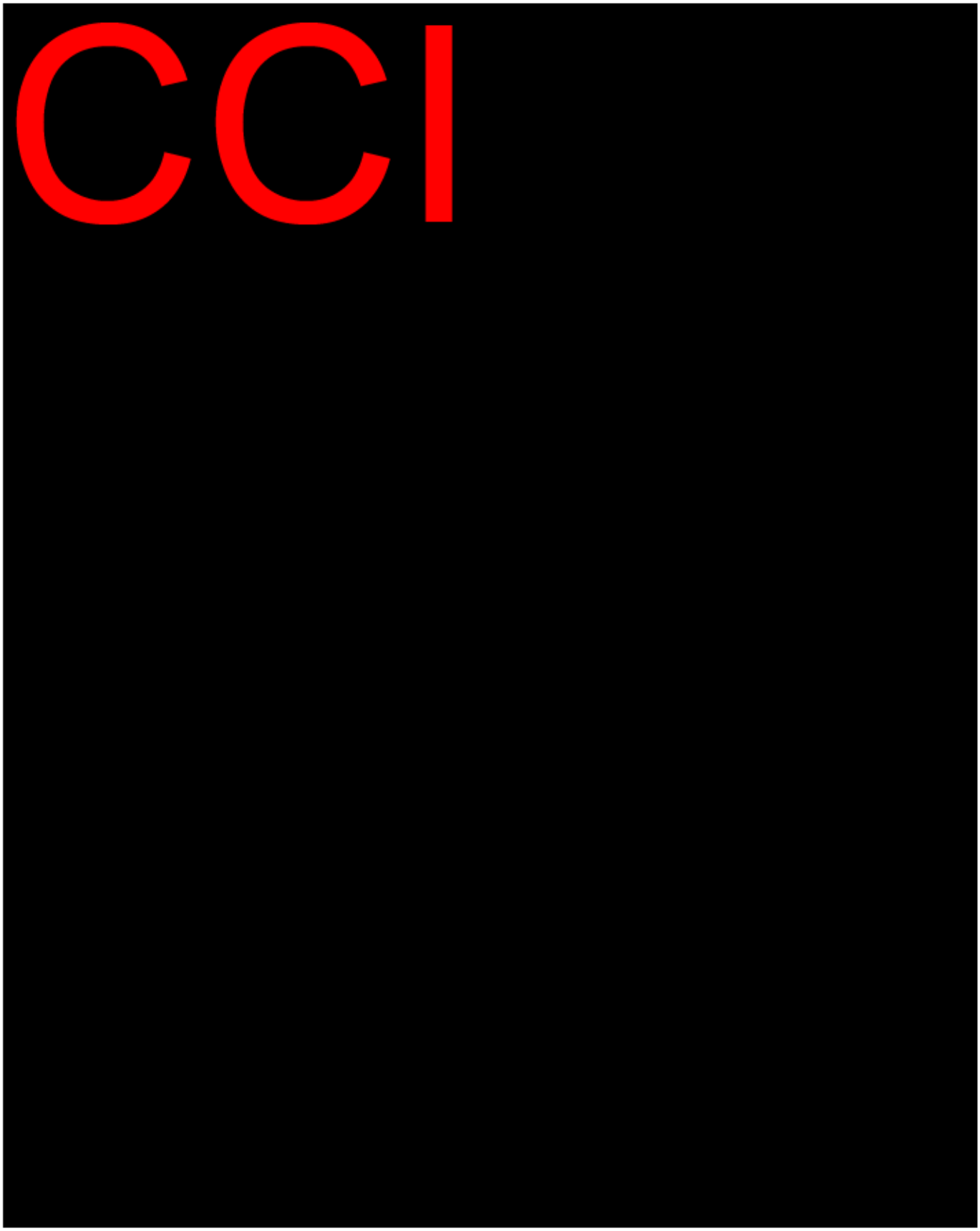
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8.2 Safety Assessments and Procedures

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

Physical examinations, assessment of vital signs, ECOG PS, and ECGs, and sampling for clinical safety laboratory assessments should be completed prior to administration of study intervention (where applicable).

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1.

8.2.1 Physical Examinations and Vital Signs

Physical examinations, vital signs and ECOG PS will be performed at Screening and at subsequent visits as indicated in the Schedule of Activities (see Section 1.3). These should be documented in the eCRF.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

A brief physical examination 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 or any recent infection or fever should be checked and investigated as necessary.

Abnormal findings are to be reassessed at subsequent visits.

Height (at Screening only) and weight will be measured and recorded.

Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

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 using a pulse oximeter in all participants for the potential early detection of ILD. See Section 8.2.3 for clinical safety laboratory assessments to be performed at sites in Japan only for potential early detection of pneumonitis.

8.2.2 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the Schedule of Activities 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 6 Clinical Laboratory Tests, at the time points listed in the Schedule of Activities. 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 local laboratories. Relevant results must be available and checked by the Investigator before administration of the study intervention, as indicated in Appendix 6, Table- A, Table- B, Table- C, Table- D, Table- E, and Table- F (refer to the Laboratory Manual).

The Sponsor must receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study must be forwarded to the CRO and the Sponsor.

The Investigator must review each laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

If a participant has a clinically significant abnormal laboratory test value that was 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 laboratory 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 in participants in Japan only for potential early detection of pneumonitis (Appendix 6 Table- F). The inclusion of these markers is for the indication of potential lung-related toxicity only; further investigations, such as chest CT, etc, will be performed for a confirmatory diagnosis.

Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at the time points specified in the Schedule of Activities, including at the end of relevant systemic exposure of the study intervention.

Additional serum or highly sensitive urine pregnancy tests may be conducted, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the study.

8.2.4 Review Committees

8.2.4.1 Safety Monitoring Committee

The safety of participants in the open-label, safety run-in part will be assessed by a SMC. Regional SMC meetings will be held after completion of the DLT evaluation period, at least 1 for each of the respective regional cohorts. Details will be provided in the SMC charter.

8.2.4.2 Independent Data Monitoring Committee

After clearance of a region by SMC, the randomized, double-blinded part of the study will be initiated (region-wise decision). To ensure participants' safety, an IDMC will be established for periodic review of safety data throughout the randomized double-blind part of the study. On the basis of these regularly scheduled safety data reviews and of an additional data review meeting to be conducted upon enrollment of 150 participants in the Phase II, the IDMC may recommend additional safety measures, including enrollment pause.

In order to make a recommendation regarding the expansion of the study into Phase III, the IDMC will review efficacy data from the first 150 antibiotics-naive participants enrolled in Phase II and safety data for all participants treated in the study until the data cutoff of this analysis. In the event that the study is expanded to 500 participants as a Phase III (further to the adaptation decision), the IDMC will be requested to review participants' efficacy and safety data and could recommend that the study be stopped earlier for efficacy or futility.

The full membership, mandate, and processes of the IDMC will be detailed in a separate IDMC charter.

8.2.4.3 Independent Review Committee

The role of the IRC will be to review radiographic image findings for the determination of the objective response and date of disease progression for the Phase II part of the study, and may be requested to do this also for the Phase III part of the study. 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 serious adverse event (SAE) are in Appendix 4. A definition of AESI is also provided.

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 [CCI] after the last study intervention administration. Thereafter, all SAEs and treatment-related nonserious AEs should be documented until the last Safety Follow-up Visit, defined as 12 weeks [CCI] after the last study intervention administration. Ongoing events at the 12-week Safety Follow-up Visit should continue to be monitored and documented until resolution or resolution with sequelae.

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/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 report form as specified in Appendix 4.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

AEs are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 and are assessed for their outcome at the 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.

Monitoring of Specific Adverse Events

Details regarding the monitoring and management of AEs of special interest can be found in Section 6.9.

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)/Independent Ethics Committee (IEC) that approved the study.

In accordance with 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/IEC'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 (SUSARs). In addition, per applicable regulations, the Sponsor/designee will inform the study Investigators and the Heads of the study sites of all SAEs which 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 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 must be recorded in the AE page/section of the eCRF for both pregnancies in female participants and pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Appendix 4, section on reporting SAEs and DLTs.

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

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

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

8.4 Treatment of Overdose

For this study, any dose of study intervention greater than 10% of the highest daily dose within a 24-hour time period will be considered an overdose.

There are no known symptoms of bintrafusp alfa overdose to date. For information regarding overdoses of gemcitabine and cisplatin, refer to the current product information applicable to the region. The Investigator should use his or her clinical judgment when treating an overdose of the study intervention.

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

8.5 Pharmacokinetics

Pharmacokinetics of bintrafusp alfa will be evaluated for all participants in the first part of the study (open-label, safety run-in) and all those in the bintrafusp alfa arm in the double-blind, randomized part (C_{eoi} and C_{trough} only); blinding will be maintained as described in Section 6.3.2. The following PK parameters will be calculated, when appropriate (Table 17):

Table 17 Pharmacokinetic Parameters

Symbol	Definition
AUC_{0-t}	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log-linear trapezoidal rule (linear up, log down)
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last}, as estimated using the linear regression from λ_z determination. $AUC_{0-\infty} = AUC_{0-t} + C_{last\ pred}/\lambda_z$
C_{EOI}	The concentration observed immediately at the end of infusion
C_{max}	Maximum observed concentration,
C_{trough}	The concentration observed immediately before next dosing (corresponding to predose or trough concentration for multiple dosing)
$t_{½}$	Apparent terminal half-life. $t_{½} = \ln(2)/\lambda_z$
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)

Whole blood samples of approximately 3.5 mL will be collected for measurement of serum concentrations of bintrafusp alfa. Collection times are specified in the Schedule of Activities (see Section 1.3, Table 3, and Table 4). The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration. The sampling timing may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

The quantification of bintrafusp alfa in serum will be performed using a validated assay method. Concentrations will be used to evaluate the PK of bintrafusp alfa.

Where collected at the same time points, the PK and CCI samples may be used interchangeably if the dedicated sample has insufficient quantity, as participants will have consented to all collections and tests.

Remaining samples collected for analyses of bintrafusp alfa serum 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.

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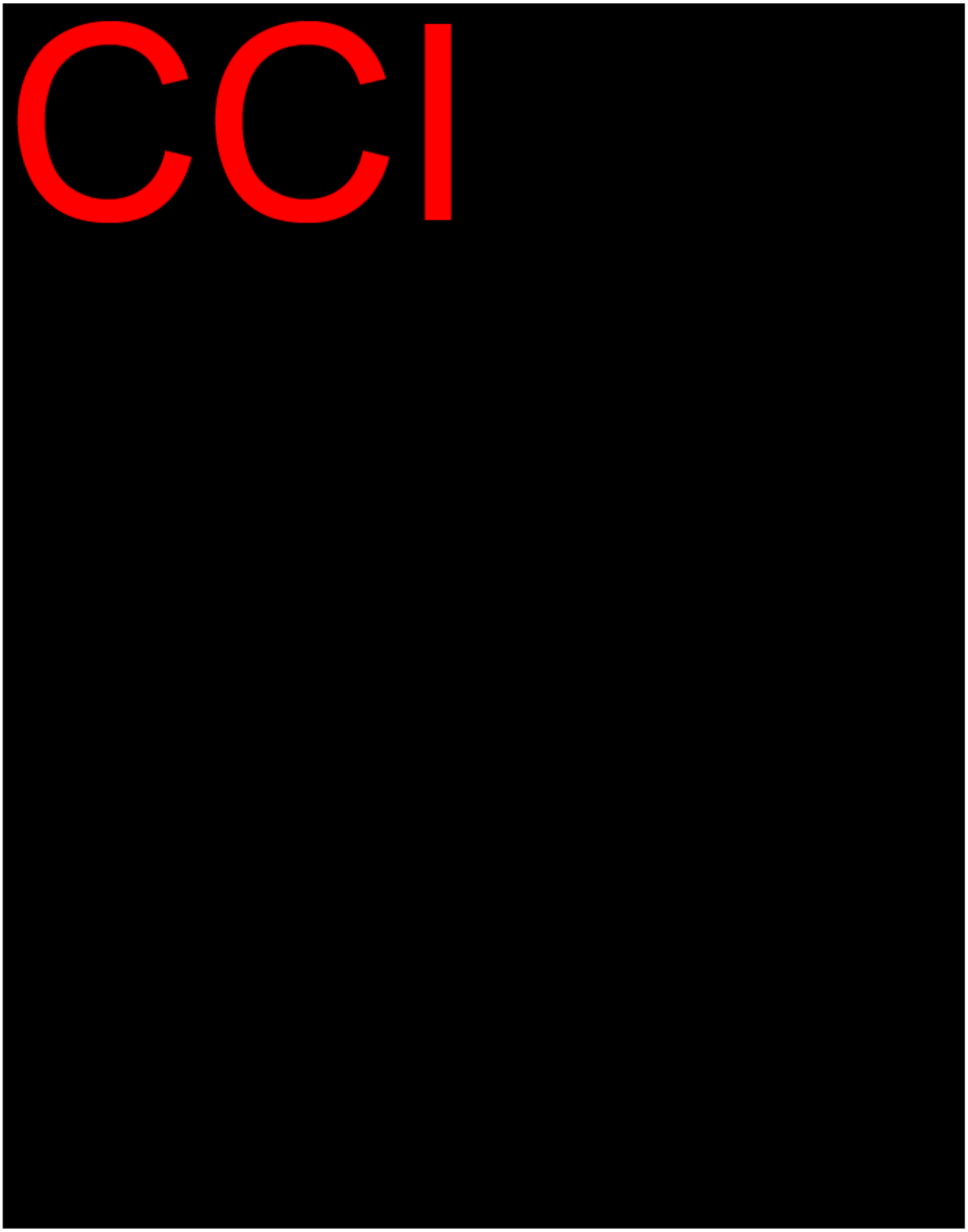
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9.1 Statistical Hypotheses

