Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	An Adaptive Phase III, Multicenter, Randomized, Open-Label, Controlled Study of M7824 (bintrafusp alfa) versus Pembrolizumab as a First-line Treatment in Patients with PD-L1 Expressing Advanced Non-small Cell Lung Cancer
Study Number:	MS200647-0037
Merck Compound Number:	M7824
Study Phase:	III
Short Title:	1L NSCLC Adaptive Phase III RCT M7824 vs Pembrolizumab
Coordinating Investigator:	PPD PPD
Sponsor Name and Legal Registered Address:	For all countries except the US and Japan: Merck KGaA, Darmstadt, Germany Frankfurter Strasse 250 64293 Darmstadt, Germany In Japan: Merck Biopharma Co., Ltd.: Japan (Affiliate of Merck KGaA, Darmstadt, Germany) Arco Tower, 1-8-1 Shimomeguro Meguro-ku, Tokyo 153-8926, Japan In the US: EMD Serono Research and Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA 01821, USA
Regulatory Agency Identifying Numbers:	CCI EudraCT 2018-001517-32
Protocol Version:	22 June 2021/Version 4.0

Medical Monitor Name and Contact Information:	PPD PPD Office phone: PPD Mobile phone: PPD

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	23 May 2018
1.1-JPN	Country-specific amendment (Japan)	02 August 2018
1.2	Region-specific amendment (European Union for countries participating in the VHP)	25 July 2018
1.3-CHN	Country-specific amendment (China)	01 September 2018
2.0	Global amendment	08 July 2019
2.1	Region-specific amendment (European Union for countries participating in the VHP)	09 September 2019
3.0	Global amendment	10 February 2020
3.1	Region-specific amendment (European Union for countries participating in the VHP)	06 May 2020
4.0	Global amendment	22 June 2021

VHP = Voluntary Harmonisation Procedure.

Protocol Version 4.0 (22 June 2021)

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

Overall Rationale for the Amendment

The primary purpose of this amendment is to update the risk classification and minimization measures. Further collections of pharmacokinetic/anti-drug antibody samples and patient reported outcome data are no longer needed and therefore removed from this amendment.

Section # and Name	Description of Change	Brief Rationale
Title Page	Change in Name and Contact information of Medical Monitor Removed "Amendment Number", "Replaces Version" and "Approval Date" rows Removed Medical Responsible information	Administrative change

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 3 Objectives and Endpoints	PK, Immunogenicity and ADA objectives have been removed	Collection of PK/ADA samples is no longer required and has been removed from the protocol
Section 1.2 Schema in Figure 1	PK and ADA have been removed from key secondary endpoints	Collection of PK/ADA samples is no longer required and has been removed from the protocol
Section 1.3 Schedule of Activities, Table 1 Schedule of Assessments – M7824 Arm, Table 2 Schedule of Assessments – Pembrolizumab Arm	PK and ADA sampling have been removed	Collection of PK/ADA samples is no longer required and has been removed from the protocol
Section 1.3 Schedule of Activities, Table 1 Schedule of Assessments – M7824 Arm, Table 2 Schedule of Assessments – Pembrolizumab Arm, Table 3 Safety and Long-term Follow-up – M7824 and Pembrolizumab Arms	Note for Documentation of AEs has been updated to refer to the Appendix 6 and Section 7.1 for further details on AE reporting	To clarify and streamline
Section 1.3 Schedule of Activities, Table 1 Schedule of Assessments - M7824 Arm, Table 2 Schedule of Assessments – Pembrolizumab Arm, Table 3 Safety and Long-term Follow-up – M7824 and Pembrolizumab Arms, Section 3 Objectives and endpoints, Section 7.2 Participant Discontinuation/Withdrawal from the Study	PRO assessments have been removed	PRO assessment are no longer required and have been removed from the protocol
Section 1.3 Schedule of Activities, Previous Table 2	M7824 Arm Pharmacokinetic and CCI Sampling table has been deleted	Collection of PK CCI
Section 1.3 Schedule of Activities, Table 3 Safety and Long-term Follow-up – M7824 and Pembrolizumab Arms	Note a has been updated to clarify that the 12-week Safety Follow-up and Long-term follow-up may be conducted via telephone calls	For consistency (week vs. month) elsewhere in the document
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Section 2.3 Benefit/Risk Assessment	Text has been updated to reflect the risk classification and minimization measures, and a reference to the IB for details of identified and potential risks for M7824 has been added	To update the risk classification and minimization measures and refer to the IB for full safety details

Section # and Name	Description of Change	Brief Rationale
Section 5 Study Population	Clarified that the participant's legal representative may provide consent where allowed by local laws and regulations	For consistency with current protocol template
Section 6.8 Special Precautions	Text in AESI subsections has been updated and moved to Section 6.9 AESI	To avoid repletion and streamline presentation
Section 6.8.1.1 Adverse Events of Special Interest/Identified Risks	Text from original 6.8.1 to 6.8.5 has been moved to Section 6.9 (Management of AESI); a cross reference to Section 6.9 has been added	To avoid repetition and streamline presentation
Section 6.8.1.2 Additional Potential Risks	Text describing potential risks from original Section 6.9 (AESI) are moved to this section and updated to remove mild to moderate bleeding and anemia as potential risk	To avoid repetition and streamline presentation and to update the risk classification
Section 6.9 Management of Adverse Events of Special Interest	Text has been moved from original sections 6.8.1 to 6.8.5, and risk classification and minimization methods have been updated, original Section 6.9 is removed	To update the risk classification and minimization measures
Section 6.9.1 Infusion-related Reactions Including Immediate Hypersensitivity	Text has been added to clarify IRR is AESI and identified risks for M7824	To consolidate and clarify the text.
Section 6.9.2 Immune-related Adverse Events	Text has been updated to provide the list of immune-related AEs Added a reference to the current NCCN guideline	To update the risk classification
Section 6.9.3 TGFβ inhibition medicated skin reactions	Remove "Potential" from section title. Clarified that skin assessments will be performed for all participants, and for participants restarting treatment after treatment discontinuation, a rebaseline skin assessment should be done. Clarified that skin AEs are also AESIs.	To update the risk classification and minimization measures
Section 6.9.4 Anemia	Removal of "treatment-related" from definition of anemia AESI	To update the risk classification
Section 6.9.5 Management of Bleeding Events	Text revised to specify that Bleeding AEs are AESIs and are considered important identified risk for M7824, and not a potential risk	To update the risk classification and minimization measures
Section 6.9.5.1 Mucosal/Non-tumor bleeding	Clarified that participants treated with M7824 were commonly reported with mild to moderate mucosal AEs. Actions to be taken with study intervention in the event of bleeding AEs have been updated	To update the risk classification and minimization measures

Section # and Name	Description of Change	Brief Rationale
Section 6.9.5.2 Tumor Bleeding	Text added to state that participants treated with M7824 were reported in lower frequencies with Grade ≥ 3 hemorrhage including tumor bleeding	To update the risk classification and minimization measures
Section 8.5 Pharmacokinetics	Previous description of PK sampling deleted and text added to clarify that PK samples are no longer collected in the study	Collection of PK samples are no longer required and have been removed from the protocol
Section 8.9 Immunogenicity Assessments	Previous description of ADA sampling deleted and text added to clarify that ADA samples are no longer collected in the study	Collection of ADA samples are no longer required and have been removed from the protocol
Section 8.10 Patient-reported Outcomes	Section has been deleted	PRO evaluations are no longer performed in this study
Section 9.3 Populations for Analyses	PK population has been removed from Table 13 Analysis Populations	Collection of PK/ADA samples is no longer required and has been removed from the protocol
Section 9.4.3 Other Analyses	Description of PK analyses removed and text added to clarify that PK analyses will be performed on samples collected in this study as descried in previous versions of the protocol	Collection of PK/ADA samples is no longer required and has been removed from the protocol
Appendix 2 Study Governance	Informed Consent Process description updated	For consistency with current protocol template
Appendix 6 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	The categories for AESIs have been updated	To update the risk classification

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1 Protocol Summary

1.1 Synopsis

Protocol Title: An Adaptive Phase III, Multicenter, Randomized, Open-Label, Controlled Study of M7824 (bintrafusp alfa) versus Pembrolizumab as a First-line Treatment in Patients with PD-L1 Expressing Advanced Non-Small Cell Lung Cancer

Short Title: 1L NSCLC Adaptive Phase III RCT M7824 vs Pembrolizumab

Rationale: Based on the acceptable safety profile and promising activity that is enhanced at higher programmed death-ligand 1 (PD-L1) expression levels in tumor cells, this adaptive Phase III study is to evaluate whether M7824 improves progression-free survival (PFS) time and/or overall survival (OS) compared with pembrolizumab as a first-line (1L) treatment for participants with advanced non-small cell lung cancer (NSCLC) with PD-L1 tumor expression. CCI [redacted] Both dual primary endpoints PFS and OS are evaluated in a confirmatory analysis to demonstrate the superiority of M7824 versus pembrolizumab using one-sided stratified log-rank tests taking the randomization strata into account and controlling the overall significance level at 2.5% one-sided. The participants in this study must not have received prior systemic therapy treatment for their advanced NSCLC and must not have epidermal growth factor receptor (EGFR) sensitizing (activating) mutation, anaplastic lymphoma kinase (ALK) translocation, ROS1 mutation, or BRAF V600E mutation, where targeted therapy is locally approved.

Objectives and Endpoints:

Objectives	Endpoints (Outcome Measures)
Primary	
To demonstrate improvement in PFS with M7824 compared with pembrolizumab	PFS according to RECIST 1.1 assessed by IRC
To demonstrate improvement in OS with M7824 compared with pembrolizumab	OS
Secondary	
Safety To evaluate the safety and tolerability of M7824 compared with pembrolizumab	Occurrence of TEAEs and treatment-related AEs
Efficacy To evaluate the objective response of M7824 compared with pembrolizumab	Objective response according to RECIST 1.1 assessed by IRC
To evaluate the DOR of M7824 compared with pembrolizumab	DOR assessed from CR or PR according to RECIST 1.1 assessed by IRC until PD, death, or last tumor assessment
AE = adverse event; CR = complete response; DOR = duration of response; IRC = Independent Review Committee; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; TEAE = treatment-emergent adverse event.	

Overall Design: This is a multicenter, adaptive Phase III, international, randomized, open-label, controlled study of intravenous M7824 monotherapy versus pembrolizumab as 1L treatment for participants with advanced NSCLC with high PD-L1 tumor expression. The study will recruit participants who have not received previous treatment for their advanced NSCLC for examination of the efficacy and safety of M7824 versus pembrolizumab. Participants will be randomly assigned to treatment arm in a 1:1 ratio. PD-L1 high is defined as ≥ 80% PD-L1 positive tumor cells as determined by the PD-L1 immunohistochemistry (IHC) 73-10 assay. These participants must not have EGFR sensitizing mutation or ALK translocation, ROS1 mutation, or BRAF V600E mutation if targeted therapy is locally approved. Primary efficacy analysis population is the full analysis set (FAS) according to the intention-to-treat (ITT) principle, i.e., all randomized participants. The adaptive trial design provides prespecified analysis rules, which allows the Independent Data Monitoring Committee (IDMC) to recommend an expansion from an initial 300 participants into a larger study with a sample size of 584 participants in total, i.e. adding 284 participants. The IDMC evaluates objective response as assessed by the Independent Review Committee (IRC) on the 73-10 PD-L1 high analysis set restricted to participants randomized at least 6 months before the data cutoff date. That interim analysis (OR IA) cutoff date is 6 months after enrolling the 100th participant tested 73-10 PD-L1 high. In this analysis, the IDMC will decide, based on ORR difference between treatment arms per study design, to either keep the study running at the initial sample size (N = 300), expand the sample size (N = 584), or stop for futility. Details of the predefined criteria to expand the study to larger sample size will be given in the IDMC charter.

Number of Participants: The initial sample size of 300 randomized participants may be expanded to a total of 584 randomized participants upon predefined adaptation criterion based on the OR IA evaluated by the IDMC.

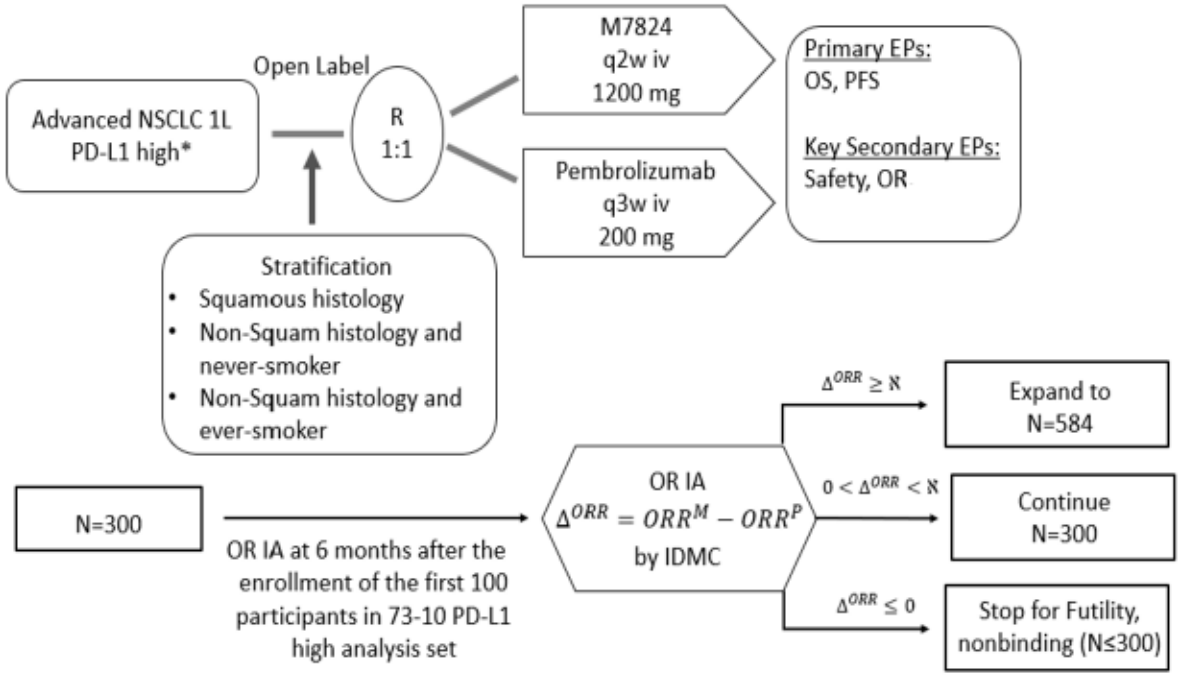
Study Intervention Groups and Duration: Participants who meet the study criteria will be randomly assigned in a 1:1 ratio to receive either:

- M7824 at a dose of 1200 mg per infusion once every 2 weeks, or
- Pembrolizumab at a dose of 200 mg per infusion once every 3 weeks.

Involvement of Special Committee(s): Yes

1.2 Schema

Figure 1 Diagram of Study Design



[redacted] Prior to Protocol V.3.0, participants with TPS ≥ 50% as determined by the PD-L1 IHC 22C3 assay performed according to local laboratory regulations prior to study enrollment were also eligible.

N refers to participants randomized and included in the FAS population.

EP = endpoint; FAS = full analysis set; 1L = first-line; IHC = immunohistochemistry; IA = interim analysis; IDMC = Independent Data Monitoring Committee; iv = intravenously; NSCLC = non-small cell lung cancer; OR = objective response; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; q2w = every 2 weeks; q3w = every 3 weeks; R = randomization; squam = squamous; TPS = tumor proportion score; ℵ adaptation decision boundary.

1.3 Schedule of Activities

Table 1 Schedule of Assessments – M7824 Arm

M7824 Assessment	Screening/ Baseline Assessments	Treatment Phase (±3 days)								End-of-Treatment Visit	Notes
	Day -28 to Randomization	V1 W1 D1	V2 W3 D15	V3 W5 D29	V4 W7 D43	V5 W9 D57	V6 W11 D71	V7 W13 D85	Until PD	On the Day of or Within 7 Days of Decision	
Administrative Procedures											
Written informed consent	X										To determine the main study eligibility criteria ahead of full screening procedures, an ICF will be used.
Inclusion/ exclusion/ Enrollment (if eligible)	X	X[a]									Enrollment will be after the confirmation of fulfilling all inclusion criteria and without matching any exclusion criterion. a: Confirmation of eligibility via an abbreviated checklist is required prior to dosing on W1D1.
Demographic data	X										
Medical history	X										
Documentation concomitant therapy	X	X	X	X	X	X	X	X	2-weekly	X	
Prior anticancer drug/radiotherapy /procedures	X										
Virology serology (HBV and HCV)	X				X[b]			X[b]	6 weekly[b]		b: Only applicable to participants with a history of HBV or HCV infection

M7824 Assessment	Screening/ Baseline Assessments	Treatment Phase (±3 days)								End-of-Treatment Visit	Notes
	Day -28 to Randomization	V1 W1 D1	V2 W3 D15	V3 W5 D29	V4 W7 D43	V5 W9 D57	V6 W11 D71	V7 W13 D85	Until PD	On the Day of or Within 7 Days of Decision	
Tumor Biopsies/Archival Tissue Collection											
[redacted]											
Pretreatment and M7824 Drug Administration											
Pretreatment and M7824 drug administration		X	X	X	X	X	X	X	2-weekly		Optional premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol iv or oral equivalent).
Safety Assessments											
Documentation of AEs	X	X	X	X	X	X	X	X	2-weekly	X	See Appendix 6 for safety recording and reporting and see Section 7.1 in case of discontinuation from the study intervention.
Physical examination	X	X	X	X	X	X	X	X	6 weekly	X	Complete PE at screening; subsequent focused PEs to be performed as per local standard practice.

M7824 Assessment	Screening/ Baseline Assessments	Treatment Phase (±3 days)								End-of-Treatment Visit	Notes
	Day -28 to Randomization	V1 W1 D1	V2 W3 D15	V3 W5 D29	V4 W7 D43	V5 W9 D57	V6 W11 D71	V7 W13 D85	Until PD	On the Day of or Within 7 Days of Decision	
Skin assessment	X				X			X	6 weekly	X	
Vital signs	X	X	X	X	X	X	X	X	2-weekly	X	Including weight and height (height at Screening only)
ECOG PS[d]	X	X[d]	X	X	X	X	X	X	2-weekly	X	d: ECOG PS 0 or 1 is required at W1D1
12-lead ECG	X										
Laboratory Assessments											
Hematology and hemostaseology	X	X		X		X		X	4-weekly	X	Details on blood tests under this category is listed in Table 16. Samples must also be drawn and results for core chemistry, hematology, and pregnancy test reviewed prior to dose administration. For participants who met study criteria at screening, but W1D1 values are not within study criteria and study continuation is desired, discuss with the Medical Monitor.
Core serum chemistry		X		X		X		X	4-weekly		Core serum chemistry are listed in Table 16. Samples must also be drawn and results for core chemistry, hematology, and pregnancy test reviewed prior to dose administration. For participants who met study criteria at screening, but W1D1 values are not within study criteria and study continuation is desired, discuss with the Medical Monitor.
Full serum chemistry Panel A	X		X		X		X		4-weekly	X	See Table 16 for individual tests in each laboratory panel. Blood samples must also be drawn and results for core chemistry parameters, hematology, and pregnancy test reviewed prior to dose administration.
Full serum chemistry Panel B	X										See Table 16 for individual tests in each laboratory panel.
Urinalysis	X	As clinically indicated									

M7824 Assessment	Screening/ Baseline Assessments	Treatment Phase (±3 days)								End-of-Treatment Visit	Notes
	Day -28 to Randomization	V1 W1 D1	V2 W3 D15	V3 W5 D29	V4 W7 D43	V5 W9 D57	V6 W11 D71	V7 W13 D85	Until PD	On the Day of or Within 7 Days of Decision	
β-hCG pregnancy test (only applicable to WOCBP)	X[e]	X		X		X		X	4-weekly		β-hCG should be determined from serum at Screening and from a urine or serum sample thereafter. Results of the most recent pregnancy test should be available prior to dosing of study intervention. e: If a confirmation of a participant's postmenopausal status is necessary, follicle-stimulating hormone and estradiol tests will be performed at Screening.
Free T_4 and TSH	X				X			X	6 weekly		
CCI											

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M7824 Assessment	Screening/ Baseline Assessments	Treatment Phase (±3 days)								End-of-Treatment Visit	Notes
	Day -28 to Randomization	V1	V2	V3	V4	V5	V6	V7	Until PD	On the Day of or Within 7 Days of Decision	
		W1	W3	W5	W7	W9	W11	W13			
		D1	D15	D29	D43	D57	D71	D85			
CCI											

AE = adverse event; β-hCG = beta-human chorionic gonadotropin; CR = complete response; CRT = chemoradiotherapy; CT = computed tomography; D = Day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EoT = End-of-Treatment; HBV = hepatitis B virus; HCV = hepatitis C virus; ICF = Informed consent form; iv = intravenous; MRI = magnetic resonance imaging; PD = progressive disease; PD-L1 = programmed death-ligand 1; PE = physical examination; PR = partial response; RT = radiation therapy; T_4 = free thyroxine; CCI TSH = thyroid-stimulating hormone; V = Visit; W = Week; WOCBP = woman of childbearing potential.

Table 2 **Schedule of Assessments – Pembrolizumab Arm**

Pembrolizumab Assessment	Screening/ Baseline Assess-ments	Treatment Phase (±3 days)								End-of-Treatment Visit	Notes
	Day -28 to Randomi-zation	V1	V2	V3	V4	V5	V6	V7	Until PD	On the Day of or Within 7 Days of Decision	
		W1	W4	W7	W10	W13	W16	W19			
		D1	D22	D43	D64	D85	D106	D127			
Administrative Procedures											
Written informed consent	X										To determine the main study eligibility criteria ahead of full screening procedures, an ICF will be used.
Inclusion/exclusion/ Enrollment (if eligible)	X	X[a]									Enrollment will be after the confirmation of fulfilling all inclusion criteria and without matching any exclusion criterion. a: Confirmation of eligibility via an abbreviated checklist is required prior to dosing on W1D1.
Demographic data	X										
Medical history	X										
Documentation concomitant therapy	X	X	X	X	X	X	X	X	3-weekly	X	
Prior anticancer drug/radiotherapy/ procedures	X										
Virology serology (HBV and HCV)	X			X[b]		X[b]		X[b]	6 weekly[b]		b: Only applicable to participants with a history of HBV or HCV infection.

Pembrolizumab Assessment	Screening/ Baseline Assess-ments	Treatment Phase (±3 days)								End-of-Treatment Visit	Notes
	Day -28 to Randomi-zation	V1	V2	V3	V4	V5	V6	V7	Until PD	On the Day of or Within 7 Days of Decision	
		W1	W4	W7	W10	W13	W16	W19			
		D1	D22	D43	D64	D85	D106	D127			
CCI											
CCI											
Pretreatment and Pembrolizumab Drug Administration											
Pembrolizumab administration		X	X	X	X	X	X	X	3-weekly		
Safety Assessments											
Documentation of AEs	X	X	X	X	X	X	X	X	3-weekly	X	See Appendix 6 for safety recording and reporting and see Section 7.1 in case of discontinuation from the study intervention.
Physical examination	X	X	X	X	X	X	X	X	6 weekly	X	Complete PE at screening; subsequent focused PEs to be performed as per local standard practice.
Skin assessment	X			X		X		X	6 weekly	X	
Vital signs	X	X	X	X	X	X	X	X	3-weekly	X	Including weight and height (height at Screening only)

Pembrolizumab Assessment	Screening/ Baseline Assess-ments	Treatment Phase (±3 days)								End-of-Treatment Visit	Notes
	Day -28 to Randomi-zation	V1 W1 D1	V2 W4 D22	V3 W7 D43	V4 W10 D64	V5 W13 D85	V6 W16 D106	V7 W19 D127	Until PD	On the Day of or Within 7 Days of Decision	
ECOG PS[d]	X	X[d]	X	X	X	X	X	X	3-weekly	X	d: ECOG PS 0 or 1 is required at W1D1
12-lead ECG	X										
Laboratory Assessments											
Hematology and hemostaseology	X	X	X	X	X	X		X	6 weekly	X	Details on blood tests under this category is listed in Table 16. Samples must also be drawn and results for core chemistry, hematology, and pregnancy test reviewed prior to dose administration. For participants who met study criteria at screening, but W1D1 values are not within study criteria and study continuation is desired, discuss with the Medical Monitor.
Core serum chemistry		X		X		X		X	6 weekly		Core serum chemistry are listed in Table 16. Samples must also be drawn and results for core chemistry, hematology, and pregnancy test reviewed prior to dose administration. For participants who met study criteria at screening, but W1D1 values are not within study criteria and study continuation is desired, discuss with the Medical Monitor.
Full serum chemistry Panel A	X		X		X		X		6 weekly	X	See Table 16 for individual tests in each laboratory panel. Blood samples must also be drawn and results for core chemistry parameters, hematology, and pregnancy test reviewed prior to dose administration.
Full serum chemistry Panel B	X										See Table 16 for individual tests in each laboratory panel.
Urinalysis	X	As clinically indicated									

Pembrolizumab Assessment	Screening/ Baseline Assess-ments	Treatment Phase (±3 days)								End-of-Treatment Visit	Notes
	Day -28 to Randomi-zation	V1 W1 D1	V2 W4 D22	V3 W7 D43	V4 W10 D64	V5 W13 D85	V6 W16 D106	V7 W19 D127	Until PD	On the Day of or Within 7 Days of Decision	
β-hCG pregnancy test (only applicable to WOCBP)	X[e]	X	X	X	X	X	X	X	3-weekly		β-hCG should be determined from serum at Screening and from a urine or serum sample thereafter. Results of the most recent pregnancy test should be available prior to dosing of study intervention. e: If a confirmation of a participant's postmenopausal status is necessary, follicle-stimulating hormone and estradiol tests will be performed at Screening.
Free T_4 and TSH	X			X		X		X	6 weekly		
[redacted]											

Pembrolizumab Assessment	Screening/ Baseline Assess-ments	Treatment Phase (±3 days)								End-of-Treatment Visit	Notes
	Day -28 to Randomi-zation	V1	V2	V3	V4	V5	V6	V7	Until PD	On the Day of or Within 7 Days of Decision	
		W1	W4	W7	W10	W13	W16	W19			
		D1	D22	D43	D64	D85	D106	D127			
CCI											

AE = adverse event; β-hCG = beta-human chorionic gonadotropin; CR = complete response; CRF = case report form; CRT = chemoradiotherapy; CT = computed tomography; D = Day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EoT = End-of-Treatment; HBV = hepatitis B virus; HCV = hepatitis C virus; ICF = Informed consent form; MRI = magnetic resonance imaging; PD = progressive disease; PE = physical examination; PR = partial response; RT = radiation therapy; T_4 = free thyroxine CCI TSH = thyroid-stimulating hormone; V = visit; W = Week; WOCBP = woman of childbearing potential.

Table 3 Safety and Long-term Follow-up – M7824 and Pembrolizumab Arms

M7824 and Pembrolizumab Assessment	Safety Follow-up Visit		Long-term Follow-up		Notes
	28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment	Every 6 weeks (± 1 week)	Every 12 weeks (± 1 week)	
Documentation concomitant therapy	X	X		X	
Documentation of AEs	X	X		X [a,b]	See Appendix 6 for safety recording and reporting and see Section 7.1 in case of discontinuation from the study intervention a: The 12-week Safety Follow-up and Long-term Follow-up may be conducted via telephone calls b: See Section 8.3.1 for definition of the AE Reporting Period and Section 8.3.3 for Follow-up of AEs/SAEs
Physical examination	X				Focused PEs to be performed as per local standard practice.
Skin assessment	X				
Vital signs	X				Including weight
ECOG PS	X				
12-lead ECG	X				
Hematology and hemostaseology	X				Details on blood tests under this category are listed in Table 16. Samples must also be drawn and results for core chemistry, hematology, and pregnancy test reviewed prior to dose administration
Full serum chemistry Panel A	X				See Table 16 for individual tests in each laboratory panel.
Urinalysis	X				
β-hCG pregnancy test	X				β-hCG should be determined from urine or serum.
Free T_4 and TSH	X				
Subsequent anticancer therapy (any line)	X	X	X		
Survival follow-up				X	

M7824 and Pembrolizumab Assessment	Safety Follow-up Visit		Long-term Follow-up		Notes
	28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment	Every 6 weeks (± 1 week)	Every 12 weeks (± 1 week)	
[redacted] CCI					

AE = adverse event; β-hCG = beta-human chorionic gonadotropin; CRF = case report form; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MRI = magnetic resonance imaging; PE = physical examination; 2L = second-line; SAE = serious adverse event; T_4 = free thyroxine; 3L = third line; TSH = thyroid-stimulating hormone.

2 Introduction

Bintrafusp alfa (M7824) is a first-in-class bifunctional fusion protein that combines a programmed death-ligand 1 (PD-L1) antibody and transforming growth factor β (TGFβ) receptor II as a TGFβ neutralizing 'trap' into a single molecule.

M7824 is designed to target PD-L1 and TGFβ, 2 major mechanisms of immunosuppression in the tumor microenvironment. The preclinical data suggest that M7824 strongly enhances antitumor activity and prolongs survival in mouse tumor models above the effect of either the anti-PD-L1 antibody avelumab or the TGFβ Trap control alone (at the same molarity as M7824).

This open-label, adaptive Phase III, randomized, controlled study is to evaluate whether M7824 improves progression-free survival (PFS) and/or overall survival (OS) compared with pembrolizumab. M7824 is indicated as monotherapy for participants with advanced non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression, with no prior systemic treatment for metastatic NSCLC.

Complete information on the chemistry, pharmacology, efficacy, and safety of M7824 is in the Investigator's Brochure.

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2.2 Background

Lung cancer is the leading cause of cancer death in the USA and results in more cancer deaths than breast cancer, prostate cancer, and colorectal cancer combined. Non-small cell lung cancer accounts for approximately 80% of all cases of lung cancer. It is estimated in 2018 there would be 234,030 new cases of lung and bronchus cancer and 154,050 people would die from their lung cancers in the USA alone (Siegel, 2018). In the EU, 275,700 deaths due to lung cancer were predicted in 2017 (Malvezzi, 2017). Worldwide, an estimated 1.8 million new cases of lung cancer were diagnosed in 2012, approximately 13% of the total of all new cancers diagnosed (Ferlay, 2013).

Immune checkpoint inhibitors have shown improved treatment outcome in patients with NSCLC; however, there is room to further improve benefits.

Pembrolizumab has been approved as a 1L monotherapy for patients with metastatic NSCLC whose TPS is $\geq$ 50% (as determined by the PD-L1 IHC 22C3 pharmDx assay) and negative for EGFR and ALK genomic tumor aberrations based on the KEYNOTE-024 study. In this PD-L1 high population, pembrolizumab showed 1-year OS of 70%, median PFS of 10.3 months and ORR of 45% (Reck, 2016). Preliminary results from the KEYNOTE-042 (Phase III study of pembrolizumab versus chemotherapy in PD-L1+ advanced NSCLC) indicate that the study met its primary endpoint of OS and would be submitted to regulatory authorities (Merck, 2018).

Further study data for KEYNOTE-042 were not disclosed at the time of this protocol. The known results of pembrolizumab, nivolumab, and atezolizumab as 1L monotherapy for NSCLC are summarized in Table 5.

Table 5 **Response Rates of Pembrolizumab, Nivolumab, and Atezolizumab as First-line Monotherapy for NSCLC**

	KEYNOTE-024	Checkmate-026		BIRCH	
	TPS ≥ 50% N=154	≥ 5% PD-L1+ N=208	≥ 50% PD-L1+ N=88	≥ 5% PD-L1+ (TC or IC) N=139	≥ 50% PD-L1+ (TC or IC) N=65
ORR (95% CI)	44.8% (36.8 to 53.0)	26% (20 to 33)	34% (24 to 45)	22% (15 to 29)	31% (20 to 43)
mPFS (months) (95% CI)	10.3 (6.7 to NR)	4.2 (3.0 to 5.6)	5.4	5.4 (3.0 to 6.9)	5.6 (2.7 to 8.3)
mOS (months) (95% CI)	NR	14.4 (11.7 to 17.4)	15.9	20.1 (20.1 to NE)	NR

(Reck, 2016; Carbone, 2017; Peters, 2017)
IC = tumor infiltrating immune cells; mOS = median overall survival; mPFS = median progression-free survival; NE = not evaluated; NR = not reported; ORR = objective response rate; CCI
TC = tumor cells; TPS = tumor proportion score.

In the 2L setting where participants had disease progression following platinum-containing chemotherapy and, if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations, anti-PD-1 antibodies, Opdivo® (nivolumab) and Keytruda® (pembrolizumab), and CCI antibodies, Tecentriq™ (atezolizumab) have been approved as monotherapy. The response rates of the approved PD-(L) inhibitors used as the 2L treatment for NSCLC participants are summarized in Table 6.

Table 6 Response Rates of Nivolumab, Pembrolizumab, and Atezolizumab as Second-line Monotherapy for NSCLC

	Checkmate-057		Checkmate-017		KEYNOTE-010		POPLAR	
	All Comer N=292	> 50% PD-L1+ N=66	All Comer N=135	> 50% PD-L1+ N=17	TPS ≥ 1% 2, 10 mg/kg N=344, 346	TPS ≥ 50% 2, 10 mg/kg N=139, 151	All Comer N=144	≥ 50% PD-L1+ TC or IC)
ORR	19% (15 to 24)	41 (29 to 54)	20% (14 to 28)	29% (10 to 56)	18.0%, 19%	30%, 29%	14.6%	37.5%
mPFS	2.1 (1.2 to 8.6)	NR	3.5 (2.1 to 4.9)	NR	3.9 (3·1 to 4·1), 4.0 (2·7 to 4·3)	5.0 (4·0 to 6·5), 5.2 (4·1 to 8·1)	2.7 (2 to 4.1)	7.8 (2.7 to 12.3)
mOS (95% CI)	12.2 (9.7 to 15.0)	NR	9.2 (7.3 to 13.3)	NR	10.4 (9·4 to 11·9), 12.7 (10·0 to 17·3)	14.9 (10·4 to NE) 17.3 (1.8 to NE)	12·6 (9·7 to 16·4)	15·5 (9·8 to NE)

(Brahmer, 2015; Borghaei, 2015; Herbst, 2016; Fehrenbacher, 2016)

IC = tumor infiltrating immune cells; mOS = median overall survival; mPFS = median progression-free survival; NE = not evaluated; NR = not reported; ORR = objective response rate; CCI
TC = Tumor cells; TPS = tumor proportion score.

The clinical profile of M7824 is being evaluated in 2 ongoing Phase I studies (EMR200647-001 and MS200647-0008) in participants with various solid tumors. See the M7824 Investigator's Brochure for a summary of clinical studies conducted to date. M7824 consistently showed higher ORRs in 2L NSCLC all-comers, CCI compared with those of other patient derived xenograft (PDx) inhibitors, including pembrolizumab, thus justifying the clinical investigation of M7824 in 1L NSCLC. Durable responses with M7824 were observed.

2.3 Benefit/Risk Assessment

M7824 is a first-in-class bifunctional molecule targeting 2 immunosuppressive pathways in the tumor microenvironment: the PD-1/PD-L1 axis and TGFβ. In EMR200647-001, the response rates in benefit of M7824 in 2L NSCLC participants are substantially better than historical controls and are further improved with higher PD-L1 tumor expression. It is anticipated that response rates would improve further when moving from pretreated disease to treatment-naïve participants, as was seen in pembrolizumab between KEYNOTE-010 and KEYNOTE-024. Improving response and survival in this patient population will be meaningful as responses to immunotherapy are known to be durable, and therapeutic, non-cytotoxic options are limited in these patients without actionable tumor mutations.

This study will randomly assign participants 1:1 between M7824 and pembrolizumab to evaluate whether clinical efficacy can be improved since KEYNOTE-024. This global study will include countries with and without approval of 1L pembrolizumab, increasing access to this life-extending class of drugs. An early futility analysis based on response rate is planned 6 months after the

enrollment of the first 100 participants with high PD-L1 expression according to 73-10 assay to ensure M7824 activity is at least comparable to pembrolizumab in this 1L setting. If pre-specified efficacy results are observed at this analysis, the sample size may be increased upon recommendation of the Independent Data Monitoring Committee IDMC (Section 9).

Prior to 24 September 2019, participants could be enrolled in this study based on PD-L1 expression results using either pre-existing local 22C3 results or 73-10 central results. As the study protocol allowed to limit the number of participants enrolled with prior local 22C3 PD-L1 test results (see Section 9.2), on 24 September 2019, investigators were notified that new participants could be enrolled only based on the 73-10 assay central results. There is a potential risk that some participants with a high PD-L1 result using the 73-10 assay would have a result of < 50% TPS using the 22C3 assay given the positive percent agreement between the 2 assays in procured NSCLC tumor samples is 80% (95% confidence interval [CI]: 63.1, 91.6) when using 73-10 as the non-reference standard (see Section 2.1). This may result in treatment of participants randomized to the pembrolizumab arm at a PD-L1 level of < 50% TPS outside of the current EU label for pembrolizumab; however, this risk for participants is minimal: tumor samples from participants enrolled in Study MS200647-0037 with high PD-L1 expression based on central 73-10 assay results were retrospectively tested with the VENTANA PD-L1 Assay (SP263 Assay), which has similar analytical performance characteristics in NSCLC compared with the 22C3 assay and is CE-marked in the EU for use with pembrolizumab in 1L NSCLC. The retrospective testing was conducted in samples from 69 participants randomized in this study on or before 23 October 2019 (data on file). Of the 69 samples tested, 66 generated valid results with the SP263 assay, which included 65 positive results and 1 negative result. The positive percent agreement between the 73-10 assay and the SP263 assay using 73-10 as the nonreference standard is 98.5% (95% CI: 91.8, 100.0). The 1 discordant sample had PD-L1 expression in 90% of tumor cells based on the 73-10 assay and 30% of tumor cells based on the SP263 assay. The high positive percent agreement (98.5%) between the 73-10 assay and the SP263 assay in participants enrolled in Study MS200647-0037 suggests that using the 73-10 assay for participant selection in this study has very low risk of enrolling participants outside of the current EU label for pembrolizumab treatment.

The identified and potential safety risks with M7824 were overall manageable and monitorable. No new safety signals emerged in the EMR200647-001/MS200647-0008 studies compared with prior therapies targeting PD-L1 or TGFβ. The emergence of an irAE is an identified risk for both M7824 and pembrolizumab. The frequency and severity of irAEs were comparable between participants treated with M7824 at 500 mg and 1200 mg, and similar to other PD-(L)1 targeting drugs, including pembrolizumab. No increased irAE risk was observed with M7824 due to blocking 2 immunosuppressive pathways.

Dermatologic AEs related to TGFβ-inhibition (including keratoacanthomas (KA) and cutaneous squamous cell cancers) are an identified risk with M7824 not seen with pembrolizumab. These lesions were previously observed in individuals with genetic mutations in the TGFβ receptor (i.e., Ferguson-Smith Syndrome), and participants treated with the TGFβ-targeting agent, fresolimumab (Goudie, 2011; Morris, 2014). In the EMR200647-001/MS200647-0008 studies, these lesions were observed in approximately 7% of participants, were well-managed with simple excision (or spontaneous resolution) and did not require any participant to discontinue treatment. The risk of

these lesions with M7824 was considered manageable on this study, especially in the context of clinical activity against an advanced cancer.

The risks for M7824 are updated based on the pooled safety data from 765 patients treated with M7824 monotherapy in the Investigator's Brochure Version 7.0 (April 2021). The risk classifications are revised in this amendment, see Section 6.9 for specifics.

Identified and potential risks of these drugs will be closely monitored in both treatment arms, along with the monitoring of all AEs. Management guidance is outlined in this protocol for specific risks, but direct guidance via communication with study medics is always available. Overall, the safety profile of both drugs is manageable. Considering the observed efficacy of M7824 in NSCLC and acceptable safety profile, the benefit/risk assessment appears favorable to conduct this study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of M7824 may be found in Section 4.2 and the Investigator's Brochure. See Sections 6.9 and 6.8 for management of AESIs and special precautions, respectively.

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

3 Objectives and Endpoints

The objectives and endpoints are defined in Table 7. Endpoint assessments are in Section 8.

Table 7 Study Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)
Primary	
To demonstrate improvement in PFS with M7824 compared with pembrolizumab To demonstrate improvement in OS with M7824 compared with pembrolizumab	PFS according to RECIST 1.1 assessed by IRC OS
Secondary	
Safety To evaluate the safety and tolerability of M7824 compared with pembrolizumab	Occurrence of TEAEs and treatment-related AEs
Efficacy To evaluate the efficacy in objective response of M7824 compared with pembrolizumab	Objective response according to RECIST 1.1 assessed by IRC
To evaluate the duration of response (DOR) of M7824 compared with pembrolizumab	DOR assessed from CR or PR according to RECIST 1.1 assessed by IRC until PD, death, or last tumor assessment
CCI [redacted]	

CCI

Long-term follow-up of survival for 5 years after the last dose of M7824 or pembrolizumab in a participant unless reported as lost to follow-up, had died, or the study is terminated.

AE = adverse event; CR = complete response; DOR = duration of response; CCI ; CCI ; IRC = Independent Review Committee; CCI ; CCI ; ORR = objective response rate; OS = overall survival; PD = progressive disease; CCI 1; PFS = progression-free survival; survival; CCI PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; TEAE = treatment-emergent adverse event; CCI

4 Study Design

4.1 Overall Design

The overall study design is shown in Figure 1. Detailed schedules of study procedures/assessments are provided in Section 8 and in Table 1 and Table 2 for the M7824 and pembrolizumab treatment arms, respectively. See Section 6.7 for details of study intervention after the end of the study.

This is a multicenter, adaptive Phase III, international, randomized, open-label, controlled study of intravenous (iv) M7824 monotherapy versus pembrolizumab as 1L treatment for participants with advanced NSCLC with high PD-L1-tumor expression. The study will enroll participants who have not received previous treatment for their advanced NSCLC for examination of the efficacy and safety of M7824 versus pembrolizumab. Participants will be randomly assigned to treatment arm in a 1:1 ratio. PD-L1 high is defined as ≥ 80% PD-L1 positive tumor cells as determined by the PD-L1 IHC 73-10 assay. These participants must not have EGFR sensitizing mutation or ALK translocation, ROS1 mutation, or BRAF V600E mutation if targeted therapy is locally approved. The adaptive trial design provides prespecified decision rules, which allow the IDMC to recommend an expansion from initial 300 participants into a larger study with a sample size of 584 participants in total, i.e. adding 284 participants. Refer to Section 4.2.6 for further details on adaptive Phase III design. Participants who meet the study criteria will be randomly assigned in a 1:1 ratio to receive either:

- M7824 at a dose of 1200 mg per infusion once every 2 weeks (q2w), or
- Pembrolizumab at dose of 200 mg per infusion once every 3 weeks (q3w).

The participants will be stratified according to tumor histology (nonsquamous versus squamous) and smoking history as follows:

- Squamous histology
- Nonsquamous histology and never smoked
- Nonsquamous histology and ever smoker (i.e, former or current).

This study includes:

- 28-day Screening period
- Treatment until confirmed progressive disease (PD) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1), unacceptable toxicity, or for up to 24 months. In the case of PD, treatment may continue past the initial determination of PD or confirmed PD if the participant's Eastern Cooperative Oncology Group Performance Status (ECOG PS) has remained stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment and if other criteria are fulfilled as outlined in this protocol (Sections 5.1 and 5). Participants in either cohort who experience stable disease (SD), partial response (PR), or complete response (CR) should continue treatment until the end of 24 months, although additional treatment may be possible. If the Investigator believes that a participant will benefit from treatment beyond 24 months, it may be permissible after discussion with the Medical Monitor and the Sponsor Medical Responsible. Of note, pembrolizumab is only allowed for

24 months per regulatory (FDA, EMA) labels; therefore, extenuating circumstances and outstanding justification must be documented to support treatment beyond 24 months in either arm.

- Safety follow-up Visits until 12 weeks after the last dose of M7824 or pembrolizumab (Safety Follow-up Visit at 12 weeks is allowed via telephone call).
- Survival follow-up up to 5 years with visits (in person or by phone call) every 12 weeks after the last dose of M7824 or pembrolizumab unless reported as lost to follow-up, dead, or after study termination (recommended every 6 weeks on 2L treatment as below).
- Participants who start 2L treatment should be monitored for response to that treatment. Investigators should follow local clinical practice for monitoring disease status on subsequent lines of therapy. The study team encourages and requests scans to be performed every 6 weeks, if feasible, in addition to a scan within 28 days prior to starting 2L treatment. These evaluations should be documented by the Investigator and uploaded to the imaging repository, if available. Best overall response according to RECIST 1.1 to this 2L treatment for metastatic disease should also be reported. A participant's progression may involve the following: objective radiological, symptomatic progression, or death due to advancing disease. This should be documented every 6 weeks until progression on 2L treatment, initiation of subsequent (third-line) treatment, withdrawal of consent, or death.

See Section 4.4 for the end of study definition.

4.1.1 Treatment Beyond Progression

Treatment beyond initial progression

Participants will receive M7824 and pembrolizumab as outlined in Section 1.3 (Schedule of Activities) until disease progression. M7824 or pembrolizumab may continue past the initial determination of disease progression according to RECIST 1.1 as long as the following criteria are met:

- Participant is in the study and treatment with M7824 or pembrolizumab is ongoing
- No new unacceptable treatment or disease-related toxicity
- Tolerance of study interventions
- Stable ECOG PS
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., central nervous system [CNS] metastases).

A radiographic assessment should be performed within 4 to 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with M7824 and pembrolizumab.

Treatment beyond confirmed progression

After confirmed PD, if the Investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the study and continue to receive monitoring according to Section 1.3 (Schedule of Activities). The decision to continue treatment beyond confirmed PD should be discussed with the Medical Monitor and documented in the study records.

Participants who continue beyond progression will be evaluated for further tumor response as per the protocol schedule. Treatment should be discontinued permanently upon documentation of further, unequivocal, disease progression unless there are no alternative therapeutic options and the benefit-risk assessment is favorable in consultation between the Investigator and the Medical Monitor. In case of continuation of treatment beyond PD, treatment will be discontinued once any other criteria for withdrawal are met (see Section 7.1).

4.1.2 Continuation of Study Intervention After Local Treatment of Disease Progression

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

- Tumor assessment showing disease progression has been performed and was documented according to RECIST 1.1 prior to the procedure.
- Brain metastases have been treated locally and are clinically stable for at least 2 weeks prior to reinitiation of study interventions.
- There are no ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable).
- Participants must be either off steroids or on a stable or decreasing dose of $\leq$ 10 mg daily prednisone (or equivalent).
- Benefit-risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator

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

- Tumor assessment showing disease progression has been performed and was documented according to RECIST 1.1 prior to the procedure.
- It has been at least 2 weeks and the participant has fully recovered from the surgery.
- Benefit-risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator.