The following hypotheses will be tested.

Primary Endpoint: Overall Survival

The following null hypothesis will be tested:

$H_0^{OS}: \lambda_M^{OS}(t) = \theta\lambda_C^{OS}(t), \theta \geq 1$ versus $H_1^{OS}: \lambda_M^{OS}(t) = \theta\lambda_C^{OS}(t), \theta < 1$

where $\lambda^{OS}(t)$ represents the hazard at time t and θ the unknown constant of proportionality of hazards in the treatment groups M (bintrafusp alfa) and C (control).

Secondary Endpoint: Progression-free Survival

The following null hypothesis will be tested:

$H_0^{PFS}: \lambda_M^{PFS}(t) = \theta\lambda_C^{PFS}(t), \theta \geq 1$ versus $H_1^{PFS}: \lambda_M^{PFS}(t) = \theta\lambda_C^{PFS}(t), \theta < 1$

where $\lambda^{PFS}(t)$ represents the hazard at time t and θ the unknown constant of proportionality of hazards in the treatment groups M (bintrafusp alfa) and C (control).

Secondary Endpoint: Objective Response

Treatment groups will be compared in terms of difference of ORR ($\Delta^{\text{ORR}} = ORR_M - ORR_C$), between the treatment groups, with M for bintrafusp alfa and C for control.

The following null hypothesis will be tested:

$H_0^{ORR}: \Delta^{ORR} \leq 0$ versus $H_1^{ORR}: \Delta^{ORR} > 0$.

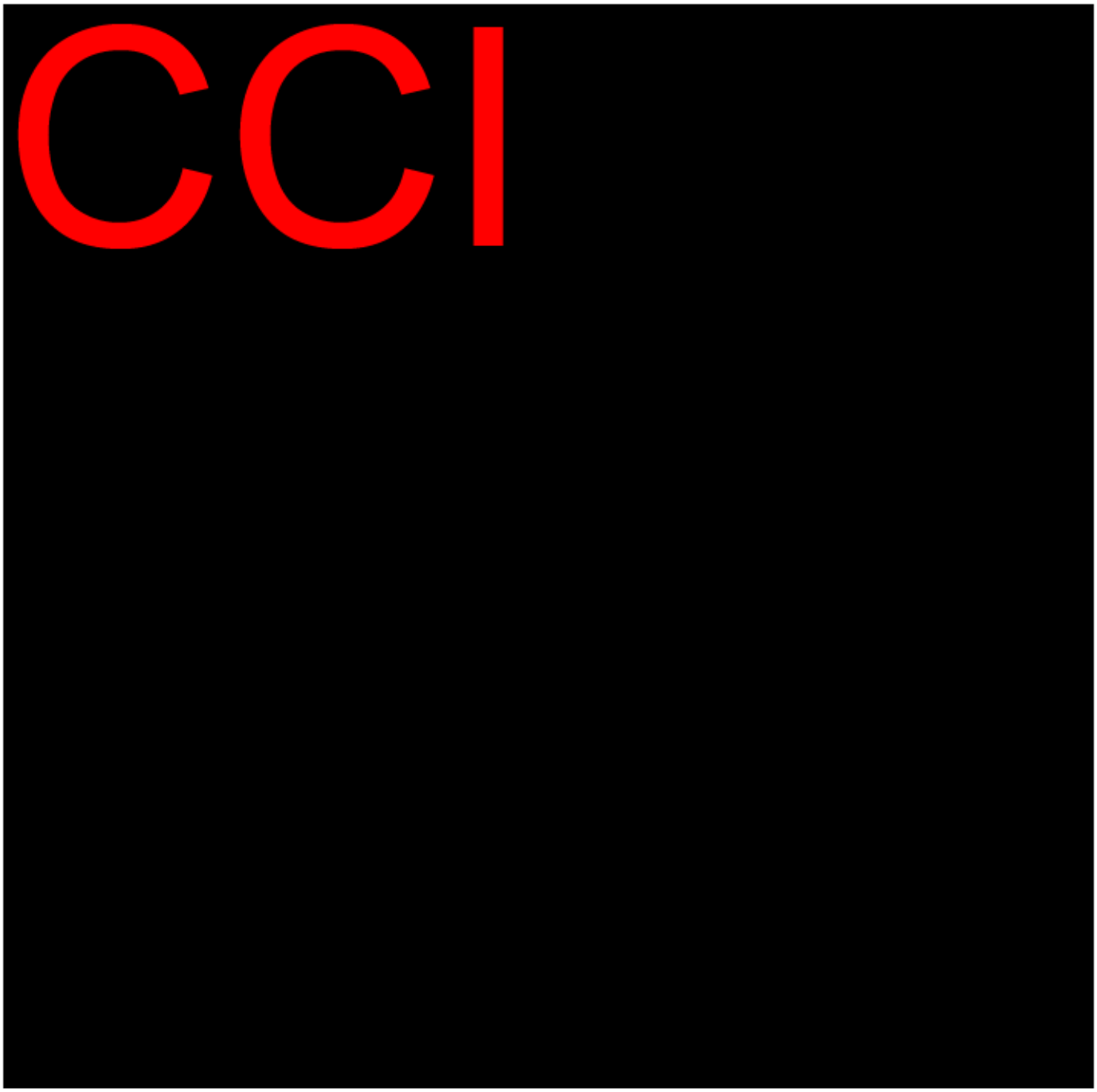
9.2 Hierarchical Testing Procedure

A hierarchical testing procedure as presented is applied to the confirmatory tests for the hypotheses specified in Section 9.1.

The hypothesis for the primary endpoint OS will be tested by a group sequential approach in interim and primary analyses at a significance level of 2.5% 1-sided. If, the OS null hypothesis is rejected, the hypothesis for the secondary endpoint, PFS, will be tested confirmatory by a group sequential approach. If, the PFS null hypothesis is rejected, the hypothesis for the secondary endpoint, ORR, will be tested likewise.

The group sequential approach for testing OS, PFS and objective response will use alpha-spending function of Lan-DeMets approach according to the actual number of observed events regarding the total event number planned for the PA for OS (334 events), i.e., the same information fraction with OS will be used for PFS and objective response. O'Brian-Fleming boundaries are used for OS and Pocock boundaries are used for PFS and objective response (Glimm 2010).

Prespecifying the order of the hypotheses to be tested, the family wise error rate for this approach to sequentially rejective multiple test procedure (Maurer 1995) is controlled at 2.5% one-sided.



9.3.1 Analysis for the Adaptation Decision

The analysis for adaptation decision will be conducted in the first 150 antibiotics-naive participants when 80 PFS events have occurred and once at least 19 weeks of follow-up for the first 150 antibiotics-naive participants randomized is reached.

In case multiple participants are randomized on the same day as the 150th antibiotics-naive participant, the analysis for adaptation decision will include all antibiotics-naive participants randomized up to this day.

The decision is based on a confirmed objective response odds ratio and PFS HR (as assessed by the IRC). The study will be expanded into Phase III if:

- Odds ratio of a confirmed objective response ($\mathbf{OR}_{OR}$) is ≥ 1.6 or
- PFS HR ($\mathbf{HR}_{PFS}$) is < 0.75, and
- a further criterion that uses more of the available interim information and allows a quantification of the future OS treatment effect based on available inter-subject information about the relationship between different efficacy endpoints is met. This criterion is based on the probability of success. Success is defined as observing an HR for OS less than a prespecified threshold. Expansion is foreseen if the probability of success is exceeding a predefined threshold on top of the above described criteria of ORR and PFS. The details about the methodology and thresholds will be specified in an appendix to the IDMC charter and IDMC analysis plan.

If the study will not be expanded to full Phase III sample size, the IDMC will consider to make a recommendation to stop the study early for futility if the observed PFS HR is > 1 and taking into account the totality of available data including available OS data at this point. This is a non-binding futility analysis.

9.3.2 Power and Type I Error

Table 19 provides the stopping boundaries as well as local power for the planned analyses based on separate Phase II and Phase III planning. Computations were done using EAST.

Table 19 Stopping Boundaries Under the Planned Schedule of Analyses

N	Number of Events		p (1-sided)			Z Score			HR at Boundary			Overall Power	Local Power	
	IA	PA	IA	PA	Overall	IA		PA	IA		PA		IA	PA
						Efficacy	Futility	Efficacy	Efficacy	Futility	Efficacy			
300[a]	-	180	-	2.5%	2.5%	-	-	-1.96	-	-	0.75	67%	-	67%
500	210	334	0.5%	2.4%	2.5%	-2.597	0.698	-1.986	0.70	1.10	0.81	90%	50%	41%

HR=hazard ratio, IA=interim analysis, PA=primary analysis.
Hazard ratio is an expected one based on the assumption of exponential distribution. The decision will be based on the p-value.
[a] Maximum sample size of Phase II.

Besides the separate planning of Phase II and Phase III, a simulation study was performed to incorporate all decision criteria for interim and primary analyses. A multi-state model was used to model the inter-subject relationship between the different endpoints. Under the null hypothesis H0, the study will be expanded in 3.5% of cases. Under the alternative H1, the study will be expanded in 41% of cases. Overall, the power of this study is 68% regardless of whether the study expands or not. Those 68% are the sum of 29% power with no expansion, 18% power at the interim analysis

with expansion, and 21% power at the primary analysis with expansion. However, the Phase III power (power given the study is expanded) is 95%. From this perspective, the study is sufficiently powered if expanded to full sample size.

9.4 Populations for Analyses

The analysis populations are specified below (Table 23). The final decision to exclude participants from any analysis population will be made during a blinded data review meeting prior to database lock and unblinding (except for the DLT analysis set).

Analysis populations include participants from both the safety run-in part and the randomized double-blind part of the study unless otherwise indicated.

Table 23 Analysis Sets

Analysis Set	Description
Screening	All participants, who provided informed consent, regardless of the participant's randomization and study intervention status in the study
Intent-to-Treat	All participants who were randomized to study intervention. Analyses performed on the ITT population will consider participants' allocation to study intervention groups as randomized
Safety Run-in	All participants from the safety run-in part who were administered any dose of any study intervention
Dose-limiting toxicity	All participants who completed the safety run-in, i.e., the 21-day DLT evaluation period, without missing a dose or being withdrawn during the DLT evaluation period for reasons other than toxicity All participants from the safety run-in part who are evaluable for DLT
Safety (SAF)	All participants from the randomized, double-blind part who were administered any dose of any study intervention. Analyses will consider participants as treated
Pharmacokinetic	All participants who completed at least 1 infusion of bintrafusp alfa and provided at least 1 sample with a measurable concentration of bintrafusp alfa
CCI	

CCI , DLT=dose-limiting toxicity, ITT=intent-to-treat.