4.2.2 Pembrolizumab as Comparator

Pembrolizumab is the only approved immuno-oncology monotherapy in 1L NSCLC. Pembrolizumab has been approved as:

- Monotherapy for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS $\geq$ 1% as determined by the PD-L1 IHC 22C3 pharmDx assay assay) with disease progression on or following platinum-containing chemotherapy. Patients had disease progression on approved targeted therapy for EGFR or ALK genomic tumor aberrations (KEYNOTE-010 study).
- Monotherapy for the 1L treatment of participants with metastatic NSCLC whose tumors had high PD-L1 expression as determined by the PD-L1 IHC 22C3 pharmDx assay (TPS $\geq$ 50%) and were negative for EGFR and ALK genomic tumor aberrations (KEYNOTE-024 study).
- Monotherapy for the 1L treatment of patients with Stage 3 NSCLC who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, whose tumors express PD-L1 (TPS $\geq$ 1%) with no EGFR or ALK genomic tumor aberrations. The approval of pembrolizumab in several countries was based on clinical data from the KEYNOTE-042 trial.
- In combination with carboplatin and pemetrexed as 1L treatment of participants with metastatic nonsquamous NSCLC (KEYNOTE-021 study). This indication is approved under accelerated approval in the USA and EU.

Note, the approved indications may differ by country.

The response rates of pembrolizumab are summarized in Section 2.2.

4.2.3 Open-label Design

This study will use an open-label design.

Due to the different dosing schedules, pembrolizumab dosed q3w while M7824 q2w, a true blinding would require a considerable number of study visits (i.e., approximately 1 week off every 6 weeks) and burden the participant. Further, dosing of pembrolizumab is over 30 minutes while for M7824 it is over 60 minutes; therefore, participants would require 2 infusions per visit.

An open-label design is selected to reduce the burden to participants and sites (including pharmacies). The planned IDMC and blinded IRC review will mitigate risk of bias by not double-blinding the study. Access to aggregated analyses per treatment arm will be restricted to the IDMC and a Firewall Team as per corresponding charters.

4.2.4 Stratification

Stratification at randomization is planned for participants with squamous histology, nonsquamous histology and never smoked, and nonsquamous histology with a smoking history. Never smoking is defined as smoking fewer than 100 cigarette-equivalents over lifetime. There is increasing evidence that higher tumor mutational burden (TMB) is predictive of improved response to immunotherapy, and that smoking may increase this TMB due to its carcinogenic chemicals. In clinical studies, emerging data suggest improved ORR in smokers versus nonsmokers; however, due to low numbers of nonsmoking NSCLC participants in prior studies, this has not been conclusively demonstrated. In EMR200647-001, approximately 20% of participants were never smokers. If this trend continues, up to 60 participants are predicted to enroll with no smoking history. As only approximately 30% of nonsmokers are expected to have squamous histology, there are predicted to be an insufficient number of PFS events to justify stratifying on nonsmokers with squamous histology; therefore, only participants with nonsquamous histology will be further stratified by smoking status.

4.2.5 PFS and OS as the Primary Endpoints

This study is the first direct comparison of 2 immunotherapies. Therefore, to further investigate the outcomes, dual primary endpoints, PFS and OS, will be explored. The interim and primary analyses of OS and PFS will be performed as outlined in Section 9.4.4.

In NSCLC, PFS and OS can be considered as primary endpoints for demonstration of efficacy for drug approval based on magnitude of effect and risk benefit profile of the drug, as per the FDA and EMA guidance.

4.2.6 Adaptive Phase III Design

In protocol Version 3.0, the study design was modified to an adaptive trial design to permit sample size adaptation based on prespecified adaptation rules evaluating the objective response at a preplanned IA. Adapting the study at an early signal of efficacy following the preplanned IA, minimizes risk to patients by deferring expansion until preliminary efficacy is observed, while

minimizing the number of exposed patients in comparison with 2 separate trials. The adaptive design is intended to preserve the global registrational intent of this trial.

While the study team will remain blinded to the aggregate results by treatment arm, the study's IDMC evaluates objective response as assessed by the IRC on the 73-10 PD-L1 high analysis set restricted to participants randomized at least 6 months before the data cutoff date. That interim analysis (OR IA) cutoff date is 6 months after enrolling the 100th participant tested 73-10 PD-L1 high. Based on the review of the data, the IDMC will recommend one of the following possible options based upon pre-specified decision rules: terminate the trial for futility, continue as initially planned with a total sample size of N=300 or increase the sample size to N=584. The integrated analysis plan (IAP) will include details and specifications for the planned analyses as well as an annex with simulation results regarding the adaptive trial design. Further, the IDMC charter will provide details on implementation of the adaptive design along with specific rules that will be used to guide adaptation decision. A comprehensive results access plan defines how trial integrity will be maintained in the presence of planned adaptations.

4.3 Justification for Dose

The RP2D for M7824 is 1200 mg administered as an intravenous infusion q2w. The selection of RP2D is based on the available clinical data from Phase I Study EMR200647-001 and Study MS200647-0008, including safety/tolerability, pharmacokinetics (PK), and pharmacodynamic (such as PD-L1 target occupancy [TO] in peripheral blood mononuclear cells (PBMC) and TGFβ trapping in blood), as well as efficacy in 2L NSCLC cohorts from Study EMR200647-001. The selection of RP2D is also supported by population PK (pop PK) and exposure-response modeling and simulation.

Safety/tolerability in Phase I

The highest dose for M7824 tested in EMR200647-001 was 30 mg/kg, which corresponds to 2100 mg for a 70-kg participant (the median body weight in the current dataset) and to 2400 mg for an 80-kg participant (corresponding to a typical median body weight for solid tumor type participants) (Freshwater, 2017; Bajaj, 2017; Zhao, 2017). Based on clinical observations, M7824 is well tolerated up to 30 mg/kg and the maximum tolerated dose was not reached. In addition, for the 2 dose levels evaluated in 2L NSCLC cohorts of Study EMR200647-001 (500 and 1200 mg iv q2w), overall safety findings were comparable and consistent with observed safety profile in Studies EMR200647-001 and MS200647-0008.

CCI and Phase I dose escalation PK and CCI

The PK dose-proportionality, peripheral PD-L1 TO/TGFβ trapping from the dose escalation phase of Study EMR200647-001 (at doses of 1, 3, 10, 20, and 30 mg/kg q2w), and CCI

CCI In participants with

CCI

Flat dose rationale

To achieve less variability in exposure, mitigate the risk of dosing errors, reduce the time necessary for dose preparation, and reduce drug wastage compared with the weight-based dosing, a flat dose approach was adopted for expansion phases of Phase I clinical studies.

The flat dosing approach for Phase II is supported by pop PK modeling and simulation using data from 350 participants from the 2 Phase I clinical studies of M7824 in multiple solid tumor types, which showed that although body weight was found to be a covariate for clearance, the estimated magnitude of the body weight exponent on clearance is < 0.5, predicting less exposure variability from flat dosing than that from body weight-based dosing (Wang, 2009). Accordingly, simulations of AUC and C_{trough} showed that variability in exposure was indeed slightly lower for flat dosing compared with weight-based dosing.

Preliminary efficacy and exposure-response analysis

CCI

CCI

4.4 End of Study Definition

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

The end of the study is defined as the data cutoff date for the primary OS analysis when the planned number of deaths had been reported. After stipulated end of study, survival follow-up may continue until the last participant has died or at the discretion of the Sponsor. The Sponsor may terminate the study at any time once access to M7824 or pembrolizumab for participants still benefiting is provisioned via a rollover study, expanded access, marketed product or another mechanism of access as appropriate.

5 Study Population

The criteria in Sections 5.1 (Inclusion Criteria) and 5.2 (Exclusion Criteria) are designed to enroll only participants, who are appropriate for the study; thereby, ensuring 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 (Study Governance).

5.1 Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

2. Are participants who have a histologically confirmed diagnosis of advanced NSCLC and:

    a. Have not received prior systemic therapy treatment for their advanced/Stage IV NSCLC. Completion of treatment with cytotoxic chemotherapy, biological therapy, and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was

completed at least 6 months prior to the diagnosis of metastatic disease. Confirmation of resolution of toxic effects of previous neoadjuvant/adjuvant chemotherapy therapy to Grade ≤ 1. For radiation toxicity or prior major surgeries, participants should have recovered from side effects and/or complications.

b. Have measurable disease based on RECIST 1.1.

c. Have a life expectancy of at least 3 months

d. Availability of tumor tissue (< 6 months old excluding bone biopsies) before the first dose is mandatory to determine PD-L1 expression level prior to enrollment. If participant received local therapy (i.e., radiation therapy [RT] or chemoradiotherapy [CRT]) after the archival biopsy was taken, a fresh biopsy will be required prior to study entry. Archival material is formalin fixed tumor tissue sample from a biopsy of a tumor lesion either at the time of or after the diagnosis of metastatic disease has been made AND from a site not previously irradiated. Biopsies obtained PRIOR to the administration of any systemic therapy administered for the treatment of a participant's tumor (such as neoadjuvant/adjuvant therapy) will not be permitted for analysis. Endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies, or surgical specimens are required. Fine needle aspiration biopsies, cell blocks, and other types of cytologic specimens are not acceptable.

e. As of Version 3.0 of this protocol, PD-L1 high status by central testing is required. PD-L1 high tumors are defined as having ≥ 80% PD-L1 positive tumor cells by the PD-L1 IHC 73-10 assay. In all cases, tumor material must be provided as specified and must have been evaluated from tissue which is < 6 months old. The tissue sample must be evaluated by the central vendor prior to randomization (validation of tissue typically occurs within 5 business days). In case a tumor specimen is assessed as not evaluable for PD-L1 expression by the central laboratory, if an additional tumor specimen is submitted AND evaluable for PD-L1 expression, the participant will be eligible to participate if PD-L1 expression is assessed as "high" by the central laboratory.

f. See Section 5 for exclusion criteria for participants with EGFR ALK, ROS1, or BRAF V600E molecular alterations.

3. ECOG PS of 0 to 1 at study entry and date of first dose

4. Have adequate organ function as indicated by the following laboratory values

a. Adequate hematological function defined by absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L, and hemoglobin ≥ 9 g/dL

b. Adequate hepatic function defined by a total bilirubin level ≤ the upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 1.5 × ULN and alkaline phosphatase ≤ 2.5 × ULN. For participants with liver involvement in their tumor, AST ≤ 5.0 × ULN, ALT ≤ 5.0 × ULN, and bilirubin ≤ 3.0 × ULN is acceptable

c. Adequate renal function defined by creatinine ≤ 1.5 × ULN or calculated creatinine clearance (CrCL) ≥ 30 mL/minute for participant with Creatinine > 1.5 × ULN (glomerular filtration rate can also be used)

   Note: CrCL should be calculated per institutional standard. If no local guideline is available, CrCL should be calculated using the Cockcroft-Gault Method:

   CrCL = ([140-age] × weight [kg] × [0.85 for females only]) / (72 × creatinine)

d. Adequate coagulation function defined as international normalized ratio or prothrombin time ≤ 1.5 × ULN unless the participant is receiving anticoagulant therapy, and activated partial thromboplastin time ≤ 1.5 × ULN unless the participant is receiving anticoagulant therapy

Sex

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

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

- Refrain from donating sperm

PLUS, either:

- Abstain from intercourse with a female

OR

- Use a male condom

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

Female participants:

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

- Not a WOCBP

OR

- If a WOCBP, use a highly effective contraceptive method (i.e., with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 3 for the following time periods:
    - Before the first dose of the study intervention(s), if using hormonal contraception:
        - Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses

          OR
        - Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay.
    - During the intervention period.
    - After the study intervention period (i.e, after the last dose of study intervention is administered) for at least 4 months after the last dose of study intervention.
- Have a negative pregnancy test, as required by local regulations, on W1D1 before the first dose of study intervention.

Additional requirements for pregnancy testing during and after study intervention are in Schedule of Activities.

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

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Participants with nonsquamous NSCLC histologies whose tumor harbors any of the following molecular alterations and targeted therapy is locally approved:

    a. EGFR sensitizing (activating) mutation. EGFR sensitizing mutations are those mutations that are amenable to treatment with tyrosine kinase inhibitors including, but not limited to, erlotinib, gefitinib, afatinib, or osimertinib.

    b. ALK translocation(s) associated with responsiveness to ALK tyrosine kinase inhibitors.

    c. ROS1 rearrangement(s) associated with responsiveness to ROS1 tyrosine kinase inhibitors.

d. BRAF V600E mutation

For participants with nonsquamous NSCLC histologies testing is required for any molecular alteration described above in which targeted therapy is locally approved. If unable to test for indicated molecular changes, formalin fixed paraffin embedded tumor tissue should be submitted to a central laboratory designated by the Sponsor for such testing. Any required testing for participants with nonsquamous histologies must be known and available in source documentation at the site prior to randomization.

Molecular testing is not required for participants known to have a tumor of predominantly squamous histology

2. Has received major surgery within 4 weeks prior to the first dose of study intervention; received thoracic RT of > 30 Gy within 6 months prior to the first dose of study intervention.

3. Previous malignant disease (other than the target malignancy to be investigated in this study) within the last 3 years. Participants with a history of cervical carcinoma in situ, superficial or noninvasive bladder cancer, or basal cell or squamous cell carcinoma in situ previously treated with curative intent are NOT excluded. Participants with other localized malignancies treated with curative intent need to be discussed with the Medical Monitor.

4. Has active CNS metastases causing clinical symptoms or metastases that require therapeutic intervention and/or carcinomatosis meningitis (including leptomeningeal carcinomatosis) identified either on Baseline brain imaging during the Screening period OR identified prior to signing the ICF. Participants with a history of treated CNS metastases (by surgery or RT) are not eligible unless they have fully recovered from treatment, demonstrate radiographic stability defined as 2 brain images, both of which are obtained after treatment to the brain metastases. These imaging scans should both be obtained at least 2 weeks apart and show no evidence of intracranial pressure. In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have returned to Baseline or resolved. Any steroids administered as part of this therapy must be completed at least 3 days prior to study intervention. Participants with CNS metastases incidentally detected during Screening which do not cause clinical symptoms and for which standard of care suggests no therapeutic intervention is indicated should be discussed with the Sponsor Medical Responsible to confirm eligibility.

5. Active autoimmune disease that has required systemic treatment in past 1 year (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs), OR is receiving systemic steroid therapy < 3 days prior to the first dose of study intervention or receiving any other form of immunosuppressive medication. Participants requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at low doses (typically ≤ 10 mg of prednisone or equivalent per day). Equivalent hydrocortisone doses are also permitted if administered as a replacement therapy. Corticosteroid use on study as a premedication for iv contrast allergies/reactions (related to scans) is allowed and must be documented. This must be discussed with Medical Monitors for clinical indications in which participants may require a higher dose. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:

a. Participants with diabetes Type I, vitiligo, alopecia, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible. Consult Medical Monitor for other autoimmune diseases.

6. Administration of steroids for other conditions through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) is acceptable

7. Known severe hypersensitivity (Grade ≥ 3 National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0) to investigational product (M7824 or pembrolizumab) or any components in their formulations, or uncontrolled asthma (ie, 3 or more features of partially controlled asthma)

8. 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)

9. Has interstitial lung disease OR has had a history of pneumonitis that has required oral or iv steroids

10. Significant acute or chronic infections including, among others:

    a. Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (no testing at Screening required). If an Investigator has a strong suspicion of HIV infection without known history for a participant in Screening, however 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.)

    b. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (HBV surface antigen positive and HBV core antibody positive with reflex to positive HBV DNA, or HBV core antibody positive alone with reflex to positive HBV deoxyribonucleic acid (DNA), or positive HCV antibody with reflex to positive HCV RNA) at Baseline. Discuss with the Medical Monitor if history of HBV or HCV infection is known. If medically indicated, participants infected with HBV must be treated and on a stable dose of antivirals (eg, entecavir, tenofovir, or lamivudine; adefovir or interferon are not allowed) at study entry and with planned monitoring and management according to appropriate labeling guidance. Participants on active HCV therapy at study entry must be on a stable dose without documented clinically significant impaired liver function test or hematologic abnormalities (must meet criteria below) and with planned monitoring and management according to appropriate labeling guidance. HBV and/or HCV viral titers must be monitored according to Section 1.3 (Schedule of Activities) in these participants.

    c. Participants with active tuberculosis (history of exposure or history of positive tuberculosis test; plus presence of clinical symptoms, physical, or radiographic findings)

11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with participation for the full duration of the study, or is not in the best interest of the participant, in the opinion of the treating Investigator. Participants with history of bleeding diathesis or recent major bleeding events considered by the Investigator as high risk for investigational drug treatment such as patients with clinically relevant bleeding events of hemoptysis Grade ≥ 2 within the last month are also excluded.

Prior/Concomitant Therapy

12. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)

13. Is expected to require any other form of systemic or localized antineoplastic therapy while on study (including maintenance therapy with another agent for NSCLC, RT, and/or surgical resection)

14. Use of a prohibited concomitant drug, as defined in Section 6.5.2

15. Has received or will receive a live vaccine within 30 days prior to the first administration of study intervention. Seasonal flu vaccines that do not contain a live virus are permitted. Contact Medical Monitor if screening extension is needed for participant vaccinated within 30 days of planned first dose

16. Has an active infection requiring systemic therapy/antibiotics (except as indicated, discuss alternative scenarios with the Medical Monitor)

Prior/Concurrent Clinical Study Experience

17. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment

Other Exclusions

18. Known active alcohol or drug abuse

19. Any psychiatric condition that would prohibit the understanding or rendering of informed consent or consistent participation in study procedures

20. Legal incapacity or limited legal capacity.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the indication for screen-fail has resolved and after discussion with the Medical Monitor.

For participants that have an abnormal laboratory value at Screening that may correct or are using a prohibited concomitant medication that will be discontinued, or undergoing a prohibited procedure that will be completed, it is recommended to discuss with the Medical Monitor about whether the Screening window can be extended, rather than screen-fail the participant. In other situations when a participant has been screen-failed, the site should contact the Medical Monitor to discuss whether the participant may 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

Study Intervention Name:	M7824	Pembrolizumab
Dose Formulation:	Sterile concentrate solution for infusion	Refer to pembrolizumab SmPC or Package Insert for more information
Unit Dose Strength(s)/ Dosage Level(s):	10 mg/mL in single-use glass vials.	Refer to pembrolizumab SmPC or Package Insert for more information
Route of Administration:	Intravenous infusion	Intravenous infusion
Dosing Instructions:	1200 mg over 1 hour (-10 minutes/+20 minutes; i.e, over 50 to 80 minutes) once every 2 weeks. See Section 6.9 for special precautions.	200 mg over 30 minutes every 3 weeks. See Section 6.9 for special precautions.
CCI		

Ph Eur = European Pharmacopoeia; SmPC = Summary of product characteristics; USP = United States Pharmacopeia.

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

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

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 and acknowledge receipt by signing or initialing and dating the appropriate document and returning it to the location specified. A copy will be archived for the Investigator Site File.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply or administer 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, container numbers, expiry dates, formulation (for study interventions prepared at the site), and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Destruction of used and unused study intervention(s) should be performed at site 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.

6.2.1 M7824

M7824 drug product should be CCI CCI until use. CCI

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

6.2.2 Pembrolizumab

Pembrolizumab drug product should be CCI CCI CCI CCI CCI

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

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Participants will be randomly assigned to treatment in a 1:1 ratio to minimize bias. The randomization will be stratified by squamous histology, nonsquamous histology and never smoked, and nonsquamous histology with a smoking history. Once a participant meets the eligibility criteria, is confirmed, and is enrolled, the participant will be randomly assigned to a unique randomization number that is associated with the treatment assignment per the randomization schedule.

Participant identifiers will comprise 17 digits, the first 10 digits representing the study number, the following 3 digits representing the site number, and the last 4 digits representing the participant number, which is allocated sequentially starting with 0001.

After confirmation of participant's eligibility and at the last practical moment prior to study intervention administration, participants will be centrally allocated to either M7824 or pembrolizumab in a 1:1 ratio using an Interactive Web Response System (IWRS) and per a computer-generated randomization list.

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

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

6.3.2 Blinding

This is an open-label study; thus, study intervention is not blinded to participants or Investigators.

The IRC will be blinded to a participant's study intervention during their efficacy assessments.

The study team is blinded for all analyses conducted by treatment arm until the IDMC recommends unblinding.

6.4 Study Intervention Compliance

In this 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 administration including the date, time, and dose of study intervention will be recorded on the electronic case report form (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 nonadherence should be documented.

Nonadherence is defined as a participant missing study intervention for nonmedical reasons and barring any extenuating circumstances in the opinion of the Investigator. Extenuating circumstances should be documented, and when possible, discussed with the Sponsor in advance. If the interval between the subsequent treatment cycle and the last administered treatment cycle is longer than 6 weeks for nonmedical reasons, the criterion for insufficient adherence is met as well.

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

6.5 Concomitant Therapy

Record in the eCRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the main 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 Permitted Medicines

The only permitted medications are the following:

1. Any medications (other than those excluded by the exclusion criteria or the prohibited medicines) that are considered necessary for the participants' welfare and will not interfere with the study intervention may be given at the Investigator's discretion.

2. Other drugs to be used for prophylaxis, treatment of hypersensitivity reactions, and treatment of fever or flu-like symptoms are described in Section 6.9 as part of precautions

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. The Medical Monitor must be contacted if a drug listed under the exclusion criteria was given, but the Investigator would like the participant to be considered for continuation on study.

6.5.2 Prohibited Medicines

As stated for the exclusion criteria in Section 5, participants must not have had prior systemic cytotoxic chemotherapy for their metastatic NSCLC OR any antibody or drug targeting T-cell coregulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody OR concurrent anticancer treatment including:

- Cytoreductive therapy
- Radiotherapy delivered for non-palliative indications (see Section 6.5.3)
- Use of any investigational drug as specified in Section 1.3 (Schedule of Activities).
- Immunotherapy, immunosuppressive drugs (i.e., chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions or for the treatment of irAEs), or other experimental pharmaceutical products. Short-term administration of systemic steroid (i.e., for allergic reactions or the management of irAEs is allowed).
- Vaccine administration within 30 days before M7824 or pembrolizumab administration. Vaccination with live vaccines while on study is prohibited. Administration of inactivated vaccines is allowed (e.g., inactivated influenza vaccines).
- Any traditional Chinese medication or herbal equivalent 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 (see Appendix 4).

If the administration of a nonpermitted concomitant drug becomes necessary during the study, the participant will be withdrawn from study intervention (the Sponsor may be contacted to discuss whether there is a possibility for a participant to continue on study). The participant should complete the End-of-Treatment Visit and be followed for survival.

6.5.3 Permitted/Prohibited Procedures

Permitted Procedures

Organ-sparing radiotherapy may be administered for palliative and/or specific clinical indications during the study. The assessment of PD will be made according to RECIST 1.1 and not based on the necessity for palliative radiotherapy. The indication for palliative radiotherapy must be documented and discussed with Medical Monitor, in advance of procedure if clinically feasible.

Prohibited Procedures

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

- Major surgery (excluding prior diagnostic biopsy) within 4 weeks before the start of the study. Discuss with Medical Monitor if unplanned major surgery is required on study to plan for timing of next dose.

6.5.4 Other Interventions

The following nondrug therapies must not be administered during the study:

- Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin).

6.6 Dose Selection and Modification

See Section 4.3 for the justification of doses used in this study.

Doses cannot be delayed beyond the treatment window. Participants must skip dose if the treatment window is missed. Every attempt should be made to perform applicable assessments in Table 1 and Table 2 for any missed visits. Complete the next visit following the schedule of assessments.

6.7 Study Intervention After the End of the Study

After a participant has completed the study or has withdrawn early, participants may receive the care they and their physicians agree upon. Participants will be followed for survival and AEs as specified in Section 4.1.

6.8 Special Precautions

6.8.1 Specific Planned Assessments

6.8.1.1 Adverse Events of Special Interest/Identified Risks

See Section 6.9 for AESIs and risk management.

6.8.1.2 Additional Potential Risks

Alterations in Wound Healing or Repair of Tissue Damage

Due to the involvement of TGFβ in tissue and skin repair, alterations in wound healing or repair of tissue damage is considered an important potential risk. No relevant event is reported in the ongoing M7824 clinical studies. Monitoring of any surgical wounds while on study is recommended. In general, a 2-week delay from treatment is recommend following minor surgery and 4 week delay for major surgery, but cases should be discussed with the Medical Monitor.

Embryo-fetal Toxicities

Embryo-fetal toxicities are a known risk of the PD-1/PD-L1 targeting class. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue (Guleria, 2005; Leber, 2010; Wafula, 2009; Zenclussen, 2013).

Embryo-fetal and reproductive toxicities have also been investigated in animal models for a humanized monoclonal antibody targeting TGFβ1. At doses as high as 30 mg/kg, no maternal reproductive toxicity or embryo-fetal lethality were observed in rabbits (Hilbish, 2016). To mitigate these potential risks, pregnant participants are excluded from the study, and all participants of childbearing/conceiving potential must use highly effective contraception.

6.8.2 Adverse Drug Reactions Requiring Treatment Discontinuation

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

Immune-related AEs, IRRs including hypersensitivity, anemia, TGFβ-mediated skin reactions, and bleeding events are managed and followed-up in their respective sections as indicated below. Permanent Treatment discontinuation may be recommended, so the relevant section must be reviewed:

- For management and guidance of suspected irAEs, see Section 6.9.2.
- For infusion-related reactions and hypersensitivity reactions guidance, see Section 6.9.1.
- For anemia guidance, see Section 6.9.4.
- For guidance and management for potentially TGFβ mediated skin AEs, see Section 6.9.3
- For guidance and management of bleeding events, see Section 6.9.5.

General guidance:

- In any case, if ≥ 2 doses are missed due to AE, the Medical Monitor should be consulted.
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks is an indication for permanent treatment **discontinuation** (except for use of steroids as hormone substitution).
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade ≤ 1 within 12 weeks after last dose of study intervention is an indication for permanent treatment discontinuation.

Grade 4 ADRs:

- Participants with Any Grade 4 ADRs require permanent treatment discontinuation except:
  a. Isolated laboratory values out of normal range that do not have any clinical correlation. Discuss with Medical Monitor regarding work-up, management, and treatment continuation versus hold versus discontinuation for isolated Grade 4 laboratory abnormalities.
  b. Endocrinopathies controlled with hormone replacement therapy.
  c. If alternative explanation is identified for Grade 4 non-tumor bleeding.

See Section 6.9.2 for other suspected Grade 4 irAEs, as most require permanent treatment discontinuation.

Grade 3 ADRs:

1. Participants with any severe or Grade 3 treatment-related adverse reactions that recur should be permanently discontinued. Exceptions may be considered as follows after discussion with Medical Monitor:
    a. Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management.
    b. Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to ≤ Grade 1 or baseline.
    c. Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
    d. Grade 3 hemoglobin decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor.
    e. Increases in ECOG PS ≥ 3 that resolves to ≤ 2 by Day 1 of the next infusion (i.e., infusions should not be given if the ECOG PS is ≥ 3 on the day of treatment and should be delayed until ECOG PS ≤ 2).
    f. Keratoacanthomas and/or cSCC (see Section 6.9.3 for management).
    g. Grade 3 non-tumor bleeding requiring intervention or hospitalization if alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic event, etc).
2. See Section 6.9.2 for suspected Grade 3 irAEs as many require permanent treatment discontinuation, including pneumonitis and nephritis.
    a. AST or ALT > 5 times ULN or total bilirubin greater than 3 times ULN must be permanently discontinued, ***except*** for participants with liver metastases (for example) who begin treatment with Grade 2 AST or ALT. These participants should be discontinued if AST or ALT increases by ≥ 50% relative to baseline and lasts for at least 1 week.
3. Persistent Grade 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade ≤ 1 within 12 weeks after dose of treatment.

Grade 2 ADRs should be managed as follows:

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

6.9 Management of Adverse Events of Special Interest

As a part of precautionary safety measures, a risk management guidance is defined for both treatment arms (M7824 and pembrolizumab) for IRRs and irAEs, which may arise on either arm due to the common mAb inhibition of PD-L1.

6.9.1 Infusion-related Reactions Including Immediate Hypersensitivity

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

Infusion-related reactions are defined as any signs or symptoms experienced by participants occurring during or within 1 day of study intervention administration. An assessment for possible IRR should be triggered based upon the development of specific symptoms within 24 hours of an infusion.

These possible IRRs are identified based on a list of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and criteria based on the timely relationship to an infusion. Events are divided into reactions versus signs and symptoms:

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

Management of Infusion-Related Reactions

Current experience in more than 700 study participants revealed that IRRs to M7824 occur seldomly and are generally mild to moderate in severity. Therefore, administration of a premedication is generally not required.

If an investigator deems necessary to administer a premedication to a particular participant, an antihistamine (e.g. 25 to 50 mg diphenhydramine) and paracetamol (acetaminophen, 500 to 650 mg iv or equivalent oral dose) 30 to 60 minutes prior to M7824 infusion is recommended. Premedication should be administered for subsequent M7824 doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local

treatment standards and guidelines as appropriate, provided it does not include systemic corticosteroids.

Table 8 Treatment Modification for Symptoms of Infusion-related Reactions

NCI-CTCAE v5.0 Grade	Treatment Modification
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Increased monitoring of vital signs as medically indicated, presuming these participants are deemed medically stable.
Grade 2 – moderate Therapy or infusion interruption indicated but if responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop M7824/ Pembrolizumab infusion. Increased monitoring of vital signs as medically indicated as participants are deemed medically stable by attending Investigator. If symptoms resolve quickly or decreased to Grade 1, resume infusion at 50% of original rate with close monitoring of any worsening otherwise dosing held until resolution of symptoms with mandated premedication for the next schedule. If worsens to Grade 3 or 4, follow treatment modification guidelines accordingly.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the M7824/Pembrolizumab infusion immediately and disconnect infusion tubing from the participant with additional appropriate medical measures and close monitoring until deemed medically stable by attending Investigator. Hospitalization may be indicated. Participants will be permanently withdrawn immediately from M7824/ Pembrolizumab treatment and must not receive any further M7824/Pembrolizumab treatment
NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs. For Grade 3 or 4 infusion-related reactions, M7824/Pembrolizumab discontinuation is mandated. For all types and grades of infusion reactions, details about drug physical constitution, method of preparation and infusion must be recorded.	

In the event of a Grade 2 IRR that does not improve or worsens after implementation of the dose modifications indicated in Table 8 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids and the infusion should be stopped for that day. At the next infusion, the Investigator may consider the addition of H2 blocker antihistamines (for example, famotidine or ranitidine), in addition to proposed premedication, for select participants. However, prophylactic steroids are NOT permitted. At next dose, if the participant has a second IRR Grade ≥ 2 on the slower infusion rate, with the addition of further medication to premedication, the infusion should be stopped, and the participant removed from treatment.

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

Symptoms may include, but are not limited to:

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

Management of hypersensitivity includes:

1. Epinephrine injection and iv dexamethasone
2. Participant should be placed on cardiac, blood pressure, heart rate, and oxygen saturation monitor immediately
3. 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), for example, ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each IV infusion.

6.9.2 Immune-related Adverse Events

Immune-related AEs are specific to immunotherapies and vary by organ system. Immune-related AEs are considered AESIs for both M7824 and pembrolizumab.

In general, the spectrum of irAEs are similar for both M7824 and pembrolizumab.

The following irAEs are important identified risks for M7824.

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

The following irAEs are important potential risks for M7824:

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

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

The recommendations for irAE management, are guided by the joint American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines (Brahmer, 2018) and National Comprehensive Cancer Network (NCCN) (NCCN Guidelines®), listed in Appendix 5. Of note, official guidance is also available from Merck Sharp & Dohme for management and drug discontinuation for certain irAEs in the pembrolizumab FDA label (Keytruda USPI). These irAEs include: pneumonitis, colitis, hepatitis, endocrinopathies (including hypophysitis, thyroid disorders, type 1 diabetes mellitus), and nephritis. This pembrolizumab-specific guidance is covered in the ASCO/NCCN guidelines; however, resources from Merck & Company for participants who develop these irAEs while on the pembrolizumab treatment arm are to be considered as well.

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

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

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 treatment discontinuation 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 treatment discontinuation is not required when the AE is manifest by a single laboratory value out of normal range without any clinical correlates. In this case, treatment should be held until the etiology is determined. If the event is not considered immune -related and resolves to Grade $\leq$ 1 restarting treatment may be considered.

For additional organ/system specific management guidelines, review ASCO guideline tables in Appendix 5.

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

6.9.3 TGFβ Inhibition Mediated Skin Reactions

TGFβ inhibition mediated skin reactions, including hyperkeratosis, KA and/or cutaneous squamous cell carcinomas (cSCC), are important identified risks for M7824 and considered as AESI. Cases of KA and cSCC have also been reported for patients under treatment with other checkpoint inhibitors as well (Freites-Martinez, 2017; Bednarek, 2018). The distribution of lesions tends to be in sun-exposed areas. Skin assessments will be performed for all participants per the SoA (see Table 1).

Management guidelines for potential TGFβ inhibition mediated skin reactions are:

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

2. Emollients may continue to be used.

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

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

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

6. Spontaneous resolution of KA lesions without surgical intervention has been observed, typically occurring within weeks after discontinuing M7824.

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

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

6.9.4 Anemia

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

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

General guidance for anemia management and evaluation:

- Participants must enter the study with hemoglobin values at least 9 g/dL; Routine blood test parameters are specified in Table 16.
- All relevant hematologic testing for treatment-related anemias should be done prior to blood transfusion, if clinically feasible.
- If a participant experiences significant anemia (e.g., < 8 g/dL), then the amount of blood to be drawn may be reduced by not taking blood at selected time points for pharmacodynamic CCI and CCI. The decision to reduce the time points for these CCI will be taken by the Investigator in consultation with the Medical Monitor. This will be documented. Blood will continue to be taken as scheduled for safety analyses, PK, and anti-drug antibodies (ADAs).
- Transfusion should be performed at the discretion of the Investigator, based on clinical assessment and considered when participant experiences significant anemia. attempt should be made to initiate work-up (as specified below) for cause of anemia prior to transfusion if clinically feasible to not confound this work-up. Guidance for evaluation of suspected anemias is provided in Table 9.
- Discuss further management with Medical Monitor for clinically significant treatment-related anemias.

Table 9 Evaluation Guidance of Suspected Anemia Adverse Events

Basic Anemia Evaluation	
1. CBC with emphasis on red cell indices (e.g., Hgb, hematocrit, MCV, RDW, MCH, MCHC, reticulocytes counts). 2. If indicated and at clinical discretion, the following should be considered: a. Iron studies (TIBC, Ferritin, Fe) b. Serum Folate and Vit B12 values c. Coagulation factors (PT, PTT, INR) d. Fecal occult blood testing e. Urinalysis f. Hormone panel: TSH, Erythropoietin g. Peripheral blood smear for cell morphological assessment	
Further Recommendation Based on Suspected Etiology (in Addition to Baseline Anemia Testing)	
Suspected hemolysis:	Bilirubin level, LDH, Coombs test, fibrinogen, haptoglobin, d-Dimer Consider Hematology consultation.
Suspected bleeding:	Consider imaging/interventional radiology consultation as indicated Consider endoscopy, as clinically indicated. Consider imaging, as clinically indicated.
Suspected aplastic anemia:	Hematology consultation. Consider bone marrow aspiration/morphologic evaluation.
CBC=complete blood count, Fe=Iron, Hgb=hemoglobin, INR=international normalized ratio, LDH=lactate dehydrogenase, MCH=Mean Corpuscular Haemoglobin, MCHC=Mean Corpuscular Haemoglobin Concentration, MCV=mean corpuscular volume, PT = prothrombin time, PTT=partial thromboplastin time, RDW= Red Blood Cell Distribution Width, TIBC=total iron binding capacity, and TSH=thyroid-stimulating hormone.	

6.9.5 Bleeding Events

Bleeding AEs are AESIs and considered important identified risk for M7824 (refer to the Investigator's Brochure).

6.9.5.1 Mucosal/Non-tumor Bleeding

Participants treated with M7824 were commonly reported with mild to moderate mucosal AEs such as epistaxis, hemoptysis, gingival bleeding and hematuria. In general, these reactions resolve without discontinuation of treatment.

- If a Grade 2 treatment-related TEAE improves to Grade ≤ 1 or completely resolves by the day before the next infusion, M7824 may be continued
- If a Grade 2 treatment-related non-tumor bleeding does not improve to Grade ≤ 1 or completely resolve by the day before the next infusion, but it is manageable and/or not clinically relevant, the Medical Monitor should be consulted to assess if it is clinically reasonable to administer the following infusion.
- For Grade 3 non-tumor bleeding, study treatment must be permanently discontinued unless an alternative explanation can be identified (such as concomitant use of antithrombotic agents,

traumatic event, etc). In case of alternative explanations for the Grade 3 bleeding event, study treatment should be held until the event recovers to Grade ≤1.

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

6.9.5.2 Tumor Bleeding

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

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

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

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

- A participant may withdraw from the study at any time, at his/her own request (i.e, withdrawal of consent), and without giving a reason.
- Occurrence of an exclusion criterion, which is clinically relevant and affects the participant's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor.
- The participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- Confirmed PD per RECIST 1.1 with the exception that participants receiving treatment may continue past PD if the participant's ECOG PS has remained stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment. See Section 4.1.
- Some ADRs require withdrawal from treatment. See Section 6.8.2 for additional details.
- Drug must not be given to a known pregnant participant.
- Use of a nonpermitted concomitant drug (without approval by the Sponsor and the Medical Responsible), as defined in Section 6.5.2, where the predefined consequence is withdrawal from the study intervention.

Please note: one reinitiating course of treatment at the same dose and schedule and treatment duration up to 24 months is allowed at the discretion of the Investigator and agreement of the Study Medical Responsible for:

- Participants who are experiencing SD, a PR, or CR on either study arm at the time of discontinuation, and then subsequently develop disease progression after stopping therapy, but prior to the end of the study.

OR

- Participants who are discontinued due to an AE that are subsequently well managed or resolved after stopping therapy, but prior to the end of the study.
- Participants meeting the definition of confirmed PD while on-treatment based on RECIST 1.1. (Participants who experience PD may continue treatment with study drugs if the Investigator believes the participant will experience clinical benefit from the treatment and there is no unacceptable toxicity resulting from the treatment. Such participants will be withdrawn from the treatment if any other criteria for withdrawal are met or if alternative treatment options are available and indicated).

A discussion between the Investigator and Sponsor's Medical Responsible should take place. The Investigator will need to confirm that the benefit of reinitiating treatment outweighs any risk involved, such as that which led to initial treatment discontinuation. For participants with only SD at time of discontinuation, the Investigator should confirm no other reasonable treatment options are available. In addition, to be eligible for reinitiation, the participant must not withdraw consent, and should be followed with regular evaluation scans as specified in Section 1.3 (Schedule of Activities). No cross-over is allowed. Prior to reinitiation of the study intervention, malignant disease must be radiologically restaged within 28 days of dosing to assess all known sites disease. Relevant safety laboratory results must be available and verified prior to reinitiating treatment. Participants who reinitiate treatment will stay on study and will be treated and monitored according to Section 1.3 (Schedule of Activities). A discussion with the study team is warranted to determine if repeating PK/CCI testing is indicated when restarting treatment. A rollover protocol may accommodate M7824 participants if available at the time of reinitiation.

Section 1.3 (Schedule of Activities) specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant must be withdrawn in the event of any of the following:

- 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.

Section 1.3 (Schedule of Activities) specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.

In case of withdrawal from treatment, the day of End-of-Treatment will correspond to the day of withdrawal (or within 7 days). The assessments scheduled for this visit should be performed, if possible, with focus on the most relevant assessments. In case participant gets enrolled into new study or any new therapy post withdrawal from study, the Safety Follow-up Visit should be scheduled prior to start of the new treatment irrespective of the 28-day safety follow-up period. In either case, the appropriate eCRFs for the End-of-Treatment Visit must be completed. In case of withdrawal, participants will be asked to continue safety and survival follow-up, which includes the collection of data on survival and subsequent anticancer therapy. After completion of the Follow-up period or after the End-of-Treatment Visit, whichever is applicable, the appropriate eCRF section for Study Termination must be completed.

7.3 Lost to Follow-up

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

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

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

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in Section 1.3 (Schedule of Activities).
- 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 Section 1.3 (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 (Study Governance).
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in Section 1.3 (Schedule of Activities).

8.1 Efficacy Assessments and Procedures

Contrast-enhanced computed tomography (CT) of chest/abdomen and pelvis covering the area from the superior extent of the thoracic inlet to the symphysis pubis is the first choice of imaging modality. The CT of the pelvis may be omitted if it is not part of the standard of care and CT of the abdomen includes the entirety of the liver and all other known sites of disease. If a participant cannot receive iodinated contrast, or if regional radiation regulations prevent full CT scan, magnetic resonance imaging (MRI) of the same area, using gadolinium enhancement (according to local protocol) is permitted in conjunction with unenhanced CT of the chest from the thoracic inlet to the inferior costophrenic recess. The same modality, and preferably the same scanner, should be used per participant throughout the study.

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

A central imaging laboratory will be used to read and interpret all CT/MRI data; however, treatment decisions will be made by the treating Investigator. Response will be evaluated according to RECIST 1.1 and immune-related RECIST (irRECIST) 1.1 by IRC blinded for treatment [redacted]

Baseline scans are taken within 28 days, and preferably within 14 days, prior to randomization. All the scans performed at Baseline need to be repeated at subsequent visits for tumor assessment. 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 during treatment scans are to be repeated using the same method at the subsequent assessment time points.

Participants will be evaluated every 6 weeks with radiographic imaging to assess response to treatment within 18 months of the participant's first dose, then every 12 weeks as scheduled in Section 1.3.

In the case of PD with discontinuation of treatment, any subsequent local tumor assessments (including scans under first subsequent treatment for OR as assessed by Investigator) should be documented in the eCRF. Confirmation after at least 4 weeks following first assessment is recommended for PD if the participant is not discontinued earlier. Any subsequent anticancer therapies and the date of any response and subsequent progression should be captured in the eCRF.

Participants who start 2L treatment should be monitored for response to that treatment as described in Section 4.1. Radiologic scans performed per local clinical practice used for monitoring response should be uploaded to the imaging repository.

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, including vital signs, ECOG PS, and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give the prescreening 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.

The AE reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of prescreening informed consent) and continues until last Safety Follow-up Visit or before start of any anticancer therapy, whichever comes first.

The safety assessments will be performed according to Section 1.3 (Schedule of Activities). Evaluations of the study data will be conducted by an IDMC to ensure safety and the validity and scientific merit of the study.

8.2.1 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 7, at the time points listed in Section 1.3 (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 the local laboratory.
- The Sponsor must receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study must be forwarded to the Contract Research Organization (CRO) and the Sponsor.
- The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

If a participant has a clinically significant abnormal laboratory test value that is not present at Baseline, the test should be closely monitored until the test value has returned to the normal range or the Investigator has determined that the abnormality is chronic or stable.

The report of the results must be retained as a part of the participant's medical record or source documents.

Abnormal laboratory findings and other abnormal investigational findings (for example, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition

(for example, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

See Section 1.3 for the Schedule of Activities.

For female participants of childbearing potential, urine or serum beta-human chorionic gonadotropin (β-hCG) test will be performed according to Section 1.3 (Schedule of Activities). Results of the most recent pregnancy test should be available prior to the next dosing of study intervention. Participants who are not WOCBP (as defined in Section 5.1) are exempted from pregnancy testing, but reason must be documented.

8.2.2 Vital Signs, Physical Examinations, and Other Assessments

Vital signs, physical examinations, and ECOG PS will be conducted at Screening and at subsequent visits as indicated in Section 1.3 (Schedule of Activities. These should be documented in the eCRF.

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.

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.

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal, Skin, and Neurologic systems. Height (at Screening) and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of pre-existing symptoms of underlying conditions and/or signs of infection and should be investigated as clinically indicated. Skin assessments should be performed as per Section 1.3 (Schedule of Activities) and as clinically indicated.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Abnormal findings are to be reassessed at subsequent visits.

A single 12-lead ECG will be obtained as outlined in Section 1.3 (Schedule of Activities) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.3 Adverse Events and Serious Adverse Events

The definitions of an Adverse Event (AE) and a Serious Adverse Event (SAE) are in Appendix 6.

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 prescreening informed consent) and continues until the study's 28-day Safety Follow-up Visit, defined as 28 days (± 5 days) after the last study intervention administration. After the End-of-Treatment Visit, related AEs should be documented until the last Safety Follow-up Visit, defined as 12 weeks (± 2 weeks) after the last study intervention. Ongoing events at the 12-week Safety Follow-up Visit should continue to be monitored and documented until resolution or resolution with sequelae.

Any SAE assessed as related to study intervention must be recorded and reported, as indicated in Appendix 6, 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 6.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

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

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs must be additionally documented and reported using the appropriate Report Form as specified in Appendix 6.

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 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) and are assessed for their outcome at the End-of-Treatment Visit. All SAEs ongoing at the End-of-Treatment Visit must be monitored and followed-up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is given in Appendix 6 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

See Section 8.3.1 for the time periods for the collection of AEs and SAEs.

Monitoring of Specific Adverse Events

If monitoring is warranted for certain ADRs for safety issues, the treating physician or Investigator is requested to follow the participant during the post-treatment long-term follow-up phase until the end of study period or the participant is "lost to follow-up" and report the management and outcome of AEs to the Sponsor. See Section 6.9 (as applicable).

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 IRB that approved the study.

In accordance with international council for harmonisation and good clinical practice (ICH GCP) and the Japanese ministerial ordinance on GCP, the Sponsor/designee will immediately inform all the study Investigators and Heads of the study sites of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IRB's approval/favorable opinion to continue the study. In line with respective applicable regulations, the Sponsor/designee will immediately inform all the study Investigators and the Heads of the study sites of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). In addition, per applicable regulations, the Sponsor/designee will inform the study Investigators and the Heads of the study sites of all SAEs 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 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 Independent Ethics Committee (IEC)/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

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

8.3.5 Pregnancy

Only pregnancies the Investigator considers to be related to the study intervention (e.g, resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) must be recorded in the AE page/section of the eCRF for both pregnancies in female participants and pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Appendix 6, section on Reporting Serious Adverse Events.

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

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

A pregnant participant is not allowed to receive study intervention. The Sponsor/designee must be notified without delay if a participant becomes pregnant or impregnates while on study. The pregnancy must be followed as indicated above.

8.4 Treatment of Overdose

For this study, any dose of M7824 greater than 2 times more (i.e., > 2400 mg) than the planned dose administered within a 24-hour time period will be considered an overdose. This is based on dose escalation study data in which participants safely received up to 30 mg/kg M7824 every 2 weeks (including with doses > 2400 mg) with no observed MTDs (refer to the Investigators' Brochure). Safety at significantly higher doses has not been clinically evaluated. No overdose limit is defined by Merck Sharp & Dohme, a subsidiary of Merck & Co., in the pembrolizumab regulatory label. For the purpose of this study, as in KEYNOTE-024, pembrolizumab overdose is defined as receiving greater than 5 times the planned dose.

In case of overdose with clinical correlation, symptomatic treatment must be used; there are no known antidotes for the compound. No specific information is available for the treatment of overdose for pembrolizumab.

In event of overdose, infusion should be discontinued, and participants should be observed closely for any signs of toxicity. Supportive treatment should be provided if clinically indicated. If an AE occurs resulting from overdose, it should follow SAE reporting criteria as indicated in Appendix 6.