9.5 Statistical Analyses

To provide overall estimates of treatment effects, data will be pooled across study centers. The factor 'center' will not be considered in statistical models or subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of participants randomized at each center.

In general, continuous variables will be summarized using number (n), mean, median, standard deviation, minimum, maximum, Q1, and Q3. Categorical variables will be summarized using frequency counts and percentages. Proportions will be calculated based on the number of participants in the analysis set of interest, unless otherwise specified in the IAP. All safety and efficacy endpoints will be summarized by treatment arm.

CCI

9.5.1 Efficacy Analyses

All efficacy analyses will be performed on the intent-to-treat (ITT) population. Participants from the safety run-in part will not be part of the ITT population and will be analyzed separately.

Efficacy endpoints and statistical analysis methods are outlined in Table 24.

Table 24 Efficacy Endpoints and Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Primary	
OS	• OS is defined as the time from randomization to the date of death due to any cause • For participants alive, OS will be censored at the last date the participant is known to be alive • KM estimates and associated statistics (OS rates at 3, 6, 9, 12, 24, and 36 months; median OS) and corresponding 95% CIs will be presented by treatment group • OS null hypothesis is tested using test statistics of stratified log-rank test (same strata as used for randomization) • Unstratified sensitivity analysis • Estimation of the treatment effect (HR θ) by a Cox proportional hazards model (stratified by randomization strata, each stratum defines separate baseline hazard function); ties handled by replacing the proportional hazards model by the discrete logistic model; 95% CIs for the HR will be calculated • Graphical check of the proportional hazard assumption CCI • CCI
Secondary	
Note: If the study is not expanded to the full sample size, the primary analysis of tumor assessment-based endpoints, such as PFS, ORR, and DOR, will be based on the IRC assessment rather than the Investigator assessment. The Investigator assessment will serve as sensitivity analysis.	
PFS according to RECIST 1.1 assessed by the Investigator	• PFS is defined as the time from randomization to the date of the first documentation of objective PD as assessed by the Investigator according to RECIST 1.1 or death due to any cause in the absence of documented PD, whichever occurs first • Progression or death, which occurred later than 2 scheduled tumor assessment intervals after the last evaluable response assessment will be censored at the date of the last evaluable response assessment for PFS analyses • PFS time will be censored at the last evaluable assessment date before the start of a new anticancer treatment if no event occurred so far. In the case of a non-evaluable baseline assessment or all post-baseline assessments being non-evaluable, the participant will be censored at the randomization date • KM estimates and associated statistics (PFS rates at 3, 6, 9, 12, and 24 months; median PFS) and corresponding 95% CIs will be presented by treatment group • PFS null hypothesis is tested using test statistics of stratified log-rank test (same strata as used for randomization) • Estimation of the treatment effect (HR θ) by a Cox proportional hazards model (stratified by randomization strata, each stratum defines separate baseline hazard function); ties handled by replacing the proportional hazards model by the discrete logistic model; 95% CIs for the HR will be calculated • Graphical check of the proportional hazards assumption • Sensitivity analyses of PFS will be performed including, but not limited to:

Endpoint	Statistical Analysis Methods
	• Alternative censoring rules, including an analysis that counts death and progression according to RECIST 1.1 as a PFS event regardless of the start of a new anticancer therapy and ignoring the number of missing evaluable tumor assessments before progression or death • Comparison of PFS as assessed by the Investigator and IRC, as applicable CCI
Objective response according to RECIST 1.1 assessed by the Investigator	• ORR, i.e., the rate of participants having an objective response of confirmed CR or PR will be calculated along with the corresponding 2-sided exact Clopper-Pearson 95% CI per treatment group • Difference in ORR is estimated based on the Cochran-Mantel-Haenszel method (taking into account the randomization strata) and test statistics are used for testing null hypothesis of objective response. Odds ratio is estimated based on logistic models for objective response. Logistic models will be fitted with the endpoint as dependent variable, subgroup, treatment, and with and without the treatment by subgroup interaction as explanatory variables
DOR according to RECIST 1.1 assessed by the Investigator	• DOR according to RECIST 1.1 as assessed by the Investigator will be defined for participants with confirmed response as the time from first response until the first documented disease progression or death • KM estimates and associated statistics (response rates at 3, 6, 9, 12, and 24 months; median DOR) and corresponding 95% Cis will be presented by treatment group. Participants without an event at the analysis cutoff date will be censored on the date of the last tumor assessment
Durable response according to RECIST 1.1 assessed by the Investigator	• DRR, i.e., the rate of participants having a confirmed objective response of CR or PR lasting > 6 months will be calculated along with the corresponding 2-sided Exact Clopper-Pearson 95% CI per treatment group • 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 and 12 months, respectively • Difference in DRR (lasting > 6 months) is estimated based on the Cochran-Mantel-Haenszel method (taking into account the randomization strata)

CCI

BTC=biliary tract cancer, CI=confidence interval, CR=complete response, DOR=duration of response, DRR=durable response rate, HR=hazard ratio, IAP=integrated analysis plan, IRC=Independent Review Committee, KM=Kaplan-Meier, ORR=objective response rate, OS=overall survival, PD=progressive disease, CCI PFS=progression-free survival, PR=partial response, RECIST 1.1=Response Evaluation Criteria in Solid Tumors Version 1.1.

9.5.2 Safety Analyses

All safety analyses will be performed on the Safety analysis set (SAF) or the Safety Run-in analysis set, with the exception of the analyses of DLT in the safety run-in part of the study, which will be performed on the DLT analysis set.

Safety endpoints include AEs (TEAEs, SAEs, treatment-related AEs, AESI, irAEs), clinical laboratory assessments, vital signs, physical examinations, ECG parameters, and ECOG PS as described in Section 8.2. Treatment-emergent AEs 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.

All AEs will be coded according to MedDRA. The severity of AEs and laboratory results will be graded using the NCI-CTCAE Version 5.0 toxicity grading scale. Immune-related AEs will be identified using a 2-level approach according to a prespecified search list of MedDRA Preferred Terms, documented in a version-controlled repository maintained by the Sponsor and finalized for analysis prior to database lock, and a medical assessment (case definition).

Safety endpoints and statistical analysis methods are outlined in Table 25.

Table 25 Safety Endpoints and Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Primary	
DLT in the safety run-in	The incidence of DLT will be tabulated for the DLT Analysis Set
Randomized, double-blind part	Not applicable
Secondary	
AEs, clinical laboratory assessments, vital signs, physical examination, ECG parameters, and ECOG PS	• Participants will be analyzed according to the actual treatment they receive • The safety endpoints will be analyzed using descriptive statistics • The incidence of TEAEs, SAEs, treatment-related AEs, AESI, and irAEs regardless of attribution, will be summarized by Preferred Term and System Organ Class for each treatment arm, and described in terms of severity and relationship to treatment • The worst on-treatment grades for chemistry and hematology laboratory results will be summarized • Shifts in toxicity grading from baseline to highest grade during the on-treatment period will be displayed • For laboratory tests without an NCI-CTCAE grade definition, results will be presented categorically (e.g., below, within, or above normal limits) • Further details of safety analyses (including AEs, clinical laboratory assessments, vital signs, physical examination, ECG parameters, and ECOG PS) will be provided in the IAP
CCI	

AE=adverse event, AESI=adverse events of special interest, DLT=dose-limiting toxicity, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group performance status, IAP=integrated analysis plan, irAE=immune-related adverse event, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, SAE=serious adverse event, TEAE=treatment-emergent adverse event.

If the study expands to Phase III, the summary and analysis of AEs will be performed based on the 3-tier approach (Crowe 2009), as further detailed in the study IAP. If the study is not expanded, the sample size for an analysis based on the 3-tier approach is regarded as too small.

9.5.3 Other Analyses

Details of the PK, CCI , and CCI analyses will be in the IAP that will be finalized before database lock. Integrated analyses across studies, such as the PopPK

analysis will be presented separately from the main CSR. Exposure-response analyses for efficacy and safety will also be presented separately from the main CSR.

Handling of missing data will be described in the IAP.

9.5.4 Sequence of Analyses

The sequence of planned analyses is as shown in Table 26.

Table 26 Sequence of Planned Analyses

	Analyses
Open-label, Safety Run-in	• Safety assessment in the 6 participants in the Asian sites' cohort and 6 participants in the non-Asian sites' cohort, or up to 12 participants in each cohort; DLT will be evaluated in the first 21 days • Analysis of efficacy endpoints when the last participant of the open-label part of the study has reached a minimum follow-up time of 12 months
Randomized, adaptation decision	• Analysis of efficacy when the target number of 80 PFS events have occurred in the first 150 antibiotics-naive participants and once at least 19 weeks of follow-up for the first 150 antibiotics-naive participants randomized is reached.
Primary analysis if final sample size is not expanded	• PA when OS events have occurred on the 60% of total Phase II participants, expected at 29 months after randomization of the first participant
Interim and primary analyses if final sample size is N = 500	• IA at the data cutoff date of 63% of OS events for the PA (210/334 events), expected at 27 months after randomization • PA when the target number of 334 OS events have occurred in a total of 500 participants, expected at 40 months after randomization of the first participant

DLT=dose-limiting toxicity, IA=interim analysis, OS=overall survival, PA=primary analysis, PFS=progression-free survival.

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CCI

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11 Appendices

Appendix 1 Abbreviations

1L	First-line
2L	Second-line
CCI [redacted]	
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
CCI [redacted]	
ASCO	American Society of Clinical Oncology
BTC	Biliary tract cancer
CCA	Cholangiocarcinoma
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CrCL	Creatinine clearance
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
DLT	Dose-limiting toxicity
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]	
ESMO	European Society for Medical Oncology
FSH	Follicle-stimulating hormone
GC	Gallbladder cancer
GCP	Good Clinical Practice
GCS	Gemcitabine, cisplatin, and S1
Gem-cis	Gemcitabine-cisplatin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus

HR	Hazard ratio
HRT	Hormone replacement therapy
IA	Interim analysis
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
IL	Item Library
ILD	Interstitial lung disease
irAE	Immune-related adverse event
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-related reactions
CCI	
IV	Intravenous
IXRS	Interactive Response System
KA	Keratoacanthoma
KL-6	Krebs von den Lungen-6
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
NCCN	National Comprehensive Cancer Network
NCCN 2018	National Comprehensive Cancer Network Guidelines 2018
NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
CCI	
ORR	Objective response rate
OS	Overall survival
PA	Primary analysis
PD	Progressive disease
CCI	
PFS	Progression-free survival
CCI	
PK	Pharmacokinetic
PopPK	Population pharmacokinetics
PR	Partial response

CCI	
PT	Prothrombin time
PTBD	Percutaneous transhepatic biliary drainage
Q3W	Every 3 weeks
Q6W	Every 6 weeks
Q12W	Every 12 weeks
CCI	
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	Ribonucleic acid
RP2D	Recommended Phase II dose
SAE	Serious adverse event
SD	Stable disease
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SoC	Standard of care
SP-A/D	Surfactant protein-A/D
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-emergent adverse event
TGFβ	Transforming growth factor beta
TMB	Tumor mutational burden
TTP	Thrombotic thrombocytopenic purpura
ULN	Upper limit of normal
VAS	Visual Analog Scale

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 Good Clinical Practice (GCP); local regulations; International Council for Harmonisation (ICH) guidelines; Health Insurance Portability and Accountability Act requirements, where applicable; and the IRB)/Independent Ethics Committee (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 re-consented to the most current, approved version.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- The original signed and dated consent will remain at the Investigator's site and will be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.