If an incidence of overdose occurs meeting the protocol-defined definition without any association of symptoms or laboratory abnormalities, then it must be transmitted by the same process specified

for SAE reporting in Appendix 6, section on Reporting Serious Adverse Events, using the terminology "accidental or intentional overdose" without adverse effects.

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 an SAE Report Form, following the procedure in Appendix 6, section on Reporting Serious Adverse Events.

8.5 Pharmacokinetics

PK samples are no longer collected in this amendment.

CCI

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8.10 Patient-reported Outcomes

Assessments are no longer performed in this amendment.

[redacted]


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9.3 Populations for Analyses

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

For purposes of analysis, the analysis populations are defined in Table 13.

Table 13 Analysis Populations

Analysis Population	Description
SCR	All participants, who signed main informed consent, regardless of the participant's randomization and study intervention status in the study.
FAS	All participants, who were randomized to study intervention. Analyses performed on the FAS population will consider participants' allocation to study intervention groups as randomized (Intention-to-treat principle). The FAS is the primary analysis population for efficacy.
CCI	
SAF	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.

FAS = Full Analysis Set;SAF = safety; SCR = screening.

9.4 Statistical Analyses

In order 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 for 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, and maximum. Categorical variables will be summarized using frequency counts and percentages. Proportions are calculated based on the number of participants in the analysis set of interest, unless otherwise specified in the IAP. All safety and efficacy endpoints will be summarized by treatment arm.

Data collected after reinitiation of treatment will be included for safety and efficacy according to the specifications in the IAP.

9.4.1 Efficacy Analyses

Primary efficacy analyses will be performed on FAS. The 2 primary endpoints of this study are PFS according to RECIST 1.1 assessed by IRC and OS. The study will be considered positive if either the OS analysis results and/or the PFS analysis results are statistically significant.

The family-wise error rate for testing the one-sided hypotheses listed in Section 9.1 is strictly controlled at a level of 2.5% one-sided following the 2-in-1 adaptive Phase II/III design based on work by Chen et al. (Chen 2018) as described in Section 9.2. Bonferroni method is used to split the alpha of 2.5% and use 0.5% for testing H_0^{PFS} and 2.0% for testing H_0^{OS} (all one-sided). If only one of the both hypotheses can be rejected the corresponding alpha will be re-allocated and the other hypothesis will be tested at the 2.5% alpha (one-sided) as shown in Figure 2 (Yining 2012). CCI Details on the applied testing procedures are given in the following section.

The group sequential approach for testing the PFS and OS endpoints will use alpha spending according to Lan-DeMets with O'Brian-Fleming-like boundaries according to the actual number of observed events at IA regarding the total event number planned for the respective primary analysis (see Table 12).

Figure 2 **Alpha re-allocation in the confirmatory hypothesis testing (dashed lines indicate that allocation is done only when the originating hypothesis was rejected)**

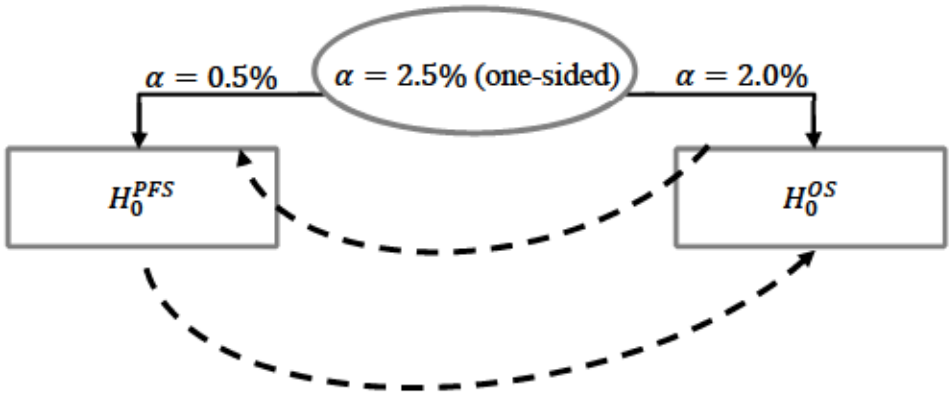

Table 14 Efficacy Endpoints and Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Primary	

PFS according to RECIST 1.1 assessed by IRC	• PFS IA and PA with cutoff when planned number of PFS events is reached as planned in Table 12, while the alpha spending is adjusted corresponding to the actual number of events at cutoff according to Lan-DeMets with O'Brian-Fleming-like boundaries considering the total number of events planned for the primary analyses.
	• PFS is defined as the time from randomization to the date of the first documentation of objective PD as assessed by the IRC 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 the last evaluable assessment date before the start of a new anticancer treatment if no event occurred so far; In case of not evaluable baseline assessment or all post-baseline assessments are non-evaluable the participant will be censored at the randomization date.
	• 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.
	• Kaplan-Meier 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.
	• Test statistics of stratified log-rank test (same strata as used for randomization) will be presented.
	• Sensitivity analyses of PFS will be done including but not limited to:
	  • 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
	  • PFS as assessed by the Investigator.
	• Subgroup analyses as specified in the IAP including but not limited to:
	  • Histology
	  • Smoking status
	  • Asian versus non-Asian.

OS	• OS IA and PA with cutoff when planned number of deaths is reached as planned in Table 12, while the alpha spending is adjusted according to Lan-DeMets with O'Brian-Fleming-like boundaries considering the total number of events planned for the primary analyses • OS analyses use a similar but reduced set of methods as applied for PFS. • OS is defined as the time from randomization to the date of death due to any cause. • For participants alive, the OS will be censored at the last date known to be alive.

Endpoint	Statistical Analysis Methods

	• Sensitivity analysis of OS will be done
	• Subgroup analyses as specified in the IAP including but not limited to:
	  • Histology
	  • Smoking status
	  • Asian versus non-Asian.

Secondary	

Objective response according to RECIST 1.1 assessed by IRC	• OR interim analysis is used for futility or respectively sample size adaptation decision – corresponding efficacy analyses are conducted on complete IRC read unconfirmed best overall response data of the first 100 randomized participants with cutoff 6 months after 100th participant randomization date (73-10 PD-L1 high population). IDMC will base decision to expand sample size on the crude ORR difference between treatment arms (ignoring randomization strata)
	• ORR – the rate of participants having an objective response, i.e. at least one overall assessment of CR or PR (before progression and before the start of a new anticancer treatment) will be calculated along with the corresponding 2-sided exact Clopper-Pearson 95% CI per treatment group.
	• Difference in ORR is estimated based on Cochran-Mantel-Haenszel method (taking into account the randomization strata) and test statistics will be presented. 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.
	• Sensitivity analyses including but not limited to:
	  • Investigator read data.
	  • Confirmed objective response

DOR according to RECIST 1.1 assessed by IRC	• Duration of response according to RECIST 1.1 as adjudicated by the IRC will be defined for participants with objective response as the time from first response until the first documented disease progression.
	• K-M 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. Subjects without an event at the analysis cutoff date will be censored on the date of the last tumor assessment.
	• Sensitivity analyses including but not limited to:
	  • Investigator read data.
	  • Confirmed objective response

CCI	

CI = confidence interval; CR = complete response; DOR = duration of response; HR = hazard ratio, IA = interim analysis; IAP=integrated analysis plan; IDMC = Independent Data Monitoring Committee; CCI ; IRC = Independent Review Committee; ORR = objective response rate; OR = overall response; OS = overall survival; PA = primary analysis; PD = progressive disease; CCI PFS=progression-free survival; PR=partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1.

9.4.2 Safety Analyses

All safety analyses will be performed on the SAF population.

Safety endpoints include AEs, clinical laboratory assessments, vital signs, physical examination, 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 (as specified in the IAP). 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 as assessed by the Investigator. Immune-related AEs are identified 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.

Table 15 Safety Endpoints and Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary Occurrence of TEAEs and treatment-related AEs	The Safety Analysis Set will include all participants who receive at least one dose of study intervention and will be based on all safety analysis reporting outcomes like adverse events, clinically relevant bioscience (AESIs) and laboratory tests outcomes. Participants will be analyzed according to the actual treatment they receive. The safety endpoints will be tabulated using descriptive statistics. • 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, and AESIs, irAEs 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). • Summary and analysis of AEs will be performed based on the 3-tier approach (Crowe, 2009) as further detailed in the study IAP. 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 event of special interest; ECG = electrocardiogram; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; IAP = Integrated Analysis Plan; CCI ; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

9.4.3 Other Analyses

PK analyses will be performed on samples collected in this study as described in the previous versions of the protocol.

- IDMC evaluates the PFS interim analysis when the number of events as given in Table 12 is reached.

- IDMC evaluates (in absence of unblinding decision at PFS IA) the PFS primary analysis when the number of events as given in Table 12 is reached or is within a range of ± 5% of that planned number at the PFS primary analysis cutoff date.

- IDMC evaluates (in absence of unblinding decision) the OS interim analysis when the number of events as given in Table 12 is reached or is within a range of ± 5% of the planned number at the PFS primary analysis cut-off date.

- The final planned analysis is the primary analysis for OS, conducted by the study team when the number of events as given in Table 12 is reached.

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CCI

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11 Appendices

Appendix 1 Abbreviations

ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
CR	Complete response
CrCL	Creatinine clearance
CNS	Central nervous system
cSCC	Cutaneous squamous cell carcinomas
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
1L	First-line
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IA	Interim analysis
IAP	Integrated Analysis Plan
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

Ig	Immunoglobulin
CCI	
ILD	Interstitial lung disease
CCI	
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-related reactions
ITT	Intention-to-Treat
iv	Intravenous
IWRS	Interactive Web Response System
KA	Keratoacanthomas
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
CCI	
PFS	Progression-free survival
PK	Pharmacokinetics
pop PK	Population pharmacokinetic
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RP2D	Recommended Phase II Dose

RT	Radiation therapy
SAE	Serious adverse event
SAF	Safety (analysis population)
SCR	Screening (analysis population)
SD	Stable disease
2L	Second-line
TGFβ	Transforming growth factor β
CCI	
TPS	Tumor proportion score
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

Appendix 2 Study Governance

Financial Disclosure

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

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally-authorized representative and answer all questions on the study.
- Participants must be informed that their participation is voluntary.
- Participants or their legally-authorized representative (where allowed by local laws and regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; the Japanese ministerial ordinance on GCP; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, participants must be re-consented to the most current, approved version.
- 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 must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.
- The Investigator will complete the participant registration form and fax it to the registration center. If the participant meets all inclusion criteria and does not meet any of the exclusion criteria, the participant registration center will receive confirmation, register the participant and inform the Investigator and the Sponsor of the registration number by fax. If the participant is ineligible for the study, a participant number will be allocated and documented.

Study Administrative

The Sponsor of this clinical study is EMD Serono Research & Development Institute, Inc. (EMD Serono R&D), Billerica, MA, in the United States (USA); Merck Biopharma Co., Ltd., Meguro-ku, Tokyo, Japan, in Japan; and Merck KGaA, Darmstadt, Germany, for sites outside the USA and Japan.

The study will be conducted at approximately 130 centers in North and South America, EU, and Asia-Pacific. Approximately 30 sites will be in the USA.

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

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

Details of structures and associated procedures will be defined in a separate Integrated Project Management Plan, which will be prepared under the supervision of the Clinical Study Leader.

For study sites in Japan, refer to the Study Organization and the Study Sites in Japan in supporting document.

An IDMC will be formed in this study (see Section 8.2).

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 Good Clinical Practice (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.
- For sites in Japan, the Sponsor initiates the study at a site after obtaining written approval from the Head of the study site, based on favorable opinion/approval from the concerned IRB.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
  - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
  - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

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

When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor 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 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

For sites in Japan, the Sponsor is entirely responsible for AEs that are associated with this study and damage 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 will provide insurance to fulfill this 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 clinical study report in consultation with the Coordinating Investigator.

Publication

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

Dissemination of Clinical Study Data

Posting of data on Clintrials.gov, EudraCT, and all other required registries is planned and will occur 12 months after the last clinic visit of the final study subject or another appropriate date to meet applicable requirements.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic eCRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the eCRF. Details for managing eCRFs are in the Manual of Operations.
- For PRO data (e.g., QoL and pain assessments), electronic patient-reported outcome will be used.
- The Investigator must maintain accurate documentation (source data) that supports the information in the eCRF.
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.

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

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the following demographic and medical information for the participant, and should be as complete as possible:
- Participant's full name, date of birth, sex, height, weight, and race, as allowed by local regulations.
    - Medical history and concomitant diseases
    - Prior and concomitant therapies (including changes during the study)
    - Study identifier (i.e., the Sponsor's study number) and participant's study number.
    - Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
    - Any medical examinations and clinical findings predefined in the protocol
    - All AEs
    - Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.
- All source data must be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document must have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.

- Data recorded on printed or electronic CRFs 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 (Head of the study site for sites in Japan) 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 Closure

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of participants by the Investigator
  - Discontinuation of further development of the Sponsor's compound.

Appendix 3 Contraception

Definitions:

Woman of Childbearing Potential (WOCBP)

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

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

A WOCBP is **not**:

1. Premenarchal

2. A premenopausal female with 1 of the following:
   Documented hysterectomy
   Documented bilateral salpingectomy/bilateral tubal ligation
   Documented bilateral oophorectomy

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

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

3. A postmenopausal female

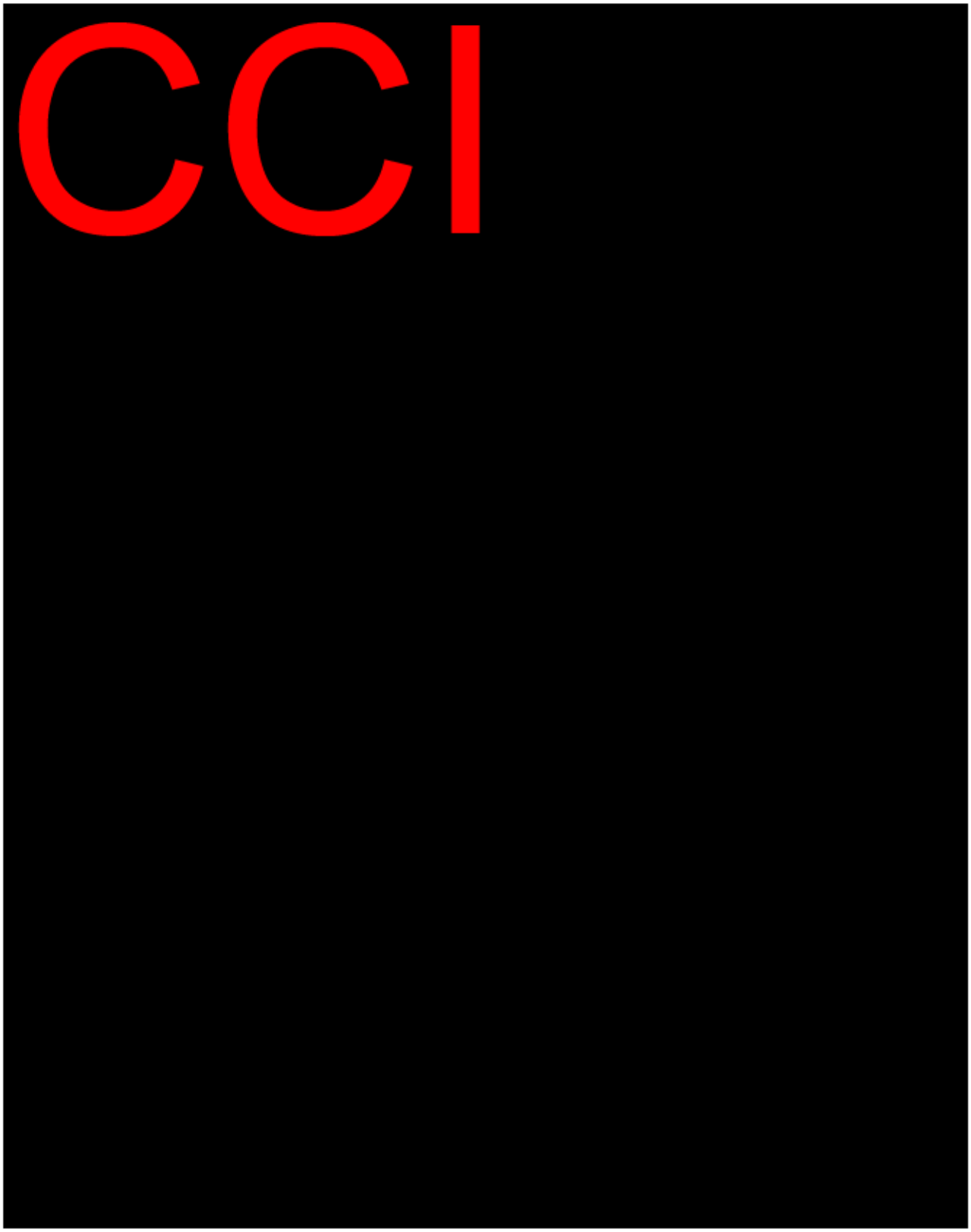
   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

   A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.

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

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods That Have Low User Dependency Implantable progestogen-only hormone contraception associated with inhibition of ovulation (not approved in Japan) Intrauterine device (IUD) Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.
Highly Effective Methods That Are User Dependent Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation Oral Intravaginal (not approved in Japan) Transdermal (not approved in Japan) Injectable (not approved in Japan) 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).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Appendix 5 The Recommendations for irAE Management, in Accordance with the Joint American Society of Clinical Oncology Clinical Practice Guidelines and National Comprehensive Cancer Network

This appendix provides recommendations to the Investigators for the management of irAEs. The contents are based on the NCCN irAE management guidelines (in Accordance with the Joint American Society of Clinical Oncology Clinical Practice Guidelines and National Comprehensive Cancer Network, Brahmer JR, 2018) and FDA recommendations to require permanent treatment discontinuation for G4 irAEs (unless otherwise indicated in the tables below). Differences with ASCO/NCCN irAE management guidelines as recommended by the FDA are shown in bold and underlined text in the tables below. Critical instructions include the requirement that treatment must be permanently discontinued for the following Grade 4 irAE toxicities: Rash/inflammatory dermatitis, nephritis, autoimmune hemolytic anemia, hemolytic uremic syndrome, aplastic anemia, immune thrombocytopenia, acquired TTP, and in certain circumstances, lymphopenia.

Adapted from:

PPD

-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Table of Tables

Table A1 Management of Skin irAEs in Patients Treated With ICPis

1.0 Skin Toxicities

1.1 Rash/inflammatory dermatitis

Definition: Erythema multiforme minor (a targetoid reaction in the skin and mucous membranes usually triggered by infections, such as herpes simplex viruses, but can be associated with an immune-related drug eruption and if progresses to erythema multiforme major, it and can be a harbinger of SCAR, such as SJS), lichenoid (resembling the flat-topped, polygonal, and sometimes scaly or hypertrophic lesions of lichen-planus), eczematous (inflammatory dermatitis characterized by pruritic, erythematous, scaly, or crusted papules or plaques on the skin, which is vulnerable to superinfection, psoriasiform [resembling the well-demarcated, erythematous, and scaly papules and plaques of psoriasis], morbilliform [a nonpustular, nonbullous measles-like exanthematous rash of the skin often referred to as "maculopapular" and without systemic symptoms or laboratory abnormalities], excluding occasional isolated peripheral eosinophilia, palmoplantar erythrodysesthesia [hand-foot syndrome; redness, numbness, burning, itching, and superficial desquamation of the palms and soles], neutrophilic dermatoses [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
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 Monitor patients with G2 irAEs closely for progression to involvement of greater BSA and/or mucous membrane involvement. Consider following patients closely using serial photography Primer on monitoring for complicated cutaneous adverse drug reactions: Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (e.g, pemphigus) and SJS/TEN
G3: Skin sloughing covering > 30% BSA with associated pain and limiting self-care ADL	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab, as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.
G4: Blisters covering > 30% BSA with associated fluid or electrolyte abnormalities	Permanently discontinue ICPi Admit patient immediately and place under supervision of a dermatologist Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg with tapering over at least 4 weeks when the toxicity resolves If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc

1.3 SCARs, including SJS, TEN, acute generalized exanthematous pustulosis, and DRESS/DIHS

Definition: Severe changes in either structure or functions of skin, the appendages or the mucous membranes due to a drug

Diagnostic work-up

Total body skin examination with attention to examining all mucous membranes as well as complete review of systems

Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease

A biologic checkup, including a CBC with differential test, and liver and kidney function tests, including urinalysis, in addition to the blood work; if the patient is febrile, blood cultures should be considered as well

Skin biopsies to assess for full-thickness epidermal necrosis, as is seen in SJS/TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses or other drug reactions, such as acute generalized exanthematous pustulosis

Consider following patients closely using serial clinical photography

If mucous membrane involvement or blistering is observed on the skin, consider early admission to a burn center for further monitoring and management Primer on monitoring for complicated cutaneous adverse drug reactions:

Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements

Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (e.g, pemphigus) and SJS/TEN

Grading	Management
All Grades	In cases of suspected SJS or any mucous membrane involvement, discontinue ICPi treatment and monitor closely for improvement, regardless of grade
G1: NA	For SCARs, there is no G1 category; if lower BSA is involved with bullae or erosions, there should remain a high concern that this reaction will progress to G3 or G4
G2: Morbilliform ("maculopapular") exanthem covering 10%-30% BSA with systemic symptoms, lymphadenopathy, or facial swelling	Hold ICPi and monitor patients closely every 3 days with G2 irAEs for progression to involvement of greater BSA and/or mucous membrane involvement Consider following patients closely using serial photography Initiate therapy with topical emollients, oral antihistamines, and medium- to high-strength topical corticosteroids Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks
G3: Skin sloughing covering < 10% BSA with mucosal involvement associated signs (e.g, erythema, purpura, epidermal detachment, mucous membrane detachment)	Hold ICPi therapy and consult with dermatology Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum Administer IV (methyl)prednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks

	Admit to burn and/or consult wound services with attention to supportive care, including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (e.g, ophthalmology; ear, nose, and throat; urology; gynecology; etc, as appropriate)
G4: Skin erythema and blistering/sloughing covering ≥ 10% to > 30% BSA with associated signs (e.g, erythema, purpura, epidermal detachment, mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (e.g, liver function test elevations in the setting of DRESS/DIHS)	Permanently discontinue ICPi Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services Consider further consultations based on management of mucosal surfaces (e.g, ophthalmology; urology; gynecology; ear, nose, and throat surgery; etc) Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal IVIG or cyclosporine may also be considered in severe or corticosteroid-unresponsive cases Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations

Additional considerations: The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immunodirected toxicity

Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS/DIHS

All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate

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

Table A2 Management of GI irAEs in Patients Treated With ICPis

2.0 GI Toxicities

2.1 Colitis

Definition: A disorder characterized by inflammation of the colon

Diagnostic work-up

G2

Work-up of blood (CBC, comprehensive metabolic panel, TSH, ESR, CRP), stool (culture, Clostridium difficile, parasite, CMV or other viral etiology, ova and parasite) should be performed

Consider testing for lactoferrin (for patient stratification to determine who needs more urgent endoscopy) and calprotectin (to follow-up on disease activity)

Screening laboratories (HIV, hepatitis A and B, and blood quantiferon for TB) to prepare patients to start infliximab should be routinely done in patients at high risk for those infections and appropriately selected patients based on infectious disease expert's evaluation

Imaging (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 May also include supportive care with medications such as Imodium if infection has been ruled out

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

Additional considerations

The use of vedolizumab (not approved in Japan) may be considered in patients refractory to infliximab and/or contraindicated to TNF-a blocker. The decision should be made on an individual basis from gastroenterology and oncology evaluation. This is based on case series showing promising results

Patients with hepatitis and irAE colitis are rare, and management should include permanently discontinuing ICPi and offering other immunosuppressant agents that work systemically for both conditions

Currently, enteritis alone as the cause of diarrhea is uncommon and requires small bowel biopsy as the evaluation tool. It may be managed similar as colitis, including corticosteroid and/or infliximab, etc

2.2 Hepatitis

Definition: A disorder characterized by a viral pathologic process involving the liver parenchyma

Diagnostic work-up

Monitor patient for abnormal liver blood tests: AST, ALT, and bilirubin prior to each infusion and/or weekly if G1 liver function test elevations. No treatment is recommended for G1 liver function test abnormality

For G2 or higher:

Work-up for other causes of elevated liver enzymes should be tested, viral hepatitis, alcohol history, iron study, thromboembolic event, liver ultrasound, cross-sectional imaging for potential liver metastasis from primary malignancy. If suspicion for primary autoimmune hepatitis is high, can consider ANAs, antismooth muscle antibodies, antineutrophil cytoplasmic antibodies. If patients with elevated alkaline phosphatase alone, g-glutamyl transferase should be tested. For isolated elevation of transaminases, consider checking CK for other etiologies

Grading	Management
All patients	Counsel all patients to be aware of and inform their health care provider immediately if they experience: Yellowing of skin or whites of the eyes Severe nausea or vomiting Pain on the right side of the abdomen Drowsiness Dark urine (tea colored) Bleeding or bruising more easily than normal Feeling less hungry than usual
G1: Asymptomatic (AST or ALT > ULN to 3.0 x ULN and/or total bilirubin > ULN to 1.5 x ULN)	Continue ICPi with close monitoring; consider alternate etiologies Monitor laboratories one to two times weekly Manage with supportive care for symptom control
G2: Asymptomatic (AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN)	Hold ICPi temporarily and resume if recover to G1 or less on prednisone ≤ 10 mg/d For Grade 2 hepatic toxicity with symptoms, may administer corticosteroid 0.5-1 mg/kg/d prednisone or equivalent if the abnormal elevation persists with significant clinical symptoms in 3-5 days Increase frequency of monitoring to every 3 days Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of idiosyncratic liver failure (Note: No clear evidence shows the liver toxicity from infliximab from other studies) In follow-up, may resume ICPi treatment followed by taper only when symptoms improve to G1 or less and corticosteroid ≤ 10 mg/d; taper over at least 1 month Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs
G3: Symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis (AST or ALT 5-20 x ULN and/or total bilirubin 3-10x3 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) Laboratories at daily or every other day; consider inpatient monitoring for patients with AST/ALT > 8 x ULN and/or elevated TB 3 x ULN Increase frequency of monitoring to every 1-2 days

	Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of liver failure (Note: No clear evidence shows that the liver toxicity from infliximab from other studies); alternatives include non–TNF-a agents as systemic immunosuppressants If no improvement is achieved with corticosteroids or for patients on combination therapy with a novel agent, with standard chemotherapy, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis
	Corticosteroid taper can be attempted around 4-6 weeks; re-escalate if needed; optimal duration unclear
G4: Decompensated liver function (e.g, ascites, coagulopathy, encephalopathy, coma; AST or ALT > 20 x ULN and/or total bilirubin > 10 x ULN)	Permanently discontinue ICPi
	Administer 2 mg/kg/d methylprednisolone equivalents
	If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil
	Monitor laboratories daily; consider inpatient monitoring
	Avoid the use of infliximab in the situation of immune-mediated hepatitis
	Hepatology consult if no improvement was achieved with corticosteroid
	Corticosteroid taper can be attempted around 4-6 weeks when symptoms improve to G1 or less; re-escalate if needed; optimal duration unclear
	Consider transfer to tertiary care facility if necessary

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

*not approved in Japan.

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

Table A3 Management of Lung irAEs in Patients Treated With ICPis

3.0 Lung Toxicities

3.1 Pneumonitis

Definition: Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging)

No symptomatic, pathologic, or radiographic features are pathognomonic for pneumonitis

Diagnostic work-up

Should include the following: CXR, CT, pulse oximetry

For G2 or higher, may include the following infectious work-up: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity

Grading	Management
G1: Asymptomatic, confined to one lobe of the lung or < 25% of lung parenchyma, clinical or diagnostic observations only	Continue ICPi if clinically indicated. Monitor participants weekly or more frequently as needed with history, physical examination and pulse oximetry; may also offer CXR. May offer one repeat CTscan in 3-4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks If symptoms appear and/or changes in the physical exam are noted, treat as G2
G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL	Hold ICPi until resolution to G1 or less Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks Consider bronchoscopy with BAL Consider empirical antibiotics Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; no clinical improvement after 48-72 hours of prednisone, treat as G3
G3: Severe symptoms, hospitalization required, involves all lung lobes or 50% of lung parenchyma, limiting self-care ADL, oxygen indicated G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation)	Permanently discontinue ICPi Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks Pulmonary and infectious disease consults if necessary Bronchoscopy with BAL ± transbronchial biopsy Patients should be hospitalized for further management

Additional considerations

GI and Pneumocystis prophylaxis with PPI and Bactrim may be offered to patients on prolonged corticosteroid use (> 12 weeks), according to institutional guidelines

Consider calcium and vitamin D supplementation with prolonged corticosteroid use

The role of prophylactic fluconazole with prolonged corticosteroid use (> 12 weeks) remains unclear, and physicians should proceed according to institutional guidelines

Bronchoscopy + biopsy; if clinical picture is consistent with pneumonitis, no need for biopsy

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

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

Table A4 Management of Endocrine irAEs in Patients Treated With ICPis

4.0 Endocrine Toxicity

Counsel patients to inform their health care provider immediately if they experience any changes in their health since their last visit, especially any of the following:

Headaches that will not go away or unusual headache patterns
Vision changes
Rapid heartbeat
Increased sweating
Extreme tiredness or weakness
Muscle aches
Weight gain or weight loss
Dizziness or fainting
Feeling more hungry or thirsty than usual
Hair loss
Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness Feeling cold
Constipation
Voice gets deeper
Urinating more often than usual
Nausea or vomiting
Abdominal pain

4.1 Thyroid

4.1.1 Primary hypothyroidism

Definition: Elevated TSH, normal or low FT4

Diagnostic work-up

TSH and FT4 every 4-6 weeks as part of routine clinical monitoring on therapy or for case detection in symptomatic patients

Grading	Management
G1: TSH < 10 mIU/L and asymptomatic	Should continue ICPi with close follow-up and monitoring of TSH, FT4 May hold ICPi until symptoms resolve to baseline
G2: Moderate symptoms; able to perform ADL; TSH persistently > 10 mIU/L	Consider endocrine consultation Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist > 10 mIU/L (measured 4 weeks apart) Monitor TSH every 6-8 weeks while titrating hormone replacement to normal TSH FT4 can be used in the short-term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low Once adequately treated, should monitor thyroid function (at least TSH) every 6 weeks while on active ICPi therapy or as needed for symptoms to ensure appropriate replacement; repeat testing annually or as indicated by symptoms once stable
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate supplementation

	Endocrine consultation May admit for IV therapy if signs of myxedema (bradycardia, hypothermia) Thyroid supplementation and reassessment as in G2

Additional considerations

For patients without risk factors, full replacement can be estimated with an ideal body weight–based dose of approximately 1.6 µg/kg/d

For elderly or fragile patients with multiple comorbidities, consider titrating up from low dose, starting at 25-50 mg

Extreme elevations of TSH can be seen in the recovery phase of thyroiditis and can be watched in asymptomatic patients to determine whether there is recovery to normal within 3-4 weeks

Under guidance of endocrinology, consider tapering hormone replacement and retesting in patients with a history of thyroiditis (initial thyrotoxic phase)

Adrenal dysfunction, if present, must always be replaced before thyroid hormone therapy is initiated

4.1.2 Hyperthyroidism

Definition: Suppressed TSH and high normal or elevated FT4 and/or triiodothyronine

Diagnostic work-up

Monitor TSH, FT4 every 4-6 weeks from the start of therapy or as needed for case detection in symptomatic patients

Consider TSH receptor antibodies if there are clinical features and suspicion of Grave disease (e.g, ophthalmopathy)

Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch transition to hypothyroidism in patients with thyroiditis and hyperthyroidism

Grading	Management
G1: Asymptomatic or mild symptoms	Can continue ICPi with close follow-up and monitoring of TSH, FT4 every 2-3 weeks until it is clear whether there will be persistent hyperthyroidism (see below) or hypothyroidism (see 4.1.1) Consider holding ICPi until symptoms return to baseline Consider endocrine consultation b-Blocker (e.g, atenolol, propranolol) for symptomatic relief Hydration and supportive care Corticosteroids are not usually required to shorten duration For persistent hyperthyroidism (> 6 weeks) or clinical suspicion, work-up for Graves disease (TSI or TRAb) and consider thionamide (methimazole or PTU) Refer to endocrinology for Graves disease
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate therapy Endocrine consultation b-Blocker (e.g, atenolol, propranolol) for symptomatic relief For severe symptoms or concern for thyroid storm, hospitalize patient and initiate prednisone 1-2 mg/kg/d or equivalent tapered over 1-2 weeks; consider also use of SSKI or thionamide (methimazole or PTU).

Additional considerations

Thyroiditis is transient and resolves in a couple of weeks to primary hypothyroidism or normal. Hypothyroidism can be treated as above. Graves disease is generally persistent and is due to increased thyroid hormone production that can be treated with antithyroid medical therapy. Physical examination findings of ophthalmopathy or thyroid bruit are diagnostic of Graves and should prompt early endocrine referral.

4.2 Adrenal – primary adrenal insufficiency

Definition: Adrenal gland failure leading to low morning cortisol, high morning ACTH, as well as hyponatremia and hyperkalemia with orthostasis and volume depletion due to loss of aldosterone

Diagnostic work-up for patients in whom adrenal insufficiency is suspected:

Evaluate ACTH (AM), cortisol level (AM)

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

Consider ACTH stimulation test for indeterminate results

If primary adrenal insufficiency (high ACTH, low cortisol) is found biochemically:

Evaluate for precipitating cause of crisis such as infection Perform an adrenal CT for metastasis/hemorrhage

Grading	Management
G1: Asymptomatic or mild symptoms	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Replacement therapy with prednisone (5-10 mg daily) or hydrocortisone (10-20 mg orally every morning, 5-10 mg orally in early afternoon) May require fludrocortisone (0.1 mg/d) for mineralocorticoid replacement in primary adrenal insufficiency Titrate dose up or down as symptoms dictate
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Initiate outpatient treatment at two to three times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg in the morning, and 10-20 mg in the afternoon) to manage acute symptoms. Taper stress-dose corticosteroids down to maintenance doses over 5-10 days Maintenance therapy as in G1.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormone Endocrine consultation See in clinic or, for after hours, make an emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation (hydrocortisone 100 mg or dexamethasone 4 mg if the diagnosis is not clear and stimulation testing will be needed) Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge Maintenance therapy as in G1

Additional considerations

Primary and secondary adrenal insufficiency can be distinguished by the relationship between ACTH and cortisol. If the ACTH is low with low cortisol, then management is as per 4.3.

Patients on corticosteroids for management of other conditions will have low morning cortisol as a result of iatrogenic, secondary adrenal insufficiency. ACTH will also be low in these patients. A diagnosis of adrenal insufficiency is challenging to make in these situations (see next section on hypophysitis).

Emergent therapy for someone with suspected adrenal insufficiency is best done with dexamethasone as a stimulation test can still be performed. If the diagnosis is already confirmed, can use hydrocortisone 100 mg.

All patients need education on stress dosing and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS.

Endocrine consultation prior to surgery or any procedure for stress-dose planning.

4.3 Pituitary - hypophysitis

Definition: Inflammation of the pituitary with varying effects on hormone function. Most commonly presenting with central adrenal insufficiency. May also have central hypothyroidism, diabetes insipidus, and hypogonadism.
Diagnostic work-up

Diagnosis: Low ACTH with a low cortisol. Low or normal TSH with a low FT4. Hypernatremia and volume depletion with diabetes insipidus. Low testosterone or estradiol with low LH and FSH.

Testing:

Evaluate ACTH, cortisol (AM), TSH, FT4, electrolytes

Consider evaluating LH, FSH, and testosterone levels in males or estrogen in premenopausal females with fatigue, loss of libido, and mood changes Consider MRI of the brain with or without contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities ± new severe headaches or complaints of vision changes

Grading	Management
G1: Asymptomatic or mild symptoms	Consider holding ICPi until patient is stabilized on replacement hormones Endocrine consultation Hormonal supplementation as in G1
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormones Endocrine consultation Hormonal supplementation as in G1 Consider initial pulse dose therapy with prednisone 1-2 mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks

Additional considerations

Be aware of the need to start corticosteroids first when planning hormone replacement therapy for multiple deficiencies

All patients need instruction on doubling doses for illness (stress dosing) and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS

Corticosteroid use can cause isolated central adrenal insufficiency

Work-up cannot be done with a simple AM cortisol in a patient on corticosteroids for other conditions

Laboratory confirmation of adrenal insufficiency should not be attempted until treatment with corticosteroids for other disease is ready to be discontinued. For long-term exposure, consult endocrinology for recovery and weaning protocol using hydrocortisone.

4.4 Diabetes

Definition: T2DM is a combination of insulin resistance and insufficiency that may require oral or insulin therapy. It may be new-onset or exacerbated during therapy for nonimmunologic reasons, such as corticosteroid exposure.

Autoimmune T1DM results from islet cell destruction and is often acute onset, with ketosis and an insulin requirement

Diagnostic work-up

Monitor patients for hyperglycemia or other signs and symptoms of new or worsening DM, including measuring glucose at baseline and with each treatment cycle during induction for 12 weeks, then every 3-6 weeks thereafter. To guide the work-up in new-onset hyperglycemia, clinicians should consider a patient's medical background, exposure history, and risk factors for each subtype of DM.

Laboratory evaluation in suspected T1DM should include testing for ketosis in urine and an assessment of the anion gap on a metabolic panel. Anti–glutamic acid decarboxylase, anti–islet cell, or anti–insulin antibodies are highly specific for autoimmune diabetes. Insulin and C-peptide levels can also assist in the diagnosis.

Grading	Management
G1: Asymptomatic or mild symptoms; fasting glucose value > ULN (160 mg/dL); fasting glucose value > ULN (8.9 mmol/L); no evidence of ketosis or laboratory evidence of T1DM	Can continue ICPi with close clinical follow-up and laboratory evaluation May initiate oral therapy for those with new-onset T2DM Screen for T1DM if appropriate, for example, acute onset with prior normal values or clinical concern for ketosis
G2: Moderate symptoms, able to perform ADL, fasting glucose value > 160-250 mg/dL; fasting glucose value> 8.9-13.9 mmol/L, ketosis or evidence of T1DM at any glucose level	May hold ICPi until glucose control is obtained Titrate oral therapy or add insulin for worsening control in T2DM Should administer insulin for T1DM (or as default therapy if there is confusion about type) Urgent endocrine consultation for any patient with T1DM; in the absence of endocrinology, internal medicine may suffice Consider admission for T1DM if early outpatient evaluation is not available or signs of ketoacidosis are present
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL G3: > 250-500 mg/dL (> 13.9-27.8 mmol/L) G4: > 500 mg/dL (> 27.8 mmol/L)	Hold ICPi until glucose control is obtained on therapy with reduction of toxicity to G1 or less Urgent endocrine consultation for all patients Initiate insulin therapy for all patients Admit for inpatient management: Concerns for developing DKA, Symptomatic patients regardless of diabetes type, New-onset T1DM unable to see endocrinology

Additional considerations

Insulin therapy can be used as the default in any case with hyperglycemia

Long-acting therapy alone is not usually sufficient for T1DM, where half of daily requirements are usually given in divided doses as prandial coverage and half as long acting.

Insulin doses will be lower in T1DM because of preserved sensitivity (total daily requirement can be estimated at 0.3-0.4 units/kg/d).

In T2DM, sliding-scale coverage with meals over a few days provides data to estimate a patient's daily requirements and can be used to more rapidly titrate basal needs.

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

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

Table A5 Management of Musculoskeletal irAEs in Patients Treated With ICPis

5.0 Musculoskeletal Toxicities

5.1 Inflammatory arthritis

Definition: A disorder characterized by inflammation of the joints

Clinical symptoms: Joint pain accompanied by joint swelling; inflammatory symptoms, such as stiffness after inactivity or in the morning, lasting > 30 minutes to 1 hour; improvement of symptoms with NSAIDs or corticosteroids but not with opioids or other pain medications may also be suggestive of inflammatory arthritis.

Diagnostic work-up

G1

Complete rheumatologic history and examination of all peripheral joints for tenderness, swelling, and range of motion; examination of the spine Consider plain x-ray/imaging to exclude metastases and evaluate joint damage (erosions), if appropriate

Consider autoimmune blood panel including ANA, RF, and anti-CCP, and anti-inflammatory markers (ESR and CRP) if symptoms persist; if symptoms are suggestive of reactive arthritis or affect the spine, consider HLA B27 testing

G2

Complete history and examination as above; laboratory tests as above

Consider US ± MRI of affected joints if clinically indicated (e.g, persistent arthritis unresponsive to treatment, suspicion for differential diagnoses such as metastatic lesions or septic arthritis)

Consider early referral to a rheumatologist, if there is joint swelling (synovitis) or if symptoms of arthralgia persist > 4 weeks

G3-4

As for G2

Seek rheumatologist advice and review

Monitoring: Patients with inflammatory arthritis should be monitored with serial rheumatologic examinations, including inflammatory markers, every 4-6 weeks after treatment is instituted.

Grading	Management
All Grades	Clinicians should follow reports of new joint pain to determine whether inflammatory arthritis is present; question whether symptom new since receiving ICPi
G1: Mild pain with inflammation, erythema, or joint swelling	Continue ICPi Initiate analgesia with acetaminophen and/or NSAIDs
G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling, limiting instrumental ADL	Hold ICPi and resume upon symptom control and on prednisone ≤ 10 mg/d Escalate analgesia and consider higher doses of NSAIDS as needed If inadequately controlled, initiate prednisone or prednisolone 10-20 mg/d or equivalent for 4-6 weeks If improvement, slow taper according to response during the next 4-6 weeks; if no improvement after initial 4-6 weeks, treat as G3 If unable to lower corticosteroid dose to < 10 mg/d after 3 months, consider DMARD Consider intra-articular corticosteroid injections for large joints Referral to rheumatology
G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL	For G3: Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to G1 or less For G4: permanently discontinue ICPi Initiate oral prednisone 0.5-1 mg/kg

	If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD Synthetic: methotrexate, leflunomide Biologic: consider anticytokine therapy such as TNF-a or IL-6 receptor inhibitors. Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis.) Test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment Referral to rheumatology.

Additional considerations

Early recognition is critical to avoid erosive joint damage.

Corticosteroids can be used as part of initial therapy in inflammatory arthritis, but due to likely prolonged treatment requirements, physicians should consider starting corticosteroid-sparing agents earlier than one would with other irAEs

Oligoarthritis can be treated early on with intra-articular corticosteroids; consider early referral.

Consider PCP prophylaxis for patients treated with high dose of corticosteroids for 12 weeks, as per local guidelines.

5.2 Myositis

Definition: A disorder characterized by muscle inflammation with weakness and elevated muscle enzymes (CK). Muscle pain can be present in severe cases. Can be life-threatening if respiratory muscles or myocardium are involved

Diagnostic work-up

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

Blood testing to evaluate muscle inflammation

CK, transaminases (AST, ALT), LDH, and aldolase can also be elevated

Troponin to evaluate myocardial involvement and other cardiac testing, such as echocardiogram, as needed

Inflammatory markers (ESR and CRP)

Consider EMG, imaging (MRI), and/or biopsy on an individual basis when diagnosis is uncertain and overlap with neurologic syndromes, such as myasthenia gravis, is suspected

Consider paraneoplastic autoantibody testing for myositis and neurologic conditions, such as myasthenia gravis
Monitoring: CK, ESR, CRP

G1: Complete examination and laboratory work-up as above

G2: Complete history and examination as above; autoimmune myositis blood panel; EMG, MRI of affected joints

Early referral to a rheumatologist or neurologist

G3-4: As for G2

Urgent referral to a rheumatologist or neurologist

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

	May require permanent discontinuation of ICPi in most patients with G2 symptoms and objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy)
G3-4: Severe weakness with or without pain, limiting self-care ADL	For G3: Hold ICPi until G1 or less and permanently discontinue if any evidence of myocardial involvement For G4: permanently discontinue ICPi Consider hospitalization for severe weakness Referral to rheumatologist or neurologist Initiate prednisone 1 mg/kg or equivalent. Consider 1-2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia) Consider plasmapheresis Consider IVIG therapy Consider other immunosuppressant therapy, such as methotrexate, azathioprine, or mycophenolate mofetil, if symptoms and CK levels do not improve or worsen after 4-6 weeks; rituximab is used in primary myositis but caution is advised given its long biologic duration In case of management with rituximab, ICPi treatment should be discontinued

Additional considerations: Caution is advised with rechallenging

5.3 Polymyalgia-like syndrome

Definition: Characterized by marked pain and stiffness in proximal upper and/or lower extremities and no signs of true muscle inflammation such as CK elevation or EMG findings of myositis. No true muscle weakness, difficulty in active motion related to pain

Diagnostic work-up

G1

Complete rheumatologic history regarding differential diagnosis and examination of all joints and skin

Check for symptoms of temporal arteritis, such as headache or visual disturbances; refer to ophthalmologist if present, and consider temporal artery biopsy ANA, RF, anti-CCP

CK to evaluate differential diagnosis of myositis

Inflammatory markers (ESR, CRP)

Monitoring: ESR, CRP

G2: Complete history and examination as above; autoimmune tests as required for differential diagnosis; early referral to a rheumatologist

G3-4: As for G2; see rheumatologist advice and review

Grading	Management
G1: Mild stiffness and pain	Continue ICPi Initiate analgesia with acetaminophen and/or NSAIDs if there are no contraindications
G2: Moderate stiffness and pain, limiting age-appropriate instrumental ADL	Consider holding ICPi and resuming upon symptom control, prednisolone < 10 mg; if worsens, treat as per G3 Initiate prednisone 20 mg/d or equivalent; if symptoms improve, start to taper dose after 3-4 weeks If no improvement or need for higher dosages after 4 weeks, escalate to G3 Consider referral to rheumatology

G3-4: Severe stiffness and pain, limiting self-care ADL	For G3: Hold ICPi and may resume, in consultation with rheumatology, if recover to G1 or less; however, note that cases of toxicity returning upon rechallenge have been reported. ICPi should be permanently discontinued in such cases For G4: permanently discontinue ICPi Referral to rheumatology Should initiate prednisone 20 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a corticosteroid-sparing agent such as methotrexate or IL-6 inhibition with tocilizumab (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis or GI metastases). Consider admission for pain control

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

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

Table A6 Management of Renal irAEs in Patients Treated With ICPis

6.0 Renal Toxicities

Nephritis and renal dysfunction: diagnosis and monitoring

For any suspected immune-mediated adverse reactions, exclude other causes

Monitor patients for elevated serum creatinine prior to every dose

Routine urinalysis is not necessary, other than to rule out UTIs, etc; nephrology may consider further

If no potential alternative cause of AKI identified, then one should forego biopsy and proceed directly with immunosuppressive therapy Swift treatment of autoimmune component important

6.1 Nephritis

Definition: Inflammation of the kidney affecting the structure

Grading	Management
G1: Creatinine level increase **> 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	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
G3	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist 3-5 days or worsen, consider additional immunosuppression (e.g, mycophenolate)
G4	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist 2-3 days or worsen, consider additional immunosuppression (e.g, mycophenolate)

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

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

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

7.0 Nervous System Toxicities

7.1 Myasthenia gravis

Definition: Fatigable or fluctuating muscle weakness, generally more proximal than distal. Frequently has ocular and/or bulbar involvement (ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, dysarthria, facial muscle weakness). May have neck and/or respiratory muscle weakness. (Note: May occur with myositis and/or myocarditis. Respiratory symptoms may require evaluation to rule out pneumonitis, myocarditis. Miller Fisher variant of Guillain-Barré syndrome (ophthalmoparesis) and the oculobulbar myositis (ptosis, ophthalmoparesis, dysphagia, neck and respiratory weakness) with ICPi may have overlapping symptoms.