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

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. All participant records or datasets transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor must inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant 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 must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

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

The study will appear in the following clinical studies registries: clinicaltrials.gov, EudraCT, Japan Pharmaceutical Information Center (JAPIC), and chinadrugtrials.org.cn.

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 support for the Contract Research Organizations (CROs) for some activities of the study. Sponsor Global Clinical Operations will perform oversight of the activities performed by the CROs.

The Clinical Trial Supplies Department of the Sponsor will supply the study medication of bintrafusp alfa that will be distributed to the sites by a CRO.

Safety laboratory assessments will be performed locally by investigational sites. Pharmacokinetic, CCI assessments will be performed under the responsibility and/or supervision of the Sponsor.

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

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

The Global Biostatistics Department will supervise the statistical analyses (with the exception of the PK data analyses, which 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 must submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.
- 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/IEC.
- 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 and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

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

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

Clinical Study Report

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

Publication

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

Dissemination of Clinical Study Data

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

Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the

Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff who had been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

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

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

Data Quality Assurance

- All participant study data will be recorded on printed or 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.

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

- Participant's full name, date of birth, sex, height, and weight
- Medical history and concomitant diseases
- 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 adverse events
- Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.

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

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

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

Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator 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 contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

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.

Appendix 3 Contraception

Definitions:

Woman of Childbearing Potential

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 woman of childbearing potential 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., Müllerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.

1. A postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.
    - A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

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 woman of childbearing potential 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.

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

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea 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 adverse event (AE) is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product.

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

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

Investigators will reference the National Cancer Institute (NCI)- Common Terminology Criteria for AEs (CTCAE), Version 5.0 (publication date: 27 November 2017), a descriptive terminology that can be used for AE reporting.

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

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

The 5 general grades are:

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

Any clinical AE with severity of Grade 4 or 5 must also be reported as a 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 the 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 electrocardiogram 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 alanine aminotransferase) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

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

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

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

Events that Do Not Meet the Definition of an SAE

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

Events Not to Be Considered as AEs/SAEs

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

AE/SAEs Observed in Association with Disease Progression

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

Adverse Events of Special Interest

Categories of AESI related to bintrafusp alfa include:

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

Other Adverse Events to be Reported Following a Specialized Procedure

Not applicable.

Recording and Follow-up of Adverse Events and/or Serious Adverse Events

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and

its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented. If an AE constitutes a DLT, this will be documented accordingly.

Specific guidance is in the Case Report Form (CRF) Completion and Monitoring Conventions provided by the Sponsor.

Reporting Serious Adverse Events and Dose-Limiting Toxicities

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.

For Japanese sites, where hospitalization of a participant is considered for observational measures, e.g., during the administration of chemotherapy, any AE occurring during the period of the hospital stay for observation only should not be reported as serious, unless 1 or more of the criteria for SAE reportability is met.

Dose-Limiting Toxicities

Each event meeting the criteria of a DLT, as specified in Section 6.6.2, must be recorded in the eCRF within 24 HOURS after becoming aware of the event. Serious DLTs must be reported in an expedited manner as SAEs, as outlined above.

Appendix 5 Liver Safety: Suggested Actions and Follow up Assessments

During treatment with bintrafusp alfa/placebo, and gemcitabine and cisplatin, hepatic impairment may occur. See Section 6.6.3 for details on necessary dose modification and Appendix 8 for management of hepatic immune-related adverse events.

Appendix 6 Clinical Laboratory Tests

The required laboratory safety tests for the full chemistry and hematology and the core chemistry and hematology are summarized in Table- A and Table- B, respectively. See the Schedule of Activities in Section 1.3 for details of which panel to run at each visit.

Anemia, urinalysis, and hepatitis assessments are summarized in Table- C, Table- D and Table- E respectively. Additional laboratory assessments are summarized in Table- F.

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Table- B Clinical Laboratory Assessments (Core Panel) ...142
Table- C Anemia Assessments ...142
Table- D Urinalysis Assessments ...142
Table- E Hepatitis Assessments ...142

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Table- A Protocol-Required Clinical Laboratory Assessments (Full Panel)

Laboratory Assessments	Parameters			
Hematology / Coagulation	Platelet count*		Mean corpuscular volume	WBC count* with Differential: • Neutrophils* • Lymphocytes* • Monocytes • Eosinophils • Basophils
	Reticulocytes[a]		MCHC	
	Hemoglobin*		MCH	
	Hematocrit*		Prothrombin Time	
	Erythrocyte Count		Activated PTT*	
			Prothrombin INR*	
Biochemistry	Blood Urea Nitrogen*	Potassium*	Aspartate aminotransferase*	Bilirubin (total, indirect/direct)*
	Creatinine*	Sodium*	Alanine aminotransferase*	Protein*
	Glucose	Calcium*	Alkaline phosphatase*	GGT
	Creatine kinase	LDH*	Magnesium	Chloride*
	Phosphate	Pancreatic amylase	Albumin*	Creatinine clearance estimated*
	Lipase	C-reactive protein*		
Details of liver chemistry stopping criteria and required actions and follow-up assessments after a liver stopping or monitoring event are given in Section 6.6.5. *Laboratory results must be reviewed by the Investigator prior to dosing.				
Other Screening Tests	• FSH and estradiol (as needed if participant is not a woman of childbearing potential only) • Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for a woman of childbearing potential). Note: Local urine testing will be standard for the protocol unless serum testing Is required by local regulation or the IRB/IEC See also Table- C, Table- D, and Table- E			
• All study-required laboratory assessments will be performed by a local laboratory				

FSH=follicle-stimulating hormone, GGT=gamma-glutamyl transferase, INR=international normalized ratio, IRB/IEC=Institutional Review Board/Independent Ethics Committee, LDH=lactate dehydrogenase, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, PTT=partial thromboplastin time, WBC=white blood cell.

a At screening/baseline, and in case of anemia monitoring (see Table 15 and Appendix 6 Table- D).

Table- B Clinical Laboratory Assessments (Core Panel)

Laboratory Assessments	Parameters	
Hematology	Erythrocyte count*	WBC Count* with Differential: • Neutrophils* • Lymphocytes* • Monocytes • Eosinophils • Basophils
	Hemoglobin*	
	Hematocrit*	
	Platelets*	
Biochemistry	Blood Urea Nitrogen*	Bilirubin (total, indirect/direct)*
	Creatinine*	Aspartate aminotransferase*
	Creatinine clearance estimated*	Alanine aminotransferase*
	C-reactive protein*	Alkaline phosphatase*
Details of liver chemistry stopping criteria and required actions and follow-up assessments after a liver stopping or monitoring event are given in Section 6.6.5. *Laboratory results must be reviewed by the Investigator prior to dosing.		
All study-required laboratory assessments will be performed by a local laboratory		

WBC=white blood cell.

Table- C Anemia Assessments

Iron Panel	Total iron binding capacity[a], iron, ferritin, serum folate, B12, reticulocytes, red cell distribution width (as clinically indicated)
All study-required laboratory assessments will be performed by a local laboratory	

a If total iron binding capacity cannot be evaluated locally, replace with transferrin.

Table- D Urinalysis Assessments

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).

Table- E Hepatitis Assessments

Hepatitis	HBV, HCV serology at baseline (hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody, and hepatitis C antibody). Then: • If one or more of the following, hepatitis B surface antigen, hepatitis B core antibody, or hepatitis B surface antibody are positive at baseline, examine HBV DNA at screening and Q6W during the study. • If hepatitis C antibody is positive at baseline, examine HCV RNA. If HCV RNA is positive, examine HCV RNA every 6 weeks. Repeat HBV DNA or HCV RNA test as per Schedule of Activities in participants with infection history.
All study-required laboratory assessments will be performed by a local laboratory	

DNA=deoxyribonucleic acid, HBV=hepatitis B virus, HCV=hepatitis C virus, RNA=ribonucleic acid.


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Appendix 7 Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow up, and Reporting

Not applicable.


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Table A 1 Management of Skin Immune-related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

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 G 2 dermatitis	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids Initiate (methyl) prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks

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

1.0 Skin Toxicities	
G3: Skin sloughing covering < 10% BSA with mucosal involvement associated signs (e.g., erythema, purpura, epidermal detachment, mucous membrane detachment)	Hold ICPi therapy and consult with dermatology Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum Administer IV (methyl) prednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks Admit to Burn Unit 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, BSA=body surface area, CBC=complete blood count, CTCAE=Common Terminology Criteria for Adverse Events, DIHS=drug-induced hypersensitivity syndrome, DNA=deoxyribonucleic acid, 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, TEN=toxic epidermal necrolysis.

Table A 2 Management of Gastrointestinal Immune-related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

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 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Continue ICPi; alternatively, ICPi may be held temporarily and resumed if toxicity does not exceed G1 Monitor for dehydration and recommend dietary changes Facilitate expedited phone contact with patient/caregiver May obtain gastroenterology consult for prolonged G1 cases
G2: Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared with baseline	Should hold ICPi temporarily until patient's symptoms recover to G1; can consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less Concurrent immunosuppressant maintenance therapy (10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases

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 7 or more stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL	Should consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less. Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent) Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance If symptoms persist ≥ 3-5 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 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, anti-smooth 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 × ULN and/or total bilirubin > ULN to 1.5 × ULN)	Continue ICPi with close monitoring; consider alternate etiologies Monitor laboratories 1 to 2 times weekly Manage with supportive care for symptom control
G2: Asymptomatic (AST or ALT > 3.0 to ≤ 5 × ULN and/or total bilirubin > 1.5 to ≤ 3 × 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 × ULN and/or total bilirubin 3-10 × 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 × ULN and/or elevated total bilirubin 3 × 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 × ULN and/or total bilirubin > 10 × 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, CBC=complete blood count, CK=creatine kinase, CMV=cytomegalovirus, CRP=C-reactive protein, CT=computed tomography, CTCAE=Common Terminology Criteria for Adverse Events, CCI [redacted], EGD=esophagogastroduodenoscopy, ESR=erythrocyte sedimentation rate, G=grade, GI=gastrointestinal, HIV=human immunodeficiency virus, ICPi=immune checkpoint inhibitor, CCI [redacted] IV=intravenous, CCI [redacted] CCI [redacted] TB=tuberculosis, TNF=tumor necrosis factor, TSH=thyroid-stimulating hormone, ULN=upper limit of normal.

Table A 3 Management of Lung Immune-related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

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, and urine culture and sensitivity	
Grading	Management
G1: Asymptomatic, confined to 1 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 1 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 1 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, CCI [redacted] IV=intravenous, CCI [redacted] PPI=proton pump inhibitor.

Table A 4 Management of Endocrine Immune-related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

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

4.0 Endocrine Toxicity	
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate supplementation Endocrine consultation May admit for IV therapy if signs of myxedema (bradycardia, hypothermia); thyroid supplementation and reassessment as in G2
Additional considerations For patients without risk factors, full replacement can be estimated with an ideal body-weight-based dose of approximately 1.6 µg/kg/d For elderly or fragile patients with multiple comorbidities, consider titrating up from low-dose, starting at 25-50 mg Extreme elevations of TSH can be seen in the recovery phase of thyroiditis and can be watched in asymptomatic patients to determine whether there is recovery to normal within 3-4 weeks Under guidance of endocrinology, consider tapering hormone replacement and retesting in patients with a history of thyroiditis (initial thyrotoxic phase) Adrenal dysfunction, if present, must always be replaced before thyroid hormone therapy is initiated	
4.1.2 Hyperthyroidism	
Definition: Suppressed TSH and high normal or elevated FT4 and/or triiodothyronine Diagnostic work-up Monitor TSH, FT4 every 4-6 weeks from the start of therapy or as needed for case detection in symptomatic patients Consider TSH receptor antibodies if there are clinical features and suspicion of Graves' 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 β-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 Grave's disease (TSI or TRAb) and consider thionamide (methimazole or PTU). Refer to endocrinology for Grave's 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 β-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. Grave's 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' disease 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 2 to 3 times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg in the morning, and 10-20 mg in the afternoon) to manage acute symptoms Taper stress-dose corticosteroids down to maintenance doses over 5-10 days Maintenance therapy as in G1
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormone Endocrine consultation See in clinic or, for after hours, make an emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation hydrocortisone 100 mg or dexamethasone 4 mg (if the diagnosis is not clear and stimulation testing will be needed) Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge Maintenance therapy as in G1

4.0 Endocrine Toxicity	
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. Antiglutamic 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, CCI [redacted] DM=diabetes mellitus, EMS=emergency medical services, FSH=follicle-stimulating hormone, FT4=free thyroxine, G=grade, CCI [redacted] 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 A 5 Management of Musculoskeletal Immune-related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

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

5.0 Musculoskeletal Toxicities	
G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL	<u>For G3:</u> Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to G1 or less <u>**For G4: permanently discontinue ICPi**</u> Initiate oral prednisone 0.5-1 mg/kg If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD Synthetic: methotrexate, leflunomide Biologic: consider anticytokine therapy such as TNF-α or IL-6 receptor inhibitors. (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis.) Test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment Referral to rheumatology
Additional considerations Early recognition is critical to avoid erosive joint damage Corticosteroids can be used as part of initial therapy in inflammatory arthritis, but due to likely prolonged treatment requirements, physicians should consider starting corticosteroid-sparing agents earlier than one would with other irAEs Oligoarthritis can be treated early on with intra-articular corticosteroids; consider early referral. Consider PCP prophylaxis for patients treated with high-dose of corticosteroids for 12 weeks, as per local guidelines	
5.2 Myositis	
Definition: A disorder characterized by muscle inflammation with weakness and elevated muscle enzymes (CK). Muscle pain can be present in severe cases. Can be life-threatening if respiratory muscles or myocardium are involved Diagnostic work-up Complete rheumatologic and neurologic history regarding differential diagnosis; rheumatologic and neurologic examination, including muscle strength; and examination of the skin for findings suggestive of dermatomyositis. Muscle weakness is more typical of myositis than pain. Consider pre-existing conditions that can cause similar symptoms Blood testing to evaluate muscle inflammation CK, transaminases (AST, ALT), LDH, and aldolase can also be elevated Troponin to evaluate myocardial involvement and other cardiac testing, such as echocardiogram, as needed Inflammatory markers (ESR and CRP) Consider EMG, imaging (MRI), and/or biopsy on an individual basis when diagnosis is uncertain and overlap with neurologic syndromes, such as myasthenia gravis, is suspected Consider paraneoplastic autoantibody testing for myositis and neurologic conditions, such as myasthenia gravis Monitoring: CK, ESR, CRP	
G1: Complete examination and laboratory work-up as above G2: Complete history and examination as above; autoimmune myositis blood panel; EMG, MRI of affected joints Early referral to a rheumatologist or neurologist G3-4: As for G2 Urgent referral to a rheumatologist or neurologist	
Grading	Management
G1: Mild weakness with or without pain	Continue ICPi If CK is elevated and patient has muscle weakness, may offer oral corticosteroids, and treat as G2 Offer analgesia with acetaminophen or NSAIDs if there are no contraindications

5.0 Musculoskeletal Toxicities	
G2: Moderate weakness with or without pain, limiting age-appropriate instrumental ADL	Hold ICPi temporarily and may resume upon symptom control, if CK is normal and prednisone dose, 10 mg; if worsens, treat as per G3 NSAIDs as needed Referral to rheumatologist or neurologist If CK is elevated 3 times or more, initiate prednisone or equivalent at 0.5-1 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	
Grading	Management
G1: Mild stiffness and pain	Continue ICPi Initiate analgesia with acetaminophen and/or NSAIDs if there are no contraindications

5.0 Musculoskeletal Toxicities	
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, ALT=alanine aminotransferase, 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, CCI [redacted], IL=interleukin, CCI [redacted], IV=intravenous, IVIG=intravenous immunoglobulin, LDH=lactate dehydrogenase, MRI=magnetic resonance imaging, NSAID=nonsteroidal anti-inflammatory drug, PCP=Pneumocystis pneumonia, RF=rheumatoid factor, TB=tuberculosis, TNF=tumor necrosis factor, US=ultrasound.

Table A 6 Management of Renal Immune-related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

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, forego biopsy and proceed directly with immunosuppressive therapy. Swift treatment of autoimmune component important	
6.1 Nephritis	
Definition: Inflammation of the kidney affecting the structure	
Grading	Management
G1: Creatinine level increase **> ULN - 1.5 x ULN**	Consider temporarily holding ICPi, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status) and baseline renal function. A change that is still < 1.5 ULN could be meaningful
G2: Creatinine **> 1.5 - 3.0 x baseline; > 1.5 - 3.0 x ULN**	Hold ICPi Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc); if other etiologies ruled out, administer 0.5-1 mg/kg/d prednisone equivalents If worsening or no improvement: 1 to 2 mg/kg/d prednisone equivalents and permanently discontinue treatment If improved to G1 or less, taper corticosteroids over 4-6 weeks. If no recurrence of chronic renal insufficiency, discuss resumption of ICPi with patient after taking into account the risks and benefits.
G3: Creatinine **> 3.0 x baseline; > 3.0 - 6.0 x ULN**	Permanently discontinue ICPi
G4: Life-threatening consequences; dialysis indicated; **> 6.0 x ULN**	**Permanently discontinue ICPi** Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc) Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent)
Additional considerations Monitor creatinine weekly Reflex kidney biopsy should be discouraged until corticosteroid treatment has been attempted	
6.2 Symptomatic Nephritis: Follow-up	
Grading	Management
G1	Improved to baseline, resume routine creatinine monitoring
G2	If improved to G1, taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring If elevations persist > 7 days or worsen and no other cause found, treat as G3

6.0 Renal Toxicities	
G3	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist > 3-5 days or worsen, consider additional immunosuppression (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, CCI
IV=intravenous, ULN=upper limit of normal, UTI=urinary tract infection.

Table A 7 Management of Nervous System Immune-related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

7.0 Nervous System Toxicities	
7.1 Myasthenia Gravis	
Definition: Fatigable or fluctuating muscle weakness, generally more proximal than distal. Frequently has ocular and/or bulbar involvement (ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, dysarthria, facial muscle weakness). May have neck and/or respiratory muscle weakness. (Note: May occur with myositis and/or myocarditis). Respiratory symptoms may require evaluation to rule out pneumonitis, myocarditis. Miller Fisher variant of Guillain-Barré syndrome (ophthalmoparesis) and the oculobulbar myositis (ptosis, ophthalmoparesis, dysphagia, neck and respiratory weakness) with ICPi may have overlapping symptoms	
Diagnostic work-up AChR and antistriated muscle antibodies in blood; if AChR antibodies are negative, consider muscle specific kinase and lipoprotein-related 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 3 times a day and gradually increase to maximum of 120 mg orally 4 times a day as tolerated and based on symptoms. Administer corticosteroids (prednisone, 1-1.5 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 Non-opioid 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's 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 vasculitic neuropathy 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's disease and other autoimmune screening AM orthostatic vitals Consider electrodiagnostic studies to evaluate for concurrent polyneuropathy Consider paraneoplastic Lambert-Eaton myasthenic syndrome, antineutrophil cytoplasmic antibodies, and ganglionic AChR antibody testing	
Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient	Low threshold to hold ICPi and monitor symptoms for a week; if to continue, monitor very closely for any symptom progression
G2: Moderate, some interference with ADL, symptoms concerning to patient	Hold ICPi and resume once return to G1 Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild) Neurologic consultation
G3-4: Severe, limiting self-care and aids warranted	Permanently discontinue ICPi Admit patient Initiate methylprednisolone 1 g daily for 3 days followed by oral corticosteroid taper Neurologic consultation

7.0 Nervous System Toxicities	
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, plus 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 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.

7.0 Nervous System Toxicities	
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, ANA=antinuclear antibodies, ANCA=antineutrophil cytoplasmic antibodies, CBC=complete blood count, CNS=central nervous system, CPK=creatine phosphokinase, CRP=C-reactive protein, CSF=cerebrospinal fluid, ECG=electrocardiogram, EMG=electromyography, ESR=erythrocyte sedimentation rate, HIV=human immunodeficiency syndrome, 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 regain, TPO=thyroid peroxidase, TSH=thyroid-stimulating hormone, TTE=transthoracic echocardiogram, VC=vital capacity, WBC=white blood cell.

Table A 8 Management of Hematologic Immune-related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

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, iron, thyroid, infection Glucose-6-phosphate dehydrogenase Evaluation of common drug causes (ribavirin, rifampin, dapsone, interferon, cephalosporins, penicillins, NSAIDs, quinine/quinidine, fludarabine, ciprofloxacin, lorazepam, diclofenac, etc) Assessment of methemoglobinemia	
Grading	Management
G1: Hgb < LLN to 10.0 g/dL; < LLN to 6.2 mmol/L; < LLN to 100 g/L	Continue ICPi with close clinical follow-up and laboratory evaluation
G2: Hgb < 10.0 to 8.0 g/dL; < 6.2 to 4.9 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 extended release, 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 should be 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

8.0 Hematologic Toxicities	
	In case of management with rituximab, ICPi treatment will be discontinued
8.3 Hemolytic Uremic Syndrome	
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia. Signs and symptoms of hemolytic uremic syndrome can include: Bloody diarrhea Decreased urination or blood in the urine Abdominal pain, vomiting, and occasionally fever Pallor Small, unexplained bruises or bleeding from the nose and mouth Fatigue and irritability Confusion or seizures High blood pressure Swelling of the face, hands, feet, or entire body	
Diagnostic work-up History and physical examination (special consideration for new history of high-risk drugs, hypertension, or cardiac causes) CBC with indices Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis. Serum creatinine ADAMTS13 (to rule out TTP) Homocysteine/methylmalonic acid Complement testing C3, C4, CH50 (complement inhibitory antibodies for suspected familial) Evaluate reticulocyte count and mean corpuscular volume Evaluation of infectious cause, including screening for EBV, CMV, HHV6 Evaluation for nutritional causes of macrocytosis (B12 and folate) Pancreatic enzymes Evaluation for diarrheal causes, Shiga toxin, Escherichia coli 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 **For G3 and G4: Permanently discontinue ICPi** Begin therapy with eculizumab therapy 900 mg weekly for 4 doses, 1200 mg Week 5, then 1200 mg every 2 weeks Red blood transfusion according to existing guidelines
8.4 Aplastic Anemia	
Definition: Condition in which the body stops producing enough new blood cells	
Diagnostic work-up History and physical examination (close attention to medications, exposure to radiation, toxins, recent viral infections), CBC, smear, reticulocyte count Viral studies, including CMV, HHV6, EBV, parvovirus Nutritional assessments including B12, folate, iron, copper, ceruloplasmin, vitamin D Serum LDH, renal function Work-up for infectious causes Identify marrow hypo/aplasia	

8.0 Hematologic Toxicities	
Bone marrow biopsy and aspirate analysis Peripheral blood analysis, including neutrophil count, proportion of GPI-negative cells by flow for PNH Flow cytometry to evaluate loss of GPI-anchored proteins Type and screen patient for transfusions and notify blood bank that all transfusions need to be irradiated and filtered	
Grading	Management
G1: Nonsevere, < 0.5 polymorphonuclear cells × 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 2 of the following: ANC < 500, peripheral platelet > 20,000, and reticulocyte < 20,000	Hold ICPi and provide growth factor support and close clinical laboratory evaluations daily Administer ATG + cyclosporine; HLA typing and evaluation for bone marrow transplantation if patient is candidate; all blood products should be irradiated and filtered Supportive care with granulocyte colony-stimulating factor may be added in addition
G3-4: Very severe, ANC > 200, platelet count > 20,000, reticulocyte count > 20,000, plus hypocellular marrow > 25%	**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 G4 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 Evans 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 the 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

8.0 Hematologic Toxicities	
	Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) 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 1-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 97; 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 or 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=anti-thymocyte globulin, CBC=complete blood count, CMV=cytomegalovirus, CNS=central nervous system, CT=computed tomography, CXR=chest x-ray, DIC=disseminated intravascular coagulation, EBV=Epstein-Barr virus, ECG=electrocardiogram, G=grade, GPI=glycosylphosphatidylinositol, Hgb=hemoglobin, HHV6=human herpes virus 6, HIV=human immunodeficiency virus, HLA=human leukocyte antigen, ICPi=immune checkpoint inhibitor, INR=international normalized ratio, irAE=immune-related adverse event, IV=intravenous, IVIG=intravenous immunoglobulin, LDH=lactate dehydrogenase, LLN=lower limit of normal, MRI=magnetic resonance imaging, NSAID=nonsteroidal anti-inflammatory drug, PB=peripheral blood, PEX=plasma ex-change, PNH=paroxysmal nocturnal hemoglobinuria, PT=prothrombin time, PTT=partial thromboplastin time, RBC=red blood cell, TTP=thrombotic thrombocytopenic purpura.