Diagnostic work-up

AChR and antistriated muscle antibodies in blood; if AChR antibodies are negative, consider muscle specific kinase and lipoprotein-related 4 antibodies in blood Pulmonary function assessment with NIF and VC

CPK, aldolase, ESR, CRP for possible concurrent myositis

Consider MRI of brain and/or spine, depending on symptoms to rule out CNS involvement by disease or alternate diagnosis

If respiratory insufficiency or elevated CPK, troponin T, perform cardiac examination with ECG and TTE for possible concomitant myocarditis

Neurologic consultation

Electrodiagnositic studies, including neuromuscular junction testing with repetitive stimulation and/or jitter studies, NCS to exclude neuropathy, and needle EMG to evaluate for myositis

Grading	Management
All grades	All grades warrant work-up and intervention given potential for progressive myasthenia gravis to lead to respiratory compromise
No G1	
G2: Some symptoms interfering with ADL MGFA severity class 1 (ocular symptoms and findings only) and MGFA severity class 2 (mild generalized weakness)	Hold ICPi and may resume in G2 patients (MGFA 1 and 2) only if symptoms resolve Should consult neurology Pyridostigmine starting at 30 mg orally three times a day and gradually increase to maximum of 120 mg orally four times a day as tolerated and based on symptoms Administer corticosteroids (prednisone, 1-1.5 mg/kg orally daily) if symptoms G2; wean based on symptom improvement
G3-4: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms, or MGFA severity class 3-4 moderate to severe generalized weakness to myasthenic crisis	Permanently discontinue ICPi Admit patient, may need ICU-level monitoring Neurology consult Continue corticosteroids and initiate IVIG 2 g/kg IV over 5 days (0.4 g/kg/d) or plasmapheresis for 5 days Frequent pulmonary function assessment Daily neurologic review

Additional considerations

Avoid medications that can worsen myasthenia: β-blockers, IV magnesium, fluoroquinolones, aminoglycosides, and macrolides Initially a 5-day course of plasmapheresis or a 2 g/kg course of IVIG over 5 days

1-2 mg/kg methylprednisolone daily, wean based on symptom improvement

Pyridostigmine, wean based on improvement

ICPi-associated myasthenia gravis may be monophasic, and additional corticosteroid-sparing agents may not be required

7.2 Guillain-Barré syndrome

Definition: Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. Often starts with sensory symptoms/neuropathic pain localized to lower back and thighs. May involve extremities (typically ascending weakness but not always), facial, respiratory, and bulbar and oculomotor nerves. May have dysregulation of autonomic nerves.

Diagnostic work-up

Neurologic consultation

MRI of spine with or without contrast (rule out compressive lesion and evaluate for nerve root enhancement/thickening)

Lumbar puncture: CSF typically has elevated protein and often elevated WBCs; even though this is not typically seen in classic Guillain-Barré syndrome, cytology should be sent with any CSF sample from a patient with cancer.

Serum antibody tests for Guillain-Barré syndrome variants (GQ1b for Miller Fisher variant a/w ataxia and ophthalmoplegia) Electrodiagnostic studies to evaluate polyneuropathy

Pulmonary function testing (NIF/VC)

Frequent neurochecks

Grading	Management
All grades	Warrant work-up and intervention given potential for progressive Guillain-Barré syndrome to lead to respiratory compromise Note: There is no G1 toxicity
G1: Mild, none	NA
G2: Moderate, some interference with ADL, symptoms concerning to patient	Discontinue ICPi
G3-4: Severe, limiting self-care and aids warranted, weakness, limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms	Permanently discontinue ICPi. Admission to inpatient unit with capability of rapid transfer to ICU-level monitoring Start IVIG (0.4 g/kg/d for 5 days for a total dose of 2 g/kg) or plasmapheresis. Corticosteroids are usually not recommended for idiopathic Guillain-Barré syndrome; however, in ICPi-related forms, a trial is reasonable (methylprednisolone 2-4 mg/kg/d), followed by slow corticosteroid taper Pulse corticosteroid dosing (methylprednisolone 1 g/d for 5 days) may also be considered for G3-4 along with IVIG or plasmapheresis Frequent neurochecks and pulmonary function monitoring Monitor for concurrent autonomic dysfunction Nonopioid management of neuropathic pain Treatment of constipation/ileus

Additional considerations

Slow prednisone taper after corticosteroid pulse plus IVIG or plasmapheresis May require repeat IVIG courses

Caution with rechallenging for severe cases

7.3 Peripheral neuropathy

Definition: Can present as asymmetric or symmetric sensory, motor, or sensory motor deficit. Focal mononeuropathies, including cranial neuropathies (e.g, facial neuropathies/Bell palsy) may be present. Numbness and paresthesias may be painful or painless. Hypo- or areflexia or sensory ataxia may be present.

Diagnostic work-up

G1

Screen for reversible neuropathy causes: diabetic screen, B12, folate, TSH, HIV, consider serum protein electrophoresis, and other vasculitic and autoimmune screen Neurologic consultation

Consider MRI of spine with or without contrast

G2: in addition to above

MRI spine advised/MRI of brain if cranial nerve Consider EMG/NCS

Consider neurology consultation

G3-4: go to Guillain-Barré syndrome algorithm

Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate	Low threshold to hold ICPi and monitor symptoms for a week If to continue, monitor very closely for any symptom progression
G2: Moderate, some interference with ADL, symptoms concerning to patient (i.e, pain but no weakness or gait limitation)	Hold ICPi and resume once return to G1 Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild) Neurontin, pregabalin, or duloxetine for pain
G3-4: Severe, limiting self-care and aids warranted, weakness limiting walking or respiratory problems (i.e, leg weakness, foot drop, rapidly ascending sensory changes) Severe may be Guillain-Barré syndrome and should be managed as such	Permanently discontinue ICPi Admit patient Neurologic consultation Initiate IV methylprednisolone 2-4 mg/kg and proceed as per Guillain-Barré syndrome management

7.4 Autonomic neuropathy

Definition: Nerves that control involuntary bodily functions are damaged. This may affect blood pressure, temperature control, digestion, bladder function, and sexual function. A case of severe enteric neuropathy with ICPi has been reported. Can present with GI difficulties such as new severe constipation, nausea, urinary problems, sexual difficulties, sweating abnormalities, sluggish pupil reaction, and orthostatic hypertension.

Diagnostic work-up

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

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

AM orthostatic vitals

Consider electrodiagnostic studies to evaluate for concurrent polyneuropathy

Consider paraneoplastic Lambert-Eaton myasthenic syndrome, antineutrophil cytoplasmic antibodies, and ganglionic AChR antibody testing

Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient	Low threshold to hold ICPi and monitor symptoms for a week; if to continue, monitor very closely for any symptom progression
G2: Moderate, some interference with ADL, symptoms concerning to patient	Hold ICPi and resume once return to G1 Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild) Neurologic consultation
G3-4: Severe, limiting self-care and aids warranted	Permanently discontinue ICPi Admit patient Initiate methylprednisolone 1 g daily for 3 days followed by oral corticosteroid taper Neurologic consultation

7.5 Aseptic meningitis

Definition: may present with headache, photophobia, and neck stiffness; often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis).

Diagnostic work-up

MRI of brain with or without contrast + pituitary protocol

AM cortisol, ACTH to rule out adrenal insufficiency

Consider lumbar puncture: measure opening pressure; check cell count and protein glucose; and perform Gram stain, culture, PCR for HSV, and other viral PCRs depending on suspicion, cytology

May see elevated WBC count with normal glucose, normal culture, and Gram stain; may see reactive lymphocytes or histiocytes on cytology

Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (i.e, pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	For G1-3: Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits For G4: permanently discontinue ICPi. In case of any aseptic meningitis events (G1-4), consider empirical antiviral (IV acyclovir) and antibacterial therapy until CSF results Once bacterial and viral infection are negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg or IV methylprednisolone 1 mg/kg if moderate/severe symptoms

7.6 Encephalitis

Definition: As for aseptic meningitis, need to exclude infectious causes, especially viral (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	For G1, 2, and 3: Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits For G4: permanently discontinue ICPi As above for aseptic meningitis in case of any encephalitis events, suggest concurrent IV acyclovir until PCR results obtained and negative Trial of methylprednisolone 1-2 mg/kg If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids methylprednisolone 1 g IV daily for 3-5 days plus IVIG 2 g/kg over 5 days If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab or plasmapheresis in consultation with neurology. In case of management with rituximab, ICPi treatment should be discontinued.

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.

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

Table A8 Management of Hematologic irAEs in Patients Treated With ICPis

8.0 Hematologic Toxicities

8.1 Autoimmune hemolytic anemia

Definition: A condition in which RBCs are destroyed and removed from the blood stream before their normal lifespan is over. Symptoms include weakness, paleness, jaundice, dark-colored urine, fever, inability to do physical activity, and heart murmur.

Diagnostic work-up

History and physical examination (with special consideration of history of new drugs and insect, spider, or snake bites)

Blood chemistry, CBC with evidence of anemia, macrocytosis, evidence of hemolysis on peripheral smear; LDH, haptoglobin, bilirubin, reticulocyte count, free Hgb DIC panel, which could include PTNIR infectious causes

Autoimmune serology

Paroxysmal nocturnal hemoglobinuria screening

Direct and indirect bilirubin; LDH; direct agglutinin test; and if no obvious cause, bone marrow analysis, CCI analysis to evaluate for myelodysplastic syndromes

Evaluation for viral/bacterial (mycoplasma, etc) causes of hemolysis studies

Protein electrophoresis, cryoglobulin analysis

Work-up for bone marrow failure syndrome if refractory, including B12, folate, copper, parvovirus, FE, thyroid, infection

Glucose-6-phosphate dehydrogenase

Evaluation of common drug causes (ribavirin, rifampin, dapsone, interferon, cephalosporins, penicillins, NSAIDs, quinine/quinidine, fludarabine, ciprofloxacin, lorazepam, diclofenac, etc)

Assessment of methemoglobinemia

Grading	Management
G1: Hgb < LLN to 10.0 g/dL; < LLN to 6.2 mmol/L; < LLN to 100 g/L	Continue ICPi with close clinical follow-up and laboratory evaluation
G2: Hgb < 10.0 to 8.0 g/dL; < 6.2to4.9mmol/L; < 100 to 80 g/L	Hold ICPi and strongly consider permanent discontinuation Administer 0.5-1 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 If no improvement or if worsening while on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, cyclosporin A, and mycophenolate mofetil RBC transfusion per existing guidelines; discuss with blood bank team prior to transfusions that a patient with possible ICPi serious AE is in house.

Additional considerations: Monitor Hgb levels on a weekly basis until the corticosteroid tapering process is complete; thereafter, less-frequent testing is needed

8.2 Acquired TTP

Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities, and neurologic abnormalities, such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.

Diagnostic work-up

History with specific questions related to drug exposure (e.g, chemotherapy, sirolimus, tacrolimus, opana ER antibiotics, quinine) Physical examination, peripheral smear

ADAMTS13 activity level and inhibitor titer

LDH, haptoglobin, reticulocyte count, bilirubin, urinalysis to rule out other causes

PT, activated PTT, fibrinogen

Blood group and antibody screen, direct antiglobulin test, CMV serology

Consider CT/MRI brain, echocardiogram, ECG

Viral studies

Note: This disorder is usually associated with a severe drop in platelets and hemolysis/anemia precipitously

Grading	Management
All grades	The first step in the management of TTP is a high index of suspicion for the diagnosis and timely recognition; hematology consult should immediately be called, as delay in identification is associated with increased mortality/morbidity. Initially, the patient should be stabilized and any critical organ dysfunction stabilized
G1: Evidence of RBC destruction (schistocytosis) without anemia, renal insufficiency, or thrombocytopenia clinically G2: Evidence of RBC destruction (schistocytosis) without clinical consequence with G2 anemia and thrombocytopenia	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting ICPi therapy Hematology consult Administer 0.5-1 mg/kg/d prednisone
G3: Laboratory findings with clinical consequences (G3 thrombocytopenia, anemia, renal insufficiency > 2) G4: Life-threatening consequences (e.g, CNS hemorrhage or thrombosis/embolism or renal failure)	For G3: Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting ICPi therapy For G4: permanently discontinue ICPi Hematology consult In conjunction with hematology, initiate PEX according to existing guidelines with further PEX dependent on clinical progress

	Administer methylprednisolone 1 g IV daily for 3 days, with the first dose typically administered immediately after the first PEX
	May offer rituximab
	In case of management with rituximab, ICPi treatment will be discontinued

8.3 Hemolytic uremic syndrome

Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia. Signs and symptoms of hemolytic uremic syndrome can include:

Bloody diarrhea

Decreased urination or blood in the urine

Abdominal pain, vomiting, and occasionally fever

Pallor

Small, unexplained bruises or bleeding from the nose and mouth Fatigue and irritability

Confusion or seizures

High blood pressure

Swelling of the face, hands, feet, or entire body

Diagnostic work-up

History and physical examination (special consideration for new history of high-risk drugs, hypertension, or cardiac causes) CBC with indices

Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis.

Serum creatinine

ADAMTS13 (to rule out TTP)

Homocysteine/methylmalonic acid

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

Evaluate reticulocyte count and mean corpuscular volume

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

Evaluation for nutritional causes of macrocytosis (B12 and folate)

Pancreatic enzymes

Evaluation for diarrheal causes, shiga toxin, Escherichia coli 0157, etc

Direct antibody test (Coombs test), haptoglobin, LDH, and other etiologies of anemia

Evaluation for common drugs causing hemolysis (tacrolimus, cyclosporine, sirolimus, etc)

Evaluation for concurrent confusion

Grading	Management
G1-2: Evidence of RBC destruction (schistocytosis) without clinical consequences of anemia, thrombocytopenia Grade 2	For G1 and G2: Continue ICPi with close clinical follow-up and laboratory evaluation
	Supportive care
G3: Laboratory findings with clinical consequences (e.g, renal insufficiency, petechiae)	For G3 and G4: Permanently discontinue ICPi
G4: Life-threatening consequences (e.g, CNS thrombosis/ embolism or renal failure)	Begin therapy with eculizumab therapy 900 mg weekly for four doses, 1,200 mg week 5, then 1,200 mg every 2 weeks
	Red blood transfusion according to existing guidelines

8.4 Aplastic anemia

Definition: Condition in which the body stops producing enough new blood cells

Diagnostic work-up

History and physical examination (close attention to medications, exposure to radiation, toxins, recent viral infections) CBC, smear, reticulocyte count

Viral studies, including CMV, HHV6, EBV, parvovirus

Nutritional assessments including B12, folate, iron, copper, ceruloplasmin, vitamin D

Serum LDH, renal function

Work-up for infectious causes

Identify marrow hypo/aplasia

Bone marrow biopsy and aspirate analysis

Peripheral blood analysis, including neutrophil count, proportion of GPI-negative cells by flow for PNH

Flow cytometry to evaluate loss of GPI-anchored proteins

Type and screen patient for transfusions and notify blood bank that all transfusions need to be irradiated and filtered

Grading	Management
G1: Nonsevere, < 0.5 polymorphonuclear cells x 10^9/L hypocellular marrow, with marrow cellularity < 25%, peripheral platelet count > 20,000, reticulocyte count < 20,000	Hold ICPi and provide growth factor support and close clinical follow-up, and laboratory evaluation Supportive transfusions as per local guidelines
G2: Severe, hypocellular marrow < 25% and two of the following: ANC < 500, peripheral platelet < 20,000, and reticulocyte < 20,000	Hold ICPi and provide growth factor support and close clinical laboratory evaluations daily Administer ATG + cyclosporine; HLA typing and evaluation for bone marrow transplantation if patient is candidate; all blood products should be irradiated and filtered Supportive care with granulocyte colony-stimulating factor may be added in addition
G3-4: Very severe, ANC > 200, platelet count > 20,000, reticulocyte count > 20,000, plus hypocellular marrow > 25%	For G3: Hold ICPi and monitor weekly for improvement; if not resolved, discontinue treatment until AE has reverted to G1 For G4: permanently discontinue ICPi Hematology consult, growth factor support Horse ATG plus cyclosporine If no response, repeat immunosuppression with rabbit ATG plus cyclosporine, cyclophosphamide For refractory patients, consider eltrombopag plus supportive care

8.5 Lymphopenia

Definition: An abnormally low level of lymphocytes in PB; for adults, counts of < 1,500/mm^3

Diagnostic work-up

History and physical examination (special attention for lymphocyte-depleting therapy such as fludarabine, ATG, corticosteroids, cytotoxic chemotherapy, radiation exposure, etc, as well as history of autoimmune disease, family history of autoimmune disease) Evaluation of nutritional state as cause

Spleen size

CBC with differential, peripheral smear and reticulocyte counts

CXR for evaluation of presence of thymoma

Bacterial cultures and evaluation for infection (fungal, viral, bacterial specifically CMV/HIV)

Grading	Management
G1-2: 500-1,000 PB lymphocyte count	Continue ICPi for G1 to G2
G3: 250-499 PB lymphocyte count	Continue ICPi, checking
G4: < 250 PB lymphocyte count	For G3 single laboratory values out of normal range without any clinical correlates, hold treatment until resolution to G1 For G4, for single laboratory values out of normal range without any clinical correlates, permanent treatment discontinuation is not required. Treatment should be held until the etiology is determined. Permanent treatment discontinuation will only be required, if lymphopenia is considered of immune-related in nature, no clear alternative explanation exists for the event, and Grade 4 lymphopenia does not resolve within 14 days. If the event is not considered immune-related and resolves to G ≤1 restarting treatment may be considered. Check CBC weekly for monitoring, initiation of CMV screening Consider holding ICPi Initiate *Mycobacterium avium* complex prophylaxis and *Pneumocystis jirovecii* prophylaxis, CMV screening. HIV/hepatitis screening if not already done May consider EBV testing if evidence of lymphadenopathy/hepatitis, fevers, hemolysis consistent with lymphoproliferative disease

8.6 Immune thrombocytopenia

Definition: An autoimmune disorder characterized by immunologic destruction of otherwise normal platelets

Diagnostic work-up

History and physical examination (special attention for lymphocyte-depleting therapy, such as fludarabine, ATG, corticosteroids, cytotoxic therapy) Family history of autoimmunity or personal history of autoimmune disease

History of viral illness

CBC

Peripheral blood smear, reticulocyte count

Bone marrow evaluation only if abnormalities in the above test results and further investigation is necessary for a diagnosis

Patients with newly diagnosed immune thrombocytopenia should undergo testing for HIV, hepatitis C virus, hepatitis B virus, and Helicobacter pylori Direct antigen test should be checked to rule out concurrent Evan syndrome

Nutritional evaluation

Bone marrow evaluation if other cell lines affected and concern for aplastic anemia

Grading	Management
G1: Platelet count < 100/μL G2: Platelet count < 75/μL	Continue ICPi with close clinical follow-up and laboratory evaluation Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1 Administer prednisone 1 mg/kg/d (dosage range, 0.5-2 mg/kg/d) orally for 2-4 weeks after which time this medication should be tapered over 4-6 weeks to the lowest effective dose IVIG may be used in conjunction with corticosteroids if a more-rapid increase in platelet count is required.
G3: Platelet count < 50/μL	Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1
G4: Platelet count < 25/μL	Permanently discontinue ICPi Hematology consult Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue treatment IVIG used with corticosteroids when a more-rapid increase in platelet count is required If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary If previous treatment with corticosteroids and/or IVIG unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more-potent immunosuppression (From American Society of Hematology guideline on immune thrombocytopenia97; consult for further details)

8.7 Acquired hemophilia

Definition: Disorder caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors

Diagnostic work-up

Full blood count to assess platelet number, fibrinogen, PT, PTT, INR; the typical finding in patients with acquired hemophilia A is a prolonged activated PTT with a normal PT

MRI, CT, and ultrasonography may be indicated to localize, quantify, and serially monitor the location and response of bleeding Medication review to assess for alternative causes

Determination of Bethesda unit level of inhibitor

Grading	Management
G1: Mild, 5%-40% of normal factor activity in blood, 0.05-0.4 IU/mL of whole blood	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits Administer 0.5-1 mg/kg/d prednisone Transfusion support as required Treatment of bleeding disorders with hematology consult
G2: Moderate, 1%-5% of normal factor activity in blood, 0.01- 0.05 IU/mL of whole blood	Hematology consult Administration of factor replacement (choice based on Bethesda unit of titer)

	Administer 1 mg/kg/d prednisone ± rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d); choice of rituximab v cyclophosphamide is patient specific and should be done with assistance of hematology consult; prednisone, rituximab, and cyclophosphamide should be given for at least 5 weeks Factors should be provided to increase level during bleeding episodes, with choice of factor based on presence or absence of inhibitor
G3-4: Severe, < 1% of normal factor activity in blood, < 0.01 IU/mL of whole blood	Permanently discontinue ICPi Admit patient Hematology consult Administration of factor replacement, choice based on Bethesda unit level of inhibitor Bypassing agents may be used (factor VII, factor VIII inhibitor bypass activity); caution should be taken in the elderly and those with coronary artery disease Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) ± rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d). Transfusion support as required for bleeding If worsening or no improvement add cyclosporine or immunosuppression/immunoadsorption

Additional considerations: The American Heart Association requires specialist clinical and laboratory expertise. Consult and/or transfer to a specialist center is often appropriate. If consultation with or transfer to a hemophilia center is not immediately possible, then investigation and treatment should be initiated while a liaison is being established.

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

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

Table A9 Management of Cardiovascular irAEs in Patients Treated With ICPis

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 CCI testing, including abnormal ECG	All grades warrant work-up and intervention given potential for cardiac compromise
G2: Abnormal screening tests with mild symptoms	Consider the following:
G3: Moderately abnormal testing or symptoms with mild activity	For G1: Hold ICPi
G4: Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions	For G2, G3, and G4: Permanently discontinue ICPi
	For G1-G4: High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms)
	Admit patient, cardiology consultation
	Immediate transfer to a coronary care unit for patients with elevated troponin or conduction abnormalities
	In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin

Qualifying statement: Treatment recommendations are based on anecdotal evidence and the life-threatening nature of cardiovascular complications. The appropriateness of rechallenging remains unknown. Note that infliximab has been associated with heart failure and is contraindicated at high doses in patients with moderate-severe heart failure.

9.2 Venous thromboembolism

Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream. Clinical signs and symptoms are variable and may include pain, swelling, increased skin vein visibility, erythema, and cyanosis accompanied by unexplained fever for DVT and dyspnea, pleuritic pain, cough, wheezing, or hemoptysis for PE

Diagnostic work-up

Evaluation of signs and symptoms of PE or DVT may include Clinical prediction rule to stratify patients with suspected venous thromboembolism Venous ultrasound for suspected DVT

CTPA for suspected PE

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	Continue ICPi based on benefit-risk assessment of individual patient Consider consult from cardiology or other relevant specialties LMWH is suggested over VKA, dabigatran, rivaroxaban apixaban, or edoxaban for initial and long-term treatment IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term
G3: Thrombosis (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 consult from cardiology or other relevant specialties Respiratory and hemodynamic support LMWH is suggested over VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial and long-term treatment IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term Further clinical management as indicated based on symptoms

Additional considerations

While it may be impossible to determine the etiology of thromboembolic disease in patients with advanced cancer and the role, if any, that ICPi treatment plays, it is reasonable to permanently discontinue the potential inciting agents given the severity and life-threatening potential of G4 complications. For G3 events, ICPi must be withheld and clinicians are to use clinical judgment and take into account the risks and benefits when deciding whether to restart ICPi treatment.

Anticoagulant therapy duration should continue for a minimum of 9-12 months to indefinitely in the setting of active cancer unless patient is asymptomatic, doing well, or in remission.

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

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

Table A10 Management of Ocular irAEs in Patients Treated With ICPis

10.0 Ocular Toxicities

Counsel all patients to inform their health care provider immediately if they experience any of the following ocular symptoms

Blurred vision

Change in color vision Photophobia

Distortion

Scotomas

Visual field changes Double vision Tenderness

Pain with eye movement Eyelid swelling Proptosis

Evaluation, under the guidance of ophthalmology

Check vision in each eye separately

Color vision

Red reflex

Pupil size, shape, and reactivity

Fundoscopic examination

Inspection of anterior part of eye with penlight

Prior conditions

Exclude patients with history of active uveitis

History of recurrent uveitis requiring systemic immunosuppression or continuous local therapy

Additional considerations

Ocular irAEs are many times seen in the context of other organ irAEs

High level of clinical suspicion as symptoms may not always be associated with severity Best to treat after ophthalmologist eye examination

10.1 Uveitis/iritis

Definition: Inflammation of the middle layer of the eye Diagnostic work-up: as per above

Grading	Management
G1: Asymptomatic	Continue ICPi Refer to ophthalmology within 1 week Artificial tears
G2: Medical intervention required, anterior uveitis	Hold ICPi temporarily until after ophthalmology consult Urgent ophthalmology referral Topical corticosteroids, cycloplegic agents, systemic corticosteroids May resume ICPi treatment once off systemic corticosteroids, which are purely indicated for ocular adverse effects or once corticosteroids for other concurrent systemic irAEs are reduced to ≤ 10 mg; continued topical/ocular corticosteroids are permitted when resuming therapy to manage and minimize local toxicity Re-treat after return to G1 or less
G3: Posterior or panuveitis	Permanently discontinue ICPi Urgent ophthalmology referral. Systemic corticosteroids and intravitreal/periocular/topical corticosteroids

G4: 20/200 or worse	Permanently discontinue ICPi Emergent ophthalmology referral Systemic corticosteroids (IV prednisone 1-2 mg/kg or methylprednisolone 0.8-1.6 mg/kg) and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion

Additional considerations: Consider use of infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment

10.2 Episcleritis

Definition: Inflammatory condition affecting the episcleral tissue between the conjunctiva and the sclera that occurs in the absence of an infection Diagnostic work-up: As per 10.0

Grading	Management
G1: Asymptomatic	Continue ICPi Refer to ophthalmology within 1 week Artificial tears
G2: Vision 20/40 or better	Hold ICPi therapy temporarily until after ophthalmology consult Urgent ophthalmology referral Topical corticosteroids, cycloplegic agents, systemic corticosteroids
G3: Symptomatic and vision worse than 2/40	Permanently discontinue ICPi Urgent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents
G4: 20/200 or worse	Permanently discontinue ICPi Emergent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents

Additional considerations: Consider use of infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment

10.3 Blepharitis

Definition: Inflammation of the eyelid that affects the eyelashes or tear production Diagnostic work-up: As per 10.0

Grading	Management
No formal grading system	Warm compresses and lubrication drops Continue therapy unless persistent and serious

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

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

Appendix 6 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions

Adverse Event

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

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

Compared to baseline (Screening or the Week 1, Day 1 visit), medical conditions that do not worsen in severity or frequency during the study are defined as baseline medical conditions and are NOT to be considered as AEs.

All newly diagnosed or worsening pre-existing conditions (clinically significant changes in frequency, and/or intensity), signs, and symptoms observed from baseline (Screening or the Week 1, Day 1 visit), whether related to study intervention or not, are to be reported as AEs.

Progression of the cancer under study is not considered an AE.

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

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

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

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

The 5 general grades are:

Grade 1 or Mild

Grade 2 or Moderate

Grade 3 or Severe

Grade 4 or Life-threatening

Grade 5 or Death

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

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

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

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

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

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

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

Serious Adverse Events

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

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongs an existing hospitalization

- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g, an overnight stay to facilitate chemotherapy and related hydration therapy application) 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 patient'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 (Method of Detecting Adverse Events and Serious Adverse Events).

Adverse Events of Special Interest (AESI)

Categories of AESIs related to M7824 include:

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

Recording and Follow-Up of AE and/or SAE

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

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

Reporting Serious Adverse Events

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee using the SAE report form in the eCRF following specific completion instructions.

Reporting of SAEs via paper report form is required as a back-up method only in the case of EDC failure. Names, addresses, and telephone and fax numbers will be included on the paper report form. All information reported via paper form must be transcribed into the eCRF 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 SAE report form must be completed immediately thereafter in the eCRF.

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 responsible Monitor, although in exceptional circumstances the drug safety department may contact the Investigator directly to obtain further information or to discuss the event.

Appendix 7 Clinical Laboratory Tests

Table 16 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments [a]	Parameters			
Hematology[b]	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: • MCV • MCH • MCHC • RDW • %reticulocytes	WBC Count with Differential: • neutrophils (ANC) • lymphocytes (absolute count) • monocytes • eosinophils • basophils	
Hemostaseology	Prothrombin time	INR	aPTT	
Full Clinical Chemistry Panel A [b]	Liver Panel: alkaline phosphatase, ALT, AST, GGT, total and indirect/direct bilirubin, albumin, total protein, and creatine kinase	Serum Electrolytes: sodium potassium, calcium, magnesium, chloride, phosphorus/ phosphates	Renal Panel: BUN/total urea, creatinine, estimated GFR, uric acid	Pancreatic Panel: amylase, lipase
	Glucose			
Full Clinical Chemistry Panel B [c]	Iron Panel: TIBC and/or transferrin, iron, ferritin, serum folate/B12	TST, QuantiFERON-TB-Gold, or T-SPOT (if positive history of tuberculosis exposure) [d]	Virology: HBV and HCV serology (repeat as per Section 1.3 if participant with infection history)	CRP
Core Chemistry	Liver Panel: alkaline phosphatase, ALT, AST, GGT, total and indirect/direct bilirubin, albumin, total protein, and creatine kinase	Serum Electrolytes: sodium, potassium, calcium, magnesium, chloride, phosphorus/ phosphates	Renal Panel: BUN/total urea, creatinine, estimated GFR, uric acid	Glucose
Thyroid Panel	• T_4, TSH			
Routine Urinalysis [e]	• Specific gravity, physical appearance, color • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum or highly sensitive urine β-hCG pregnancy test (as needed for women of childbearing potential) [b].			

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

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

b Samples must be drawn and results for core chemistry, hematology, and pregnancy test reviewed prior to dose administration.

c Performed at Screening only.

d Discuss with Medical Monitor if another test not listed is standard of care for your institution.

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


CCI

Appendix 9 Protocol Amendment History

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

Protocol Version 3.1 (06 May 2020)

Overall Rationale for the Amendment

The primary purpose of this region-specific amendment is to update the Benefit/Risk assessment with additional information on the CCI assay for countries in the European Union.

Section # and Name	Description of Change	Brief Rationale
Document Header and throughout document	Corrected spelling of bintrafusp and corrected other typographical and formatting issues	Administrative update
2.3 Benefit/Risk Assessment	CCI	

Protocol Version 3.0 (10 February 2020)

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

Overall Rationale for the Amendment

The primary purpose of this global amendment is to change the design to an adaptive Phase III trial with sample size adjustments based on prespecified decision rules at the first interim analysis as evaluated by the Independent Data Monitoring Committee, independent of the study team. In addition, endpoints were changed and premedication for infusion-related reaction was changed to optional. The key changes are listed below.

Section # and Name	Description of Change	Brief Rationale
Title page	Study title was revised	To reflect the change to an adaptive study design
Title page	Amendment number added	Administrative update
Title page	Study phase added	Administrative update
Title page	Study phase changed from II to III	Administrative update
Title page	Sponsor name and legal registered address	Administrative update
Title page	Protocol version changed	Administrative update
Title page	Replaces version added	Administrative update
Title page	Approval date added	Administrative update
1.1 Synopsis 1.2 Schema, 2 Introduction 3 Objectives and Endpoints 4 Study Design	Changed study design from Phase II to an adaptive Phase III design with adaptation rule based on OR	These changes are to allow sample size adjustment based on predefined criterion and adequately powered study for dual primary endpoints PFS and OS.

Section # and Name	Description of Change	Brief Rationale
CCI		
1.2 Schema	New figure was added for schema	New figure was added for schema to reflect the new study design.
CCI		
1.3 Schedule of Activities Table 1 Pretreatment and M7824 drug administration	Optional was added for premedication	To substantiate that premedication is optional
1.3 Schedule of Activities Table 1, Table 2, Table 3, and Table 4	Revised schedule of activities for hematology and hemostaseology, core serum chemistry, full serum chemistry panel	Text is modified for requirements of sample collection prior to dosing and deleted text on the need to have the results reviewed within 3 days prior to dosing
1.3 Schedule of Activities Table 1, Table 3, and Table 4, PRO questionnaires	From: If necessary, participants may complete the PRO questionnaires on a paper form, which will be transcribed to the electronic tablet by site staff To: If necessary, participants may complete the PRO questionnaires on a paper CRF (e.g., if an electronic tablet or site pad is not available), which will be transcribed to the electronic tablet by the site staff	Revised text is updated for clarity and consistency.
CCI		
CCI 2.3 Benefit/Risk assessment	Rationale was provided for the change in study design based on feedback from health authorities	CCI
1.1 Synopsis 2 Introduction 3 Objectives and Endpoints 4 Study Design CCI	Revised Primary Endpoints from PFS and OR to PFS and OS	Based on health authority recommendation.

Section # and Name	Description of Change	Brief Rationale
4.2.3 Open-Label Design	Addition of text: Access to aggregated analyses per treatment arm will be restricted to IDMC and Firewall Team as per corresponding charters.	To preserve data integrity
4.2.6 Adaptive Phase III Design	Added text to clarify changes on the study design	Added text to clarify changes on the study design and adequately powered study for dual primary endpoints PFS and OS.
4.4 End of Study Definition	Revised definition of end of study	Text is updated for consistency with current Sponsor standard
CCI		
5.2 Exclusion Criteria	Exclusion criteria # 4 was modified: From: These imaging scans should both be obtained at least 4 weeks apart and show no evidence of intracranial pressure. To: These imaging scans should both be obtained at least 2 weeks apart and show no evidence of intracranial pressure.	Text is updated to substantiate the design
5.2 Exclusion Criteria	Updated Bleeding language	Addition of new language as per feedback from IDMC
6.3.1 Study Intervention Assignment	IVRS changed to IWRS	As per the new intervention assignment method
6.8.1 Infusion-related Reactions Including Immediate Hypersensitivity	Updated premedication requirements	To substantiate that premedication is optional
6.8.4 Anemia	Table 10 Evaluation Guidance of Suspected Treatment-related Anemia Adverse Events is revised	Better understandable and more useful for clinical practice
6.8.5 Management of Bleeding Events	Addition of text: Low grade mucosal	New text for management of Grade 2 non-tumor bleeding
7.2 Participant Discontinuation/Withdrawal from the Study 8.2 Safety Assessments and Procedures	Deletion of text	Updated language as per new template
8.3.5 Pregnancy	Addition of new text	Updated language as per new template.
CCI		
9.3 Populations for Analyses	Primary analysis population revised to full analysis set, which includes all participants randomized according to the intention to treat (ITT) principle	To be compliant with health authority feedback and align with new study design

Section # and Name	Description of Change	Brief Rationale
9.4.1 Efficacy Analyses	Revision of text to align with modification of study design	These changes are to allow sample size adjustment based on predefined criterion and adequately powered study for dual primary endpoints PFS and OS.
10 References	Addition of reference "Chen C, Anderson K, Mehrotra DV, et al. A 2-in-1 adaptive phase 2/3 design for expedited oncology drug development. Contemp Clin Trials. 2018;64:238-42. "Ritchie G, Gasper H, Man J, et al. Defining the most appropriate primary end point in phase 2 trials of immune checkpoint inhibitors for advanced solid cancers. JAMA Oncol. 2018;4(4):522-28." "Yining Ye, Ai Li, Lingyun Liu and Bin Yao. A group sequential Holm procedure with multiple primary endpoints. Statistics in Medicine, 2012. 10.1002/sim.5700" Deletion of reference "Hommel G1, Bretz F, Maurer W. Powerful short-cuts for multiple testing procedures with special reference to gatekeeping strategies. Stat Med. 2007 Sep 30;26(22):4063-73."	References for the FWER control in the new adaptive phase III design
Appendix 5 The Recommendations for irAE Management in Accordance with the Joint American Society of Clinical Oncology Clinical Practice Guidelines and National Comprehensive Cancer Network	Revised the recommendations for immune-related adverse events (irAE) management	Revised to update irAE management guidelines and FDA recommendations. Instructions include the requirement that treatment must be permanently discontinued for certain Grade 4 irAE toxicities.
Throughout	Minor editorial and document formatting revisions	Minor text revisions are made for clarity, readability, consistency of language across the development program, and compliance with current Sponsor guidelines.

Protocol Version 2.1 (09 September 2019)

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

Overall Rationale for the Amendment

The protocol was amended based on feedback from the regulatory agencies of countries in the European Union participating in the VHP.

Section # and Name	Description of Change	Brief Rationale
Title page	Protocol version number is updated	To reflect current amendment
Section 4.2.2 Pembrolizumab as Comparator	The results from KN-042 are deleted. In addition, it is specified that for pembrolizumab in patients with Stage 3 NSCLC, the EMA assessment is still ongoing.	To clarify the approval status of pembrolizumab in EU.
Section 6.9.5 Management of Bleeding Events	"For Grade 2 non-tumor bleeding, see Section 6.8.2 for general management of Grade 2 ADRs." Is added	To clarify the management for Grade 2 non-tumor bleeding events.
Section 9.4.1 Efficacy Analyses	"Intention-to-Treat (mITT)" is changed to "mITT"	This should be modified Intention-to-Treat, as mITT is defined in Section 4.1, therefore "mITT" is used.
Appendix 9 10, 11, 12	Protocol version number and amendment history is updated	To reflect current amendment

Protocol Version 2.0 (08 July 2019)

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

Overall Rationale for the Amendment

The protocol was amended to incorporate feedback on immune-related adverse event management guidelines from the FDA.

Section # and Name	Description of Change	Brief Rationale
Title Page, 2 Introduction, 4.3 Justification for Dose, 5.1 Inclusion Criteria, 8.3.4 Regulatory Reporting Requirements for Serious Adverse Events, Appendix 2 Study Governance, Appendix 3 Contraception, Appendix 5 The Recommendations for irAE Management	Text revised to clarify procedures for sites based in Japan, per Protocol Amendment 1.1	To be compliant with Japan regulatory requirement and local law
1.3, Schedule of Activities, 3 Objectives and Endpoints, 8.10 Patient-Reported Outcomes	[redacted]	
1.3, Schedule of Activities		
1.3, Schedule of Activities;		

Section # and Name	Description of Change	Brief Rationale
CCI		
4.2.2 Pembrolizumab as Comparator	Added most recent approval for Pembrolizumab therapy	To include most recent data
4.3 Justification for Dose	Amended Phase I safety, CCI, and preliminary efficacy analysis information	To include most recent data
5.1 Inclusion Criteria, Appendix 3	Revised criteria for contraception	Text is updated for consistency with current Sponsor standards and consistency across the development program.
5.2 Exclusion Criteria	Exclusion Criterion 1 was updated to clarify details of molecular alterations Exclusion Criterion 7 was modified to clarify excluded hypersensitivity reactions. Exclusion Criterion 11 was updated to exclude major bleeding events Exclusion Criterion 17 updated participants cannot be enrolled if participated in another clinical study within 4 weeks of first dose	To clarify and provide further information Text is updated in line with other study requirements. This change is to complete the exclusion criterion by including excipients in investigational product (M7824 or pembrolizumab). To exclude participants with history of bleeding diatheses or recent major bleeding events To align with M7824 program
5.4 Screen Failures	Added text to specify conditions which a participant can be rescreened	To clarify re-screening procedures
6.3.1 Study Intervention Assignment	Removed reference to IWRS	To clarify study will use IVRS
6.4 Study Intervention Compliance	Amended text on nonadherence	To clarify criterion for nonadherence to study treatment
6.5.2 Prohibited Medicines, Appendix 4	Added text clarifying use of traditional Chinese medicines and a list of prohibited medicines.	This change is to indicate traditional Chinese medicines with anticancer properties are prohibited.
6.6 Dose Selection and Modification	Added text regarding dose delay beyond treatment window	To clarify dose cannot be delayed beyond treatment window and should be skipped if missed
6.8.2 Immune-related Adverse Events	Added text regarding Grade 4 events requiring permanent treatment discontinuation	This change is made for consistency with current risk information.
6.8.3 Potential TGFβ-mediated Skin Adverse Events	Updated text for management of potential TGFβ-mediated skin events	To update in line with skin toxicity guidelines
6.8.5 Management of Bleeding Events	Added text to describe management of bleeding events	Revised to update irAE management guidelines and FDA recommendations. Instructions include the requirement that treatment must be permanently discontinued for certain Grade 4 irAE toxicities.
6.9.1.2 Potential Risks	Added text to describe mucosal	This change is made for consistency with

Section # and Name	Description of Change	Brief Rationale
	bleeding events	current risk information.
6.9.2 Adverse Drug Reactions Requiring Treatment Discontinuation	Added text to describe management of bleeding events	This change is made for consistency with current risk information.
6.9.2 Adverse Drug Reactions Requiring Treatment Discontinuation	Included management of bleeding events	To provide risk management for bleeding events.
8.1 Efficacy Assessments and Procedures	Added text to describe allowances for CT scan	To clarify procedures for CT scan
9.3 Populations for Analyses	CCI	
Appendix 5 The Recommendations for irAE Management	CCI	
Appendix 6	Modified nonserious AESI reporting	Discontinued expedited reporting of nonserious AESIs
Throughout	Minor editorial and document formatting revisions	Minor text revisions are made for clarity, readability, consistency of language across the development program, and compliance with current Sponsor guidelines.

Protocol Version 1.3 (01 September 2018)

Overall Rationale for the Amendment

The protocol was amended for compliance with local requirements.

Section # and Name	Description of Change	Brief Rationale
Section 1.3, Schedule of Activities; Table 1 and Table 3	CCI	
Section 5.2, Exclusion Criteria	Exclusion Criterion 7 was modified to clarify excluded hypersensitivity reactions.	This change is to clarify the exclusion criterion by including excipients in investigational product (M7824 or pembrolizumab) consistent with the pembrolizumab label in China.
CCI		

Protocol Version 1.2 (25 July 2018)

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

Overall Rationale for the Amendment

The protocol was amended based on feedback from the regulatory agencies of countries in the European Union participating in the VHP.

Section # and Name	Description of Change	Brief Rationale
Section 5.2, Exclusion Criteria	Exclusion Criterion 7 was modified to clarify excluded hypersensitivity reactions.	This change is to complete the exclusion criterion by including excipients in investigational product (M7824 or pembrolizumab).
Section 9.2, Sample Size Determination, Table 13	A footnote was added to clarify the study operating characteristics.	This change is to clarify the sample size calculations.

Protocol Version 1.1-JPN (02 August 2018)

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

Overall Rationale for the Amendment

The rationale for change is to align Japan-GCP and local regulatory requirements in Japan.

Section # and Name	Description of Change	Brief Rationale
Title Page, Sponsor Name and Legal Registered Address	Added the Sponsor name and address in Japan	To be compliant with Japan regulatory requirement
2 Introduction	Added a note to an indication which is not approved in Japan	To be compliant with Japan regulatory requirement
4.3 Justification for Dose	Added a sentence about the findings regarding exposure in Asian and non-Asian subjects	To provide the information supporting the dose rationale in Japanese.
5.1 Inclusion Criteria	Added a note for the consent when a patient is < 20 years of age	A person needs to be 20 years or over to be recognized as an adult under the Japanese law.
5.2 Exclusion Criteria	Exclusion Criterion 7 was modified to clarify excluded hypersensitivity reactions.	This change is to complete the exclusion criterion by including excipients in investigational product (M7824 or pembrolizumab) to be compliant with Japanese pembrolizumab label.

Section # and Name	Description of Change	Brief Rationale
8.3.4 Regulatory Reporting Requirements for Serious Adverse Events	Replaced the mandatory text to the one for studies to be conducted in Japan	To be compliant with Japan regulatory requirement
Appendix 2 Study Governance, Study Administrative	Added the Sponsor name in Japan Added the Japanese ministerial ordinance on GCP Added a reference to a supporting document	To be compliant with Japan regulatory requirement To clarify where to find the organization and site information in Japan.
Appendix 2 Study Governance, Regulatory and Ethical Considerations	Added the mandatory text for studies to be conducted in Japan	To be compliant with Japan regulatory requirement
Appendix 2 Study Governance, Clinical Study Insurance and Compensation to Participants	Added the mandatory text for studies to be conducted in Japan	To be compliant with Japan regulatory requirement
Appendix 2 Study Governance, Source Documents	Replaced the mandatory text to the one for studies to be conducted in Japan	To be compliant with Japan regulatory requirement
Appendix 3 Contraception	Added a note to contraception which is not approved in Japan	To be compliant with Japan regulatory requirement
Table A2 Management of GI irAEs in Patients Treated With ICPis	Added a note to a medication which is not approved in Japan	To be compliant with Japan regulatory requirement

Appendix 10 Sponsor Signature Page

Study Title:	An Adaptive Phase III, Multicenter, Randomized, Open-Label, Controlled Study of M7824 (bintrafusp alfa) versus Pembrolizumab as a First-line Treatment in Patients with PD-L1 Expressing Advanced Non-small Cell Lung Cancer
Regulatory Agency Identifying Numbers:	CCI [redacted] EudraCT 2018-001517-32
Clinical Study Protocol Version:	22 June 2021/Version 4.0

I approve the design of the clinical study:

_____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	
Institution:	EMD Serono Research & Development Institute, Inc., an affiliate of Merck KGaA
Address:	45A Middlesex Turnpike Billerica, MA 01821, USA
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Appendix 11 Coordinating Investigator Signature Page

Study Title:	An Adaptive Phase III, Multicenter, Randomized, Open-Label, Controlled Study of M7824 (bintrafusp alfa) versus Pembrolizumab as a First-line Treatment in Patients with PD-L1 Expressing Advanced Non-small Cell Lung Cancer
Regulatory Agency Identifying Numbers:	CCI EudraCT 2018-001517-32
Clinical Study Protocol Version:	22 June 2021/Version 4.0
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.

_____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	Coordinating Investigator
Institution:	PPD
Address:	PPD
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Appendix 12 Principal Investigator Signature Page

Study Title:	An Adaptive Phase III, Multicenter, Randomized, Open-Label, Controlled Study of M7824 (bintrafusp alfa) versus Pembrolizumab as a First-line Treatment in Patients with PD-L1 Expressing Advanced Non-small Cell Lung Cancer
Regulatory Agency Identifying Numbers:	CCI [redacted] EudraCT 2018-001517-32
Clinical Study Protocol Version:	22 June 2021/Version 4.0
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:	[Insert Name and highest degree or for a single center study, insert from Title Page]
Function/Title:	
Institution:	[Insert Name of Institution or for a single center study, insert from Title Page]
Address:	[Insert Full Mailing Address (eg, Street, City, postal code, and Country)]
Telephone number:	[Insert Full number, including country code]
Fax number:	[Insert Full number, including country code]
E-mail address:	