Table A 9 Management of Cardiovascular Immune-related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

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 anti-thymocyte 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 for 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	

ACC=American College of Cardiology, AHA=American Heart Association, BNP=brain natriuretic peptide, CT=computed tomography, CTPA=computed tomography pulmonary angiography, CXR=chest x-ray, DVT=deep vein thrombosis, ECG=electrocardiogram, G=grade, ICPi=immune checkpoint inhibitor, CCI [redacted], IV=intravenous, LMWH=low-molecular-weight heparin, MRI=magnetic resonance imaging, PE=pulmonary embolism, VKA=vitamin K agonist.

Table A 10 Management of Ocular Immune-related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

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

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

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


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Appendix 10 Country-specific Requirements

With the following exceptions, all country-specific protocol requirements are outlined within the protocol.

Japan

In Japan, all participants enrolled in the safety run-in cohort must undergo in-house observation in a hospital setting for until at least 24 hours after the first administration of the study intervention. Thereafter, hospitalization can be extended to up until the end of the DLT evaluation period if it is appropriate for the safety of the participant. See also Sections 4.1.1 and 6.6.2.

In Japan, if the study is not expanded to the planned N=500 part, it is regarded that the efficacy of bintrafusp alfa is not confirmed statistically throughout this study, as study is a confirmatory study.


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Appendix 11 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

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

Definitions

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

Measurable Disease

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

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

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

Non-measurable Disease

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

Bone lesions:

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

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

- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

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

Target Lesions

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

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

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

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

Non-target Lesions

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

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

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

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

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

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

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

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

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

RESPONSE CRITERIA

Evaluation of Target Lesions

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

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

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

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

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

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

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

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

Evaluation of Non-target Lesions

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

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

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

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

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

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

New Lesions

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

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

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

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

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

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

Evaluation of Best Overall Response

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

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

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

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

Note:

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

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

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

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

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

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

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

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

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

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

Duration of Overall Response

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

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

Duration of Stable Disease

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

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

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

Appendix 12 Protocol Amendment History

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

Protocol Version 4.0 (20 April 2021)

Overall Rationale for the Amendment

The primary driver for this amendment is to specify that efficacy data from the first 150 antibiotics-naive participants enrolled in Phase II will be used for the decision on the expansion into Phase III. In addition, a dose modification of bintrafusp alfa/placebo for management of bleeding events has been added.

Section # and Name	Description of Change	Brief Rationale
Title Page	Removed "Medical Responsible", "Amendment Number", and "Replaces Version" fields	To be consistent with current Sponsor protocol template (Version 15)
Title Page	Changed details of Medical Monitor	Details related to Medical Monitor responsible for the study have been updated.
1.1 Synopsis 1.2 Schema: Figure 1 Overall Study Design Schema 4.1 Overall Design Figure 2 Outline of Randomized, Double-blind Study Design 9.3.1 Analysis for the Adaptation Decision Section 9.5.4 Sequence of Analyses, Table 26 Sequence of Planned Analyses	An additional criterion has been added to the definition of the efficacy analysis set to be used for the analysis for decision on the expansion to Phase III sample size.	Since Study Protocol Version 3.0 (dated 27 July 2020), patients with systemic antibiotics treatment during screening were excluded and therefore, the full Phase III sample size is expected to be largely antibiotics-naive. The criterion of being antibiotics-naive has been added to the definition of the efficacy analysis set to be used for the analysis for decision on the expansion to Phase III sample size in order to have a population more representative of the anticipated population in the full Phase III sample size.
1.1 Synopsis CCI [redacted] 9.3.1 Analysis for the Adaptation Decision 9.3.3 Power and Type I Error Control Table 19	Futility criterion has been introduced for expansion decision and Overall Survival (OS) analysis.	The futility criterion will aid the Independent Data Monitoring Committee (IDMC) with their recommendation to stop the study early for futility, if applicable.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1.2 Randomized, Double-blind Part 8.2.4.2 Independent Data Monitoring Committee	A description has been added to provide clarity on the type of study population to be analyzed for efficacy and safety analysis for expansion into Phase III. This clarification would also help IDMC's assessment of efficacy and safety data and to provide their recommendation for expansion into the Phase III.	Accumulating evidence shows that antibiotics used before checkpoint inhibitors are associated with poor prognosis. Study Protocol Version 3.0 amended exclusion criteria to participants with systemic antibiotic use during Screening, leading to a full Phase III sample size of largely antibiotics-naïve participants. In order to have a population more representative of the anticipated overall study population, the adaptation decision will be based on antibiotics-naive participants.
1.3 Schedule of Activities Table 1 and Table 2 Section 11 Appendix 6 Table E	A clarification has been provided on measures to be taken when Hepatitis B test positivity is reported at Screening.	The aim of 6 weeks follow-up if one or more of HB-surface antigen, HB-core antibody or HB-surface antibody test is positive, is to test the potential reactivation of HBV, although the risk is very low.
1.3 Schedule of Activities Table 1 and Table 2	A note has been added related to Patient Reported Outcome (PRO) Questionnaires completion in case of study treatment interruption.	Addition of note will help assessment of PROs in case of dose delay or interruption during the study.
1.3 Schedule of Activities Table 3 and Table 4	A note has been added on antidrug CCI and pharmacokinetic (PK) sampling	The note will clarify the requirement of pre-dose CCI and PK samples when dosing is deferred at the visit or when no visit takes place.
2.3 Benefit/Risk Assessment	Dermatologic adverse events (AEs) are reclassified as important identified risks.	The risk reclassification was based on in depth analysis of a pooled safety dataset of N = 765 participants who received bintrafusp alfa monotherapy at 1200 mg Q2W
4.1 Overall Design	A note has been added to guide in checking enrollment of the study population.	The monitoring of enrollment will ensure that a study population is obtained, which is representative across the participating global regions (for e.g., Asian versus non-Asian countries).
CCI		
4.3.2 Bintrafusp alfa with Chemotherapy	Edits are done to highlight dose modification of the study intervention in a specific condition.	These edits will help further understanding of conditions for dose modification of the study intervention.
5 Study Population Appendix 2	Edits are done related to informed consent process.	To be consistent with current Sponsor protocol template (Version 15)

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Inclusion criterion number 2 has been updated	The criterion has been updated to provide more clarity on exclusion of participants with histological subtype such as sarcomatoid tumor or HCC mixed subtype for which gemcitabine and cisplatin treatment are not considered as the standard of care.
5.2 Exclusion Criteria	Exclusion criterion number 5 has been edited. Clarification has been provided to ensure exclusion of participants who require antibiotic treatment and systemic therapy during the screening period	To define the period more clearly and ensure consistent wording across the 2 exclusion criteria to avoid ambiguity due to imprecise wording.
5.2 Exclusion Criteria	Exclusion criterion number 13 has been updated for prior adjuvant therapy duration	The specification for prior adjuvant therapy duration will help to select participants for the study.
6.4 Study Intervention Compliance	A sentence has been added related to dose modification of the study intervention.	The information will aid in documentation of dose modification, if any during the study in the electronic case report form (eCRF).
6.5.3 Prohibited Medicines	Vaccine administration criterion has been revised.	The criterion was revised to provide clarity on which vaccines are allowed or prohibited for the study participants during the conduct of the study.
6.6.1 Dosing Instructions	Details are added on study treatment administration. Edits are done in this section to indicate dose modification of bintrafusp alfa/placebo to 1200 mg is allowed in the study.	The details will help investigator/designee on ensuring timing of the study treatment administration. This will help the Investigator to understand dose modification of bintrafusp alfa/placebo is allowed in the study to manage bleeding events.
6.6.3 Treatment Modification Table 7	Title has been modified and a note added on handling of other AEs (e.g., infections). A sentence has been deleted related to dose modification in case of several toxicities. Edits are done in this section to indicate dose modification of bintrafusp alfa/placebo to 1200 mg is allowed in the study. Information related to dose modification of bintrafusp alfa/placebo to 1200 mg for management of bleeding events has been added in the table	The note added will help in handling other AEs such as infections. The sentence has been deleted to avoid repetition of the information presented in the section. This will help the Investigator to understand dose modification of bintrafusp alfa/placebo is allowed in the study to manage bleeding events.
6.6.3.2 Gemcitabine and/or Cisplatin-related Adverse Drug Reactions	A note has been introduced related to resolution of anemia.	The note will help to assess if the study intervention should be continued in case anemia does not resolve from Grade 2 to Grade ≤ 1
6.6.4 Dose Modification of Gemcitabine, Cisplatin, and Bintrafusp alfa/Placebo for Renal Impairment	Specifications on creatine clearance have been added for administration of gemcitabine and cisplatin.	The criterion will help to take decision on dose modification of gemcitabine and cisplatin in case of renal toxicity.

Section # and Name	Description of Change	Brief Rationale
6.9 Management of Adverse Events of Special Interest and other Potential Risks Section 11 Appendices, Appendix 4	Risk recategorization has been done and the list of events has been updated accordingly	The risk re-classification was based on in depth analysis of a pooled safety dataset of N=765 participants who received bintrafusp alfa monotherapy at 1200 mg Q2W.
6.9.1 Infusion-related Reactions Including Immediate Hypersensitivity	Infusion related reactions are reclassified from "important identified risks" to "identified risk" for bintrafusp alfa.	
6.9.2 Immune-related Adverse Events	Risk reclassification has been done and the list of events has been updated accordingly	
6.9.3 TGFβ inhibition mediated Skin Reactions	Risk recategorization has been done.	
6.9.4 Anemia	Term treatment-related anemia events has been revised to anemia and reclassified from "important potential risk" to "important identified risk" for bintrafusp alfa. Also, details are updated for management of anemia.	
6.9.5 Bleeding Events	Bleeding events are reclassified from "potential risk" to "important identified risk" for bintrafusp alfa	
6.9.6.1 Impaired Wound Healing	The risk name "Alterations in Wound Healing or Repair of Tissue Damage" has been changed to "Impaired Wound Healing".	
6.9.1 Infusion-related Reactions Including Immediate Hypersensitivity	Further details are added on treatment modification for Grade 3 or Grade 4 infusion related reactions including immediate hypersensitivity	The details added on treatment modification will help in resolution of the event.
6.9.4 Anemia	Further details have been added in general guidance for anemia management and evaluation.	The guidance will help Investigator to take decision on continuation of study intervention administration in case of anemia.
6.9.5 Bleeding Events	Details have been added with regards to action to be taken on the study intervention in case of rapid decrease of hemoglobin (Hgb) and Grade 1 or greater bleeding events.	These details will help the Investigator in understanding study treatment interruption, modification or re-escalation in case of rapid decrease of Hgb and Grade 1 or greater bleeding events during the study.
7.1.1 Permanent Treatment Discontinuation	A paragraph has been deleted, which is related to tumor assessment and other assessments in case of premature withdrawal from the study intervention for reasons other than PD.	The paragraph has been deleted to avoid redundancy of information presented in the section.
7.1.2 Treatment Beyond Initial Progression	Clarification provided for adaption decision analysis.	The additional wordings will provide more clarity on adaption decision analysis.
7.3 Lost to Follow up	Edits are done related to Lost to Follow-up information.	To be consistent with current Sponsor protocol template (Version 15)
8.1.1 Tumor Response	Antibiotics-naive criterion has been	To ensure participants representative

Section # and Name	Description of Change	Brief Rationale
	added	of the criterion added for the adaption decision.
10 References	New reference has been added	New references have been added to further enhance understanding about: stopping boundaries for non-binding futility analysis. Outcome of use of antibiotics before treatment with checkpoint inhibitors.
Note: Minor changes have been performed throughout the protocol to address consistency pertaining to major changes done in the protocol or to add further clarity and precision.		

Protocol Version 3.0 (27 July 2020)

This amendment is considered a substantial amendment 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 allow the continued recruitment at the time 150 participants are randomized as recommended by EMA Follow-up Protocol Assistance (EMEA/H/SA/3934/2/FU/1/2019/PA/II).

Section # and Name	Description of Change	Brief Rationale
Title Page Appendix 13, Sponsor Signature Page Appendix 14, Coordinating Investigator Signature Page Appendix 15, Principal Investigator Signature Page	Added the ClinicalTrials.gov number	For transparency and easy track.
Title Page 7.2 Participant Discontinuation/Withdrawal from the Study 8 Study Assessments and Procedures 8.5 Pharmacokinetics CCI 9.5.3 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 (Version 14).

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Overall Study Design Schema (Figure 1) 4.1 Overall Design 4.1.2 Randomized, Double-blind Part (Figure 2) 4.2 Scientific Rationale for Study Design 4.4 End of Study Definition 9.3 Sample Size Determination 9.3.1 Analysis for the Adaptation Decision 9.3.2 Probability of Study Expansion 9.3.3 Power and Type I Error Control (Table 19) 9.5.1 Efficacy Analyses (Table 24) 9.5.4 Sequence of Analysis (Table 26)	- Updated maximal number of participants for Phase II - Updated text to clarify that initial 150 participants recruited in Phase II will be analyzed for an expansion decision into Phase III - Updated a minimum follow-up period at least 19 weeks for the first 150 participants randomized is included - Updated Figure 1 and 2 - Updated assumptions of sample size calculation (i.e., number of participants and time periods).	- Updated text to allow continued participant recruitment without pause prior to adaptation decision as recommended by EMA Follow-up Protocol Assistance (EMEA/H/SA/3934/2/FU/1/2019/PA/II) - Updated follow-up period to allow for data maturity to observe confirmed response.
1.1 Synopsis 8.2.4.2 Independent Data Monitoring Committee 8.2.4.3 Independent Review Committee and throughout the protocol, as applicable	Added the information about the Independent Data Monitoring Committee (IDMC) and Independent Review Committee (IRC) responsibility for Phase II and Phase III study	- To be aligned with IDMC Statistical Analysis Plan - To provide details about the IDMC responsibility.
1.3 Schedule of Activities and throughout the protocol, as applicable	Clarified that procedures and activities should be scheduled from Week 1, Day 1 (W1D1)	For clarity
	Updated note for Inclusion/exclusion criteria	For clarity
	Updated note for Premedication and bintrafusp alfa /placebo administration	To keep the dose intensity of bintrafusp alfa/placebo when dosing flexibility is needed
	Updated note for Premedication/hydration and gemcitabine/cisplatin	For clarity
	Updated note for Full chemistry and hematology and Core chemistry and hematology	To clarify the timing that laboratory tests must be reviewed before dosing
	Updated note for Urinalysis	To clarify that only dipstick is required even if dipstick is accompanied with microscopy.
	Updated note for Tumor evaluation	To clarify and modify the tumor evaluation window from ± 3 days to ± 7 days (except week 7, when the window is -0 to +7 days)
	Updated the window for Safety Follow-up Visit 28 days from ± 5 to ± 7 Days After Last Treatment	To allow an extension
	Updated notes and Objective response to subsequent (2L) treatment in Table 2	To clarify the radiological assessment in Long-term Follow-up for participants that started subsequent anticancer therapy
	CCI [redacted]	

Section # and Name	Description of Change	Brief Rationale
	Updated note for Liquid biopsy (plasma)	Removed time-window of liquid biopsy prior to dosing to streamline the procedure
CCI		
CCI		
5.2 Exclusion Criteria	Updated exclusion criteria 2 and 5	To clarify the timing
	Updated exclusion criterion 5	To clarify exclusion criteria for participants with biliary obstruction
	Updated exclusion criterion 16	For consistency with Section 6.5.4
5.4 Screen Failures	Addition of requirement of re-biopsy as a criteria of discussion with Medical Monitor for screening window extension	For clarity
6.1 Study Intervention(s) Administration (Table 6)	Bintrafusp alfa was included as the international nonproprietary name for M7824	For consistency across the development program
6.5.3 Prohibited Medicines	Clarified prophylactic use of steroid	To allow local guidance
6.6.1 Dosing Instructions	Clarified administration of chemotherapy	To allow local practice for gemcitabine and cisplatin administration
6.6.3.2 Gemcitabine and/or Cisplatin-related Adverse Drug Reactions	Clarified the dose modification for neutropenia and thrombocytopenia in the case of gemcitabine and/or cisplatin-related adverse drug reactions.	For clarity
6.6.4 Dose Modification of Gemcitabine, Cisplatin, and Bintrafusp alfa/Placebo for Renal Impairment	Added clarification about the creatinine clearance (CrCl) calculation	For clarity
6.6.5 Disease Specific Risk: Hepatic Impairment	Added a clarification that immune-related cholangitis should	For clarity

Section # and Name	Description of Change	Brief Rationale
	be differentiated if medically indicated	
6.8 Special Precautions	Considered cisplatin for subsequent infusion	For clarity
6.9.1 Infusion-related Reactions Including Immediate Hypersensitivity (Table 14)	Added clarification about the order of infusion	For clarity
7.1.2 Treatment Beyond Initial Progression	- Removed the information about regression and clarified the text related to the continuation of gemcitabine and cisplatin until confirmed progressive disease (PD). - Clarified that radiological images will be collected from all participants and these will be assessed by IRC if required.	To simplify the treatment decision tree for treatment beyond progression
7.1.3 Treatment Beyond Confirmed Progression and throughout the protocol, as applicable	- Deleted information about treatment beyond confirmed progression - Updated Figure 3	To simplify the study protocol after the progression period. In addition, it is not reasonable to allow further treatment after confirmed PD for the comparator arm which does not include immunotherapy.
8.1.1 Tumor Response Appendix 11, Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 throughout the protocol, as applicable	- Clarified the MRI areas - Removed the information for central imaging read and interpretation for all scan - Added RECIST 1.1 as Appendix 11. - Clarified that radiological images collected from the remaining 350 participants must be submitted.	- For clarity - To correct inconsistency. Central Imaging is only for Phase II. - For consistency across the development program
8.2.1 Physical Examinations and Vital Signs	Removed the specific information about the readings of blood pressure and pulse	For consistency across the development program
8.2.4.1 Safety Monitoring Committee	Updated section	For clarity
9.5.1 Efficacy Analyses (Table 24)	Updated duration of response (DOR) endpoint to be aligned with objectives	For consistency
Appendix 8, Management of Immune-related Adverse Events (Table A2)	To remove the information that Vedolizumab is not approved in Japan	To revise and provide correct information since Vedolizumab is already approved in Japan for the treatment of Ulcerative colitis (from 2018) and Crohn´s disease
Appendix 10, Country-specific requirements	Added information about Japan and Korean/Taiwan specific requirements	For clarity and to explain that the 2 PRO items can only be implemented once the local language versions are available and approved by the Ethics Committee/Institutional Review Board (EC/IRB)
Throughout the protocol	Minor editorial and formatting revisions; correction of minor typographical errors	To make minor revisions for correctness, readability, consistency of language across the bintrafusp alfa development program, and for

Section # and Name	Description of Change	Brief Rationale
		compliance with current Sponsor guidelines

Protocol Version 2.1 (03 December 2019)

This amendment is considered a substantial amendment 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

CCI [redacted]

The key changes incorporated are:

- To describe a single primary endpoint (overall survival) in the randomized, double-blind part of the study rather than dual primary endpoints
- To remove the requirement for initial progressive disease as determined by the Investigator to be verified by an Independent Review Committee (IRC)
- The analysis of progression-free survival (PFS) and other tumor-based efficacy endpoints will now be based on Investigator assessment; analysis based on IRC assessment will only be performed if the study is not expanded to Phase III
- To acknowledge that, for the purposes of marketing authorization in Japan, if the study is not expanded into Phase III, it will not be acceptable as a confirmatory study
- To provide additional information on the power to detect differences in efficacy among the different biliary tract cancer anatomical subgroups
- To exclude participants with history of bleeding diathesis and provide further guidance on dose modifications for bleeding events according to NCI-CTCAE severity grade and site of bleeding
- To include additional patient-reported outcome measures to enable participants' experience of the study intervention to be further characterized
- To allow chemotherapy to be given on Day 15 of a given cycle if administration on Day 1 or Day 8 was not possible.

Changes implemented in this protocol amendment will only be implemented at each site following review/favorable opinion of the amendment by the responsible Institutional Review Board/Independent Ethics Committee, as indicated in Appendix 2. Sites should ensure they are following the appropriate approved protocol version at any given time, particularly with respect to the recruitment of participants in the open-label, safety run-in part.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.2 Scientific Rationale for Study Design 9.1 Statistical Hypotheses 9.3 Sample Size Determination 9.5 Statistical Analyses Table 5, Table 24, and Table 26, and throughout the protocol, as applicable	Progression-free survival (PFS) changed from a primary to a secondary endpoint If the adaptation decision results in the full Phase III sample size (N = 500), the Investigator will become the main assessor for PFS	To have overall survival (OS) as a single primary endpoint
4.2 Scientific Rationale for Study Design Figure 3 5.1 Inclusion Criteria 6.5.4 Other Interventions 7.1 Discussion of Study Intervention Table 16 8.1.1 Tumor Response, and throughout the protocol, as applicable	Removal of verification of progressive disease (PD) by an Independent Review Committee (IRC) following Investigator determined PD	Verification of PD by an IRC was introduced as a quality measure for the primary endpoint, PFS per IRC. With PFS having been demoted to a secondary endpoint, this is no longer required
4.4 End of Study Definition	Updated end of study definition with data cutoff for primary OS analysis for Phase III and Phase II study	To address regulatory agency feedback
9.2 Hierarchical Testing Procedure	Provision of hierarchical testing procedures for the endpoints OS, PFS, and objective response rate	Required due to the change from dual primary endpoints to a single primary endpoint
9.5.1 Efficacy Analyses (Table 24)	Clarification of the analyses used for testing null hypothesis	To address regulatory agency feedback
9.5.4 Sequence of Analyses	Clarification of the sequence of analyses	Required due to the change from dual primary endpoints to a single primary endpoint
Appendix 10 Country-specific Requirements	Explanation that in Japan, if the study is not expanded into Phase III, it is not expected to satisfy the condition of a confirmatory study	To address regulatory agency feedback
1.1 Synopsis 4.1.1 Open-label, Safety Run-in Part	Clarification that participants will be recruited sequentially in each cohort of the open-label, safety run-in part	To address regulatory agency feedback
1.1 Synopsis 4.1.2 Randomized, Double-blind Part 6.3.1 Study Intervention Assignment Table 24	The definition of the stratification factor relating to classification of biliary tract cancer (BTC) at diagnosis has been refined	To ensure all potential diagnoses of BTC at diagnosis are captured within the definition of the related stratification factor
9.3.4 Subgroup Analyses for Biliary Tract Cancer Subtypes Table 20, Table 21, Table 22, and Table 24	Information provided regarding the power to detect differences in efficacy among the anatomical BTC subgroups	To address regulatory agency feedback
5.1 Inclusion Criteria	Text added to ensure the histological origin of ampullary carcinomas is recorded	To address regulatory agency feedback

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria 6.6.3.1 Bintrafusp alfa/Placebo-related Adverse Drug Reactions 6.9.5.1 Management of Bleeding Events	Exclusion of participants with relevant prior/current medical history of bleeding events. Information provided regarding the management of bleeding events during study intervention	To exclude participants with history of bleeding diathesis or recent major bleeding events To provide guidelines for the management of bleeding events and indications for when participants should have study intervention held or discontinued
1.3 Schedule of Activities, Table 1 and Table 2 Table 6 6.6.1 Dosing Instructions	Dosing instructions amended to allow a missed dose of chemotherapy on Day 1 or Day 8 of a given cycle to be administered on Day 15 of the same cycle	To maintain dose intensity of chemotherapy where possible
CCI		
CCI		
CCI		
6.6.3.1 Bintrafusp Alfa/Placebo-related Adverse Drug Reactions 6.9.3 Skin Adverse Events	Information regarding the management of bintrafusp alfa/placebo-related adverse drug reactions and the management of skin adverse events has been updated	To ensure guidance is consistent with language used across the bintrafusp alfa development program
CCI		

Section # and Name	Description of Change	Brief Rationale
CCI		
Throughout the protocol	Protocol requirements clarified for: pregnancy testing; hepatitis; inclusion criteria 3 and 4; dosing instructions; anti-emesis treatment; patient-reported outcomes; and Tables A, B, E, and F	To implement protocol clarifications outlined in the MS200647_0055 Clarification Letter, dated 22 July 2019
Throughout the protocol	Protocol requirements clarified for: inclusion criterion 1; exclusion criteria 5 and 18; management of emesis; management of biliary tract obstruction; and replacement of participants in the open-label, safety run-in part. Assumptions for sample size calculation also clarified	Protocol clarifications
Throughout the protocol	"M7824" has been replaced by the international nonproprietary name, "bintrafusp alfa" throughout the protocol	To ensure consistency with other regulatory documents in the bintrafusp alfa development program
Throughout the protocol	Minor editorial and formatting revisions; correction of minor typographical errors	To make minor revisions for correctness, readability, consistency of language across the bintrafusp alfa development program, and for compliance with current Sponsor guidelines

Protocol Version 2.0 (11 October 2019)

This amendment is considered a substantial amendment 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 address feedback on Version 1.0 of the protocol from regional and national regulatory agencies (European Medicines Agency, the US Food and Drug Administration, and the Pharmaceutical and Medical Devices Agency in Japan). The key changes incorporated are:

- To describe a single primary endpoint (overall survival) in the randomized, double-blind part of the study rather than dual primary endpoints
- To remove the requirement for initial progressive disease as determined by the Investigator to be verified by an Independent Review Committee (IRC)
- The analysis of progression-free survival (PFS) and other tumor-based efficacy endpoints will now be based on Investigator assessment; analysis based on IRC assessment will only be performed if the study is not expanded to Phase III

- To acknowledge that, for the purposes of marketing authorization in Japan, if the study is not expanded into Phase III, it will not be acceptable as a confirmatory study
- To provide additional information on the power to detect differences in efficacy among the different biliary tract cancer anatomical subgroups
- To exclude participants with history of bleeding diathesis and provide further guidance on dose modifications for bleeding events according to NCI-CTCAE severity grade and site of bleeding
- To include additional patient-reported outcome measures to enable participants' experience of the study intervention to be further characterized
- To allow chemotherapy to be given on Day 15 of a given cycle if administration on Day 1 or Day 8 was not possible.

Changes implemented in this protocol amendment will only be implemented at each site following review/favorable opinion of the amendment by the responsible Institutional Review Board/Independent Ethics Committee, as indicated in Appendix 2. Sites should ensure they are following the appropriate approved protocol version at any given time, particularly with respect to the recruitment of participants in the open-label, safety run-in part.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.2 Scientific Rationale for Study Design 9.1 Statistical Hypotheses 9.3 Sample Size Determination 9.5 Statistical Analyses Table 5, Table 24, and Table 26, and throughout the protocol, as applicable	Progression-free survival (PFS) changed from a primary to a secondary endpoint If the adaptation decision results in the full Phase III sample size (N = 500), the Investigator will become the main assessor for PFS	To have overall survival (OS) as a single primary endpoint
4.2 Scientific Rationale for Study Design Figure 3 5.1 Inclusion Criteria 6.5.4 Other Interventions 7.1 Discussion of Study Intervention Table 16 8.1.1 Tumor Response, and throughout the protocol, as applicable	Removal of verification of progressive disease (PD) by an Independent Review Committee (IRC) following Investigator determined PD	Verification of PD by an IRC was introduced as a quality measure for the primary endpoint, PFS per IRC. With PFS having been demoted to a secondary endpoint, this is no longer required
4.4 End of Study Definition	Updated end of study definition with data cutoff for primary OS analysis for Phase III and Phase II study	To address regulatory agency feedback
9.2 Hierarchical Testing Procedure	Provision of hierarchical testing procedures for the endpoints OS, PFS, and objective response rate	Required due to the change from dual primary endpoints to a single primary endpoint
9.5.1 Efficacy Analyses (Table 24)	Clarification of the analyses used for testing null hypothesis	To address regulatory agency feedback
9.5.4 Sequence of Analyses	Clarification of the sequence of analyses	Required due to the change from dual primary endpoints to a single primary endpoint

Section # and Name	Description of Change	Brief Rationale
Appendix 10 Country-specific Requirements	Explanation that in Japan, if the study is not expanded into Phase III, it is not expected to satisfy the condition of a confirmatory study	To address regulatory agency feedback
1.1 Synopsis 4.1.1 Open-label, Safety Run-in Part	Clarification that participants will be recruited sequentially in each cohort of the open-label, safety run-in part	To address regulatory agency feedback
1.1 Synopsis 4.1.2 Randomized, Double-blind Part 6.3.1 Study Intervention Assignment Table 24	The definition of the stratification factor relating to classification of biliary tract cancer (BTC) at diagnosis has been refined	To ensure all potential diagnoses of BTC at diagnosis are captured within the definition of the related stratification factor
9.3.4 Subgroup Analyses for Biliary Tract Cancer Subtypes Table 20, Table 21, Table 22, and Table 24	Information provided regarding the power to detect differences in efficacy among the anatomical BTC subgroups	To address regulatory agency feedback
5.1 Inclusion Criteria	Text added to ensure the histological origin of ampullary carcinomas is recorded	To address regulatory agency feedback
5.2 Exclusion Criteria 6.6.3.1 Bintrafusp alfa/Placebo-related Adverse Drug Reactions 6.9.5.1 Management of Bleeding Events	Exclusion of participants with relevant prior/current medical history of bleeding events. Information provided regarding the management of bleeding events during study intervention	To exclude participants with history of bleeding diathesis or recent major bleeding events To provide guidelines for the management of bleeding events and indications for when participants should have study intervention held or discontinued
1.3 Schedule of Activities, Table 1 and Table 2 Table 6 6.6.1 Dosing Instructions	Dosing instructions amended to allow a missed dose of chemotherapy on Day 1 or Day 8 of a given cycle to be administered on Day 15 of the same cycle	To maintain dose intensity of chemotherapy where possible
[redacted]		
6.6.3.1 Bintrafusp Alfa/Placebo-related Adverse Drug Reactions	Information regarding the management of bintrafusp alfa/placebo-related	To ensure guidance is consistent with language used

Section # and Name	Description of Change	Brief Rationale
6.9.3 Skin Adverse Events	adverse drug reactions and the management of skin adverse events has been updated	across the bintrafusp alfa development program
[redacted]		
Throughout the protocol	Protocol requirements clarified for: pregnancy testing; hepatitis; inclusion criteria 3 and 4; dosing instructions; anti-emesis treatment; patient-reported outcomes; and Tables A, B, E, and F	To implement protocol clarifications outlined in the MS200647_0055 Clarification Letter, dated 22 July 2019
Throughout the protocol	Protocol requirements clarified for: inclusion criterion 1; exclusion criteria 5 and 18; management of emesis; management of biliary tract obstruction; and replacement of participants in the open-label, safety run-in part. Assumptions for sample size calculation also clarified	Protocol clarifications
Throughout the protocol	"M7824" has been replaced by the international nonproprietary name, "bintrafusp alfa" throughout the protocol	To ensure consistency with other regulatory documents in the bintrafusp alfa development program
Throughout the protocol	Minor editorial and formatting revisions; correction of minor typographical errors	To make minor revisions for correctness, readability, consistency of language across the bintrafusp alfa development program, and for compliance with current Sponsor guidelines

Protocol Version 1.1 (19 September 2019)

This amendment is considered 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 the participants nor the scientific integrity of the study.

Overall Rationale for the Amendment

The primary purpose of this amendment is to address feedback and questions on Version 1.0 of the protocol received during European VHP procedure. The key changes incorporated are:

- Revision and clarification of inclusion and exclusion criteria to assure participant safety
- Clarification of the management of study participants at the end of study

- Revision of the criteria for Grade 3 M7824/placebo-related adverse drug reactions that do not require discontinuation of study intervention.

Changes implemented in this protocol amendment will only be implemented at each site following review/favorable opinion of the amendment by the responsible Institutional Review Board/Independent Ethics Committee, as indicated in Appendix 2. Sites should ensure they are following the appropriate approved protocol version at any given time, particularly with respect to the recruitment of participants in the open-label, safety-run-in part.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Revision of inclusion criteria 8 and 14 with respect to hematological function and sexual activity/egg donation, respectively	To address regulatory agency feedback
5.2 Exclusion Criteria	Revision of exclusion criterion 5 with respect to active viral infection requiring systemic treatment Addition of a new criterion to exclude participants who are suitable for liver transplantation	To address regulatory agency feedback
4.4 End of Study Definition	Provision added for: • participants who are still receiving study intervention or undergoing survival follow-up at the end of study to be enrolled in an extension study or non-interventional study • the Sponsor to terminate the study at any time once access to study intervention for participants still benefiting is provided	To address regulatory agency feedback
6.6.3.1 M7824/Placebo-related Adverse Drug Reactions	For Grade 3 adverse drug reactions that do not require treatment discontinuation: • Definition of "transient" added • New criteria relating to Eastern Cooperative Oncology Group Performance Status and endocrinopathies added	To address regulatory agency feedback
1.3 Schedule of Activities, Table 1 and Table 2	Protocol requirements clarified for vital signs assessments	To address regulatory agency feedback
6.9.1 Infusion-related Reactions Including Immediate Hypersensitivity, Table 13	Definition of "prolonged" added	To address regulatory agency feedback

Appendix 13 Sponsor Signature Page

Study Title:	A Phase II/III, Multicenter, Randomized, Placebo-controlled Study of Gemcitabine Plus Cisplatin With or Without Bintrafusp alfa (M7824) as First-line Treatment of Biliary Tract Cancer
Regulatory Agency Identifying Numbers:	CCI [redacted] EudraCT: 2019-001992-35 ClinicalTrials.gov: NCT04066491
Clinical Study Protocol Version:	14 July 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:	Merck Biopharma Co., Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany)
Address:	PPD
Telephone number:	
Fax number:	
E-mail address:	

Appendix 14 Coordinating Investigator Signature Page

Study Title:	A Phase II/III, Multicenter, Randomized, Placebo-controlled Study of Gemcitabine Plus Cisplatin With or Without Bintrafusp alfa (M7824) as First-line Treatment of Biliary Tract Cancer
Regulatory Agency Identifying Numbers:	CCI [redacted] EudraCT: 2019-001992-35 ClinicalTrials.gov: NCT04066491
Clinical Study Protocol Version:	14 July 2021/Version 5.0
Site Number:	

I approve the design of the clinical study, am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, 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:	PPD
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Appendix 15 Principal Investigator Signature Page

Study Title:	A Phase II/III, Multicenter, Randomized, Placebo-controlled Study of Gemcitabine Plus Cisplatin With or Without Bintrafusp alfa (M7824) as First-line Treatment of Biliary Tract Cancer
Regulatory Agency Identifying Numbers:	CCI [redacted] EudraCT: 2019-001992-35 ClinicalTrials.gov: NCT04066491
Clinical Study Protocol Version:	14 July 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: