Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase II, Multicenter, Randomized, Open-Label, Controlled Study of M7824 versus Pembrolizumab as a First-line Treatment in Patients with PD-L1 Expressing Advanced Non-small Cell Lung Cancer
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1 Protocol Summary

1.1 Synopsis

Protocol Title: A Phase II, Multicenter, Randomized, Open-Label, Controlled Study of M7824 versus Pembrolizumab as a First-line Treatment in Patients with PD-L1 Expressing Advanced Non-small Cell Lung Cancer

Short Title: 1L NSCLC Phase II 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 Phase II study is to evaluate whether M7824 improves progression-free survival (PFS) time and/or best overall response (BOR) compared with pembrolizumab as a first-line (1L) treatment for participants with, advanced non-small cell lung cancer (NSCLC) with PD-L1 tumor expression. The NSCLC second-line (2L) cohort in the EMR200647-001 study observed an objective response rate (ORR) according to independent assessment of 37.0% (95% CI: 19.4, 57.6) in PD-L1 positive tumors (≥1%) and at 85.7% (95% CI: 42.1, 99.6) in participants with PD-L1 high tumors (≥ 80%) dosed at 1200 mg; historically, response rates to PD-L1 monotherapy in 2L NSCLC with PD-L1 high tumors ranged from 29% to 41%. In 2L PD-L1 positive NSCLC tumors (≥1% by the PD-L1 IHC 22C3 pharmDx assay), an ORR of 18.0% to 18.5% was observed in patients treated with pembrolizumab. Furthermore, as seen with other checkpoint inhibitor NSCLC studies, the ORR in patients treated with M7824 is expected to increase when moving from 2L to 1L. In the KEYNOTE-024 study, the ORR of 1L monotherapy pembrolizumab in participants with advanced NSCLC and PD-L1 high expressing tumors was 44.8%. Improving the response to first-line treatment with a noncytotoxic therapy would be clinically meaningful to patients. This study will evaluate disease response and survival primary endpoints to assess clinical benefit. 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)	Timeframe
Primary		
To evaluate whether M7824 improves ORR compared with pembrolizumab in first-line participants with advanced NSCLC with high PD-L1 tumor expression	BOR according to RECIST 1.1 assessed by IRC	Time from randomization to planned final assessment for unconfirmed BOR, expected at 26 months.
To evaluate whether M7824 improves PFS compared with pembrolizumab in first-line participants with advanced NSCLC with high PD-L1 tumor expression	PFS according to RECIST 1.1 assessed by IRC	Time from randomization to planned final assessment for PFS after 192 events expected at 37 months.

Objectives	Endpoints (Outcome Measures)	Timeframe
Secondary		
• Safety To evaluate the safety and tolerability of M7824 compared with pembrolizumab	• Occurrence of TEAEs and treatment-related AEs according to NCI-CTCAE v5.0	From randomization to the last safety follow-up visit, expected at approximately 47 months.
• Efficacy - To evaluate whether M7824 improves overall survival time compared with pembrolizumab	• OS	From randomization to when 200 OS events occur; OS PA expected at 49 months from first participant in the study.[a]
- ORR assessed by Investigators	• BOR according to RECIST 1.1 assessed by Investigator	Time from randomization to planned final assessment for unconfirmed BOR, expected at 26 months.
- PFS assessed by Investigators	• PFS according to RECIST 1.1 assessed by Investigator	Time from randomization to planned final assessment for PFS after 192 events expected at 37 months.
- DOR	• DOR assessed from CR or PR according to RECIST 1.1 assessed by IRC until PD, death, or last tumor assessment	Time from CR or PR to planned endpoint after 192 PFS events, expected at 37 months.
• PK To characterize PK profile of M7824	PK profile of M7824 in terms of C_{eoi} PK profile of M7824 in terms of Ctrough	Predose samples at Weeks 1,3,5,7 then 6 weekly during treatment; postdose (within 30 min) samples at 6 weekly during treatment and up to study's Safety Follow-up Visit at 28 days after last study intervention administration.
• Immunogenicity To characterize the immunogenicity of M7824	Immunogenicity as measured by ADA assays at Baseline and on-treatment.	From randomization up to study's Safety Follow-up Visit, defined as 28 days after last study intervention administration.

ADA = anti-drug antibodies; AE = adverse event; BOR = best overall response; C_{eoi} = concentration at end of infusion; Ctrough = concentration at the end of the dosing interval; CR = complete response; DOR = duration of response; IRC = Independent Review Committee; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PA = primary analysis; PD = progressive disease; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; TEAE = treatment-emergent adverse event.

a At discretion of Sponsor, may extend survival analysis for all participants..

Overall Design: This is a multicenter, 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. 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 (tumor proportion score [TPS]) as determined by the 73-10 assay. Participants with TPS ≥ 50% as determined by the PD-L1 IHC 22C3 pharmDx assay performed according to local

laboratory regulations prior to study enrollment are also eligible. Participants who have not received previous treatment for their advanced NSCLC will be enrolled in this study for examination of the efficacy and safety of M7824 versus pembrolizumab. These participants must not have EGFR sensitizing mutation or ALK translocation, ROS1 mutation, or BRAF V600E mutation if targeted therapy is locally approved.

Number of Participants: A sample size of 300 randomized participants is planned in order to observe 192 PFS events (tumor progression or death due to advancing disease) at the primary analysis, which is projected for 37 months after the first participant is randomized. Assuming a PD-L1 high proportion of approximately 20%, the screening failure rate is at least 80% and 1500 participants need to be screened.

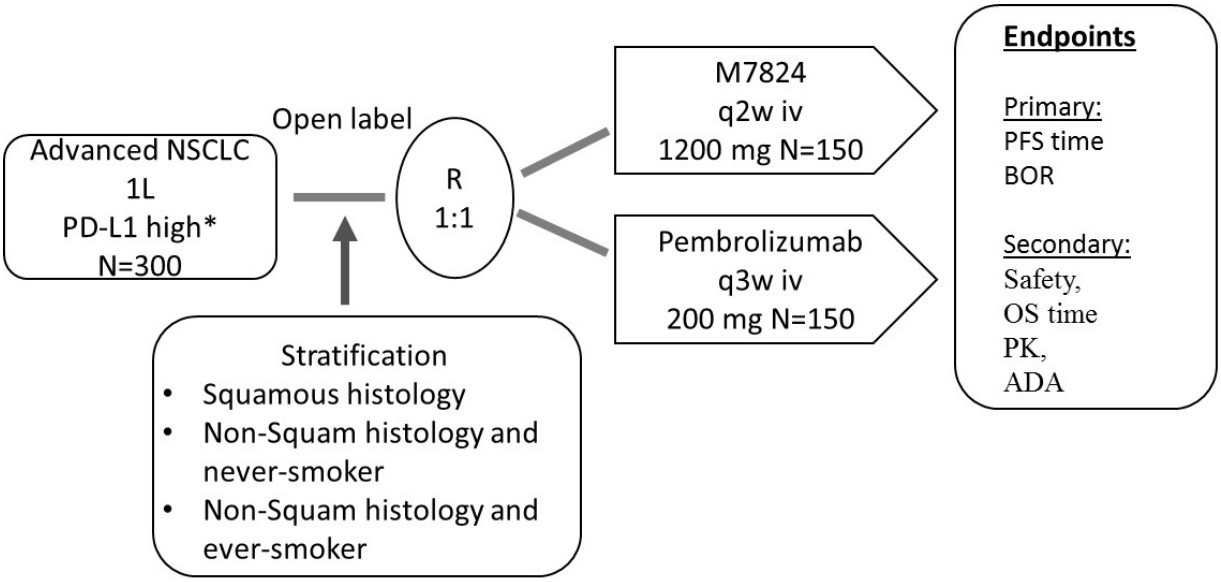
Study Intervention Groups and Duration: Participants who meet the study criteria will be randomly assigned in a 1:1 ratio to receive either:

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

Involvement of Special Committee(s): Yes

1.2 Schema

Figure 1 Diagram of Study Design



* PD-L1 high is defined as ≥ 80% PD-L1 positive tumor cells as determined by the 73-10 assay. Participants with TPS ≥ 50% as determined by the PD-L1 IHC 22C3 pharmDx assay performed according to local laboratory regulations prior to study enrollment are also eligible.

ADA = anti-drug antibodies; BOR = best overall response; 1L = first-line; IHC = immunohistochemistry; iv = intravenously; NSCLC = non-small cell lung cancer; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PK = pharmacokinetic; q2w = every 2 weeks; q3w = every 3 weeks; R = randomization; squam = squamous; TPS = tumor proportion score.

1.3 Schedule of Activities

Table 1 Schedule of Assessments – M7824 Arm

M7824 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	W3	W5	W7	W9	W11	W13			
		D1	D15	D29	D43	D57	D71	D85			
Administrative Procedures											
Written informed consent	X										To determine the main study eligibility criteria ahead of full screening procedures, a prescreening ICF may be used.
Inclusion/ exclusion/ Enrollment (if eligible)	X	Xa									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 Assess-ments	Treatment Phase (±3 days)								End-of-Treatment Visit	Notes
	Day -28 to Randomi-zation	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											
Tumor tissue collection	X				X[c]					X[c]	Tumor tissue Availability of either tumor archival material (< 6 months old) or fresh biopsies collected within 28 days (excluding bone biopsies) before the first dose is mandatory to determine PD-L1 expression level prior to enrollment. If participant received local therapy (ie, RT or CRT) after the archival biopsy was taken, a fresh biopsy will be required prior to study entry. Participants who previously had PD-L1 high results (via the PD-L1 IHC 22C3 pharmDx assay performed according to local laboratory regulations) on tissue < 6 months old will be eligible for enrollment after verification of source documentation and prior to internal PD-L1 testing. However, adequate tissue for biomarker testing must be confirmed prior to the first dose. c: Week 7 and EoT biopsies are optional. Tissue from unscheduled procedures may also be submitted (see Section 8.8).
Pretreatment and M7824 Drug Administration											
Pretreatment and M7824 drug administration		X	X	X[d]	X[d]	X[d]	X[d]	X[d]	2-weekly[d]		Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose is mandatory only for the first 2 infusions (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol iv or oral equivalent). d: Premedication is not required after the first 2 doses if no IRR (see Section 6.8.1).

M7824 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	W3	W5	W7	W9	W11	W13			
		D1	D15	D29	D43	D57	D71	D85			
Safety Assessments											
Documentation of AEs	X	X	X	X	X	X	X	X	2-weekly	X	Adverse events will be documented at each visit
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	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[e]	X	X[e]	X	X	X	X	X	X	2-weekly	X	e: 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 prior to dose administration and results to be reviewed within 48 hours. 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 prior to dose administration and results to be reviewed within 48 hours. 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.

M7824 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	W3	W5	W7	W9	W11	W13			
		D1	D15	D29	D43	D57	D71	D85			
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 prior to dose administration and results to be reviewed within 48 hours.
Full serum chemistry Panel B	X										See Table 16 for individual tests in each laboratory panel.
Urinalysis	X	As clinically indicated									
β-hCG pregnancy test (only applicable to WOCBP)	X[f]	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. f: If a confirmation of a participant's postmenopausal status is necessary, follicle-stimulating hormone and estradiol tests will be performed at Screening.
T_4 and TSH	X				X			X	6-weekly		
Patient-reported Outcomes											
PRO questionnaires: EORTC-QLQ-C30, NSCLC-SAQ & EQ-5D-5L	X	X			X			X	6-weekly	X	The patient-reported outcomes/quality of life questionnaires (EQ-5D-5L, NSCLC-SAQ, and EORTC-QLQ-C30) should be completed in the same sequence at the indicated visits, using a validated electronic tablet, validated site pad format by all participants prior to any of the other study-related assessments being performed, that is, physical examinations, blood draws, study intervention administration, etc. as feasible

M7824 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	W3	W5	W7	W9	W11	W13			
		D1	D15	D29	D43	D57	D71	D85			
Tumor Assessments											
Tumor evaluation/staging (CT Scan/MRI/ other established methods)	X				X			X	6 weekly up to 18 months then 12 weekly		Confirmation of CR and/or PR should be performed preferably at the next regularly scheduled 6 weekly assessment, but no sooner than 4 weeks after the initial documentation. A brain CT/MRI scan is required at Screening if not performed within 6 weeks prior to randomization, and beyond as clinically indicated. A bone scan should be done as clinically indicated at Screening and beyond. Bone metastases detected at Screening need to be followed at the tumor evaluation visits.
PK, ADA and Biomarker											
PK and ADA sampling	See Table 2 for PK and ADA sampling times										
Whole blood for pharmaco-genetics		X									Whole blood sample for participants who provide separate informed consent.
Blood sample for TMB		X			X					X	Blood samples for TMB will be collected prior to study intervention infusion as scheduled
Pharmaco-dynamic biomarkers	X	X/X (pre/ post-dose)	X/X (pre/ post-dose)	X/- (pre-dose)							Predose samples are collected prior to infusion. Postdose samples are collected within 30 minutes post end of infusion. Baseline sample is optional.

M7824 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	W3	W5	W7	W9	W11	W13			
		D1	D15	D29	D43	D57	D71	D85			

ADA = anti-drug antibody; AE = adverse events; 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; EORTC-QLQ-C30 = 30-item European Organisation for Research and Treatment of Cancer-Quality of Life Department scale; EoT = End-of-Treatment; EQ-5D-5L = European Quality Of Life 5-dimensions 5-level questionnaire; HBV = hepatitis B virus; HCV = hepatitis C virus; IHC = immunohistochemistry; IRR = infusion-related reaction; iv = intravenous; MRI = magnetic resonance imaging; NSCLC-SAQ = non-small cell lung cancer symptom assessment questionnaire; PD = progressive disease; PD-L1 = programmed death-ligand 1; PE = physical examination; PK = pharmacokinetics; PR = partial response; PRO = patient-reported outcome; RT = radiation therapy; T_4 = free thyroxine; TMB = Tumor mutational Burden; TSH = thyroid-stimulating hormone; V = Visit; W = Week; WOCBP = woman of childbearing potential.

Table 2 M7824 Arm Pharmacokinetic and Immunogenicity Sampling

M7824 Assessment	Screening / Baseline Assessments	Treatment Phase (±3days)						End-of-Treatment Visit	Safety Follow-up Visit		Notes
		V1	V2	V3	V4	V7					
		W1	W3	W5	W7	W13					
	Day -28 to Randomization	D1 pre/end infusion	D15 pre/end infusion	D29 pre/end infusion	D43 pre/end infusion	D85 pre/end infusion	Until Progression preinfusion	On the Day of or Within 7 Days of Decision	Up to 28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment	
Blood sample for PK		X/X	X/-	X/-	X/X	X/X	6 weekly	X	X		Samples for PK analysis to be taken before (pre) infusion (as close to the start of the infusion as possible), immediately after the completion of infusion (end, as close to the completion as possible but no later than 30 minutes post end of infusion). The predose sample should still be drawn even if dosing is ultimately deferred at the study visit. The exact time of each draw must be recorded. A protocol deviation will be defined by a sample not being drawn.
Blood sample for ADA		X/-	X/-	X/-	X/-	X/-	6 weekly to/including Week 25, then every 12 weeks.	X	X		Blood samples for ADA analysis will be collected prior to study intervention infusions as scheduled while on treatment, and at the End-of-Treatment Visit, and remaining sample from this visit may be used to test for PK.

ADA = anti-drug antibody; D = Day; PK = pharmacokinetics; V = Visit; W = Week.

Table 3 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, a prescreening ICF may 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]	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			
Tumor Biopsies/Archival Tissue Collection											
Tumor tissue collection	X			X[c]						X[c]	Tumor tissue Availability of either tumor archival material (< 6 months old) or fresh biopsies collected within 28 days (excluding bone biopsies) before the first dose is mandatory to determine PD-L1 expression level prior to enrollment. If participant received local therapy (ie, RT or CRT) after the archival biopsy was taken, a fresh biopsy will be required prior to study entry. Participants who previously had PD-L1 high results (via the PD-L1 IHC 22C3 pharmDx assay performed according to local laboratory regulations) on tissue < 6 months old will be eligible for enrollment after verification of source documentation and prior to internal PD-L1 testing. However, adequate tissue for biomarker testing must be confirmed prior to the first dose. c: Week 7 and EoT biopsies are optional. Tissue from unscheduled procedures may also be submitted (see Section 8.8).
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	Adverse events will be documented at each visit.

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			
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	6-weekly	X	
Vital signs	X	X	X	X	X	X	X	X	3-weekly	X	Including weight and height (height at Screening only)
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 prior to dose administration and results to be reviewed within 48 hours. 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 prior to dose administration and results to be reviewed within 48 hours. 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 prior to dose administration and results to be reviewed within 48 hours.

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			
Full serum chemistry Panel B	X										See Table 16 for individual tests in each laboratory panel.
Urinalysis	X	As clinically indicated									
β-hCG pregnancy test (only applicable to WOCBP)	X[e]	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.
T_4 and TSH	X			X		X		X	6-weekly		
Patient-reported Outcomes											
PRO questionnaires: EORTC-QLQ-C30, NSCLC-SAQ, and EQ-5D-5L	X	X		X		X		X	6-weekly	X	Patient-reported outcomes/quality of life questionnaires (EQ-5D-5L, NSCLC-SAQ and EORTC-QLQ-C30) should be completed in the same sequence at the indicated visits, using a validated electronic tablet, validated site pad format by all participants prior to any of the other study-related assessments being performed, that is, physical examinations, blood draws, study intervention administration, etc. as feasible

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			
Tumor Assessments											
Tumor evaluation/staging (CT Scan/MRI/other established methods)	X			X		X		X	6 weekly up to 18 months then 12 weekly		Confirmation of CR and/or PR should be performed preferably at the next regularly scheduled 6-week assessment, but no sooner than 4 weeks after the initial documentation. A brain CT/MRI scan is required at Screening if not performed within 6 weeks prior to randomization, and beyond as clinically indicated. A bone scan should be done as clinically indicated at Screening and beyond. Bone metastases detected at Screening need to be followed at the tumor evaluation visits.
PK, ADA and Biomarker											
Whole blood for pharmacogenetics		X									Whole blood sample for participants who provide separate informed consent.
Blood sample for TMB		X		X						X	Blood samples for TMB will be collected prior to study intervention infusion as scheduled
Pharmacodynamic biomarkers	X	X/X (pre/ post-dose)	X/X (pre/ post-dose)	X/- (pre-dose)							Predose samples are collected prior to infusion. Postdose samples are collected within 30 minutes post end of infusion. Baseline sample is optional.

ADA = anti-drug antibody; AE = adverse events; 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; EORTC-QLQ-C30 = 30-item European Organisation for Research and Treatment of Cancer-Quality of Life Department scale; EoT = End-of-Treatment; EQ-5D-5L = European Quality Of Life 5-dimensions 5-level questionnaire; HBV = hepatitis B virus; HCV = hepatitis C virus; IHC = immunohistochemistry; MRI = magnetic resonance imaging; NSCLC-SAQ = non-small cell lung cancer symptom assessment questionnaire; PD = progressive disease; PE = physical examination; PK = pharmacokinetics; PR = partial response; PRO = patient-reported outcome; RT = radiation therapy; T_4 = free thyroxine; TMB = Tumor mutational Burden; TSH = thyroid-stimulating hormone; V = visit; W = Week; WOCBP = woman of childbearing potential.

Table 4 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 3 months (± 1 week)	
Documentation concomitant therapy	X	X		X	
Documentation of AEs	X	X		[a,b]	Main questions include any new safety concerns, any new anticancer treatment started (details with dates), and participant death. Any SAE assessed as related to study intervention must be reported whenever it occurs, irrespective of the time elapsed since the last administration of study intervention. a: May be conducted via phone call in long-term follow-up phase. 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.
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.
T_4 and TSH	X				
PRO: EORTC-QLQ-C30, NSCLC-SAQ, and EQ-5D-5L	X	X			The patient-reported outcomes/quality of life questionnaires (EQ-5D-5L, NSCLC-SAQ, and EORTC QLQ-C30) should be completed in the same sequence at the indicated visits, using a validated electronic tablet, validated site pad format prior to any of the other study-related assessments being performed.

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 3 months (± 1 week)	
Subsequent anticancer therapy (any line)	X	X	X		
Survival follow-up				X	
Response and progression on subsequent (2L) treatment		X	X		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 Documentation should continue to occur until progression on subsequent 2L treatment, start of next line (ie, 3L) treatment, withdrawal of consent, or death. Progression can be defined radiographically, symptomatically, or if participant dies due to advancing disease.
Tumor evaluation/staging (CT Scan/MRI/other established methods)	X	X[b]	X[b]		b: Tumor evaluations should continue to be performed and documented by Investigator per local clinical practice on subsequent (ie, 2L treatment). This is encouraged to occur every 6 weeks. These scans should be continued until progression, start of next line (ie, 3L) treatment, withdrawal of consent, or death. These evaluation scans should be documented by the Investigator and uploaded to the imaging repository, if available.

AE = adverse event; β-hCG = beta-human chorionic gonadotropin; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC-QLQ-C30 = 30-item European Organisation for Research and Treatment of Cancer-Quality of Life Department scale; EQ-5D-5L = European Quality Of Life 5-dimensions 5-level questionnaire; MRI = magnetic resonance imaging; NSCLC-SAQ = non-small cell lung cancer symptom assessment questionnaire; PE = physical examination; PRO = patient-reported outcome; 2L = second line; SAE = serious adverse event; T_4 = free thyroxine; 3L = third line; TSH = thyroid-stimulating hormone.

2 Introduction

M7824 (MSB0011359C) 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. The anti-PD-L1 moiety of M7824 is identical to the Sponsor's anti-PD-L1 monoclonal antibody avelumab (Bavencio®), except for 3 amino acid substitutions in the heavy chain constant regions that result in a different human immunoglobulin (Ig) G1 allotype, and 1 amino acid substitution in the heavy chain for antibody fusion protein stability. Avelumab has been approved for metastatic Merkel cell carcinoma and locally advanced or metastatic urothelial carcinoma.

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, Phase II, randomized, controlled study is to evaluate whether M7824 improves progression-free survival (PFS) and/or objective response rate (ORR) 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.

2.1 Study Rationale

Immune checkpoint inhibitors have shown improved treatment outcome in patients with NSCLC; however, there is room to further improve benefits. A novel agent such as M7824, which targets the tumor microenvironment where it blocks both the cell intrinsic PD-L1/PD-1 interaction and the immunosuppressive TGFβ, is hypothesized to be more effective than agents that target only a single pathway.

M7824 has demonstrated an acceptable safety profile to date in patients with solid tumors, including NSCLC (refer to current Investigator's Brochure). The maximal tolerated dose was not reached in up to 30 mg/kg in the dose escalation part of the global Phase I Study EMR200647-001. The pooled safety from 10 expansion cohorts from EMR200647-001 showed that most of the observed events were either in line with those expected in participants with advanced solid tumors or with similar class effects of monoclonal antibodies (mAb) blocking the PD-1/PD-L1 axis. Immune-related AEs (irAEs) and infusion-related reactions (IRRs) are identified as risks for both M7824 and pembrolizumab. In addition, skin adverse events (AEs) attributed to TGFβ are other adverse events of special interest (AESI) for M7824. While skin lesions due to TGFβ inhibition are an identified risk for M7824, they have been manageable and have not lead to permanent discontinuations in Studies EMR200647-001 or MS200647-0008. M7824 was evaluated at 2 dose levels (500 and 1200 mg) in a total of

80 participants in the second-line (2L) NSCLC cohort in EMR200647-001, the safety profiles were comparable at the 2 dose levels.

M7824 has demonstrated promising antitumor activities in Phase I studies. The response rate from the 80 participants in the 2L NSCLC cohort (none of whom received prior immunotherapy), at the time of primary analysis (24 weeks after the first dose in the last participant) are summarized in Table 5. Notably, response rates significantly improved at higher PD-L1 tumor cell expression. In participants treated at 1200 mg, the recommended Phase II dose (RP2D) of M7824, ORR was 25.0% in all-comers, 37.0% in participants with PD-L1 positive tumors (≥ 1%), 20% in PD-L1 low tumors (≥ 1% and < 80%), and 85.7% in PD-L1 high tumors (≥ 80%).

This subgroup analysis of the efficacy data based on PD-L1 was conducted using the 73-10 assay to determine the PD-L1 expression level on tumor cells (Table 5).

Table 5 Response Rates of M7824 in EMR200647-001 Second-line NSCLC Cohort

	BOR n (%)		ORR		DCR	
	PR	SD	%	95% CI	%	95% CI
Overall						
Regardless of PD-L1 status (N=80)	17 (21.3)	12 (15.0)	21.3	(12.9, 31.8)	36.3	(25.8, 47.8)
< 1% PD-L1+ (N=17)	1 (5.9)	3 (17.6)	5.9	(0.1, 28.7)	23.5	(6.8, 49.9)
≥ 1% PD-L1+ a (N=58)	16 (27.6)	9 (15.5)	27.6	(16.7, 40.9)	43.1	(30.2, 56.8)
≥ 1% and < 80% PD-L1+ (N=45)	8 (17.8)	9 (20.0)	17.8	(8.0, 32.1)	37.8	(23.8, 53.6)
≥ 80% PD-L1+ a (N=13)	8 (61.5)	0 (0.0)	61.5	(31.6. 86.1)	61.5	(31.6, 86.1)
PD-L1 unknown (N=5)	0 (0.0)	0 (0.0)	0.0	(0.0, 52.2)	0.0	(0.0, 52.2)
1200 mg						
Regardless of PD-L1 status (N=40)	10 (25.0)	8 (20.0)	25.0	(12.7, 41.2)	45.0	(29.3, 61.5)
< 1% PD-L1+ (N=10)	0 (0.0)	3 (30.0)	0.0	(0.0, 30.8)	30.0	(6.7, 65.2)
≥ 1% PD-L1+ a (N=27)	10 (37.0)	5 (18.5)	37.0	(19.4, 57.6)	55.6	(35.3, 74.5)
≥ 1% and < 80% PD-L1+ (N=20)	4 (20.0)	5 (25.0)	20.0	(5.7, 43.7)	25.0	(8.7, 49.1)
≥ 80% PD-L1+ a (N=7)	6 (85.7)	0 (0.0)	85.7	(42.1, 99.6)	85.7	(42.1, 99.6)
PD-L1 unknown (N=5)	0 (0.0)	0 (0.0)	0.0	(0.0, 70.8)	0.0	(0.0, 70.8)
500 mg						
Regardless of PD-L1 status (N=40)	7 (17.5)	4 (10.0)	17.5	(7.3, 32.8)	27.5	(14.6, 43.9)

Source: 15DEC201715.2.1.2P5, 15.2.10.8P5 and 15.2.10.11P5

BOR = confirmed best overall response by Independent Review Committee; DCR = disease control rate; IHC = immunohistochemistry; ORR = objective response rate; PD-L1 = programmed death-ligand 1; PR = partial response, SD = stable disease.

a Dako PD-L1 IHC test (clone 73-10).

Compared with the 22C3 assay (approved in the USA and other regions), the 73-10 assay seems to be more sensitive with 80% PD-L1 positive tumor most similar to tumor proportion score

(TPS) 50% as determined by the 22C3 assay used for studies with pembrolizumab. The 73-10 assay was developed at Dako North America, Inc. and has been analytically verified per internal procedures. The overall percentage agreement between the 73-10 and 22C3 assays from 148 commercial tumor samples was 93.9% (95% CI: 88.8% to 97.2%), positive percent agreement was 80% (95% CI: 63.1% to 91.6%), and negative percent agreement 98.2% (95% CI: 98.3% to 99.8%), using the ≥80% cut-off for 73-10 and TPS ≥50% for 22C3 using 73-10 as non-reference standard.

Based on the acceptable safety profile and promising antitumor activity which improved in participants with PD-L1 high NSCLC, this Phase II, randomized, controlled study is to evaluate whether M7824 improves PFS and/or best overall response (BOR) compared with pembrolizumab as a first-line (1L) treatment for participants with advanced NSCLC with high PD-L1 tumor expression. The promising activity of M7824 observed as a 2L treatment is expected to translate or increase as a 1L therapy as seen in other checkpoint inhibitor NSCLC studies. 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 approved locally.

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 ≥ 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 overall survival (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 6.

Table 6 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

IC = tumor infiltrating immune cells; mOS = median overall survival; mPFS = median progression-free survival; NE = not evaluated; NR = not reported; ORR = objective response rate; PD-L1 = programmed death-ligand 1; TC = tumor cells; TPS = tumor proportion score.
(Reck, 2016; Carbone, 2017; Peters, 2017)

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 anti-PD-L1 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 7.

Table 7 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)

IC = tumor infiltrating immune cells; mOS = median overall survival; mPFS = median progression-free survival; NE = not evaluated; NR = not reported; ORR = objective response rate; PD-L1 = programmed death-ligand 1; TC = Tumor cells; TPS = tumor proportion score.
(Brahmer, 2015; Borghaei, 2015; Herbst, 2016; Fehrenbacher, 2016)

The clinical profile of M7824 is being evaluated in 2 ongoing Phase I studies (EMR200647-001 and EMR200647-0008) 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, PD-L1-positive, and, respectively, PDL1-high participants compared with those of other 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 to ensure M7824 activity is at least comparable to pembrolizumab in this 1L setting.

The prior pembrolizumab studies used the 22C3 pharmDx assay to test PD-L1 expression. This study will accept participants who have had a prior high (≥ 50%) test result with this assay, but will otherwise use the more sensitive DAKO 73-10 PD-L1 test at ≥ 80% to enroll participants. EMD Serono completed an initial exploratory evaluation in 148 commercial NSCLC formalin-fixed paraffin-embedded tumor samples and found an overall percent agreement of 93.9% (95% CI: 88.8% to 97.2%), a positive percent agreement of 93.3% (95% CI: 77.9% to 99.2%) and a negative percent agreement of 94.1% (95% CI: 88.2% to 97.6%) using the ≥80% cut-off for Dako PD-L1 IHC 73-10 pharmDx compared to the approved ≥ 50% cut-off for the Dako PD-L1 IHC 22C3 pharmDx (using 22C3 as the non-reference standard). Based on these data, it is anticipated that most participants with a prior high PD-L1 result with 22C3 pharmDx would also have a high PD-L1 result with 73-10 pharmDx. Conversely, there is a potential risk that some participants with a high PD-L1 result on the 73-10 test would have a result < 50% on the 22C3 pharmDx assay since the positive percent agreement between the 2 assays is 80% (95% CI: 63.1% to 91.6%) when using 73-10 as a non-reference standard (see Section 2.1). The impact of this risk for participants is believed to be minimal in this study considering participants will be randomized between treatment arms, and emerging clinical data from M7824 (NSCLC 2L cohort in EMR200647-001) and pembrolizumab (KEYNOTE-042 study) which demonstrate monotherapy activity in NSCLC patients with lower PD-L1 expression. In addition, pending disclosure of the KEYNOTE-042 study data, this study may be later modified to enroll participants with lower PD-L1 expression level if the potential benefit appears favorable.

The identified and potential safety risks with M7824 were overall manageable and monitorable. No new safety signals emerged in the EMR200647-001/-008 studies compared with prior therapies targeting PD-(L)1 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 (ie, Ferguson-Smith Syndrome), and participants treated with the TGFβ-targeting agent, fresolimumab (Goudie, 2011; Morris, 2014). In the EMR200647-001/-008 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.

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 M7824's observed efficacy

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 (Scientific Rationale for Study Design) and the Investigator's Brochure.

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, endpoints, and endpoint timelines are defined in Table 8. Endpoint assessments are in Section 8.

Table 8 Study Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	Timeframe
Primary		
• To evaluate whether M7824 improves ORR compared with pembrolizumab in first-line participants with, advanced NSCLC with high PD-L1 tumor expression	BOR according to RECIST 1.1 assessed by IRC	Time from randomization to planned final assessment for unconfirmed BOR, expected at 26 months.
• To evaluate whether M7824 improves PFS compared with pembrolizumab in first-line participants with advanced NSCLC with high PD-L1 tumor expression	PFS according to RECIST 1.1 assessed by IRC	Time from randomization to planned final assessment for PFS after 192 events expected at 37 months.
Secondary		
• Safety To evaluate the safety and tolerability of M7824 compared with pembrolizumab	• Occurrence of TEAEs and treatment-related AEs according to NCI-CTCAE v5.0	From randomization to the last 12-week safety follow-up visit, expected at 47 months.
• Efficacy To evaluate whether M7824 improves overall survival time compared with pembrolizumab	• OS	From randomization to assessment when 200 OS events occur, OS PA expected at 49 months from first participant in the study.[a]
- ORR assessed by Investigators	• BOR according to RECIST 1.1 assessed by Investigator	Time from randomization to planned final assessment for unconfirmed BOR, expected at 26 months.
- PFS assessed by Investigators	• PFS according to RECIST 1.1 assessed by Investigator	Time from randomization to planned final assessment for PFS after 192 events expected at 37 months.

Objectives	Endpoints (Outcome Measures)	Timeframe
- DOR	• DOR assessed from CR or PR according to RECIST 1.1 assessed by IRC until PD, death, or last tumor assessment	Time from CR or PR to planned assessment after 192 PFS events, expected at 37 months.
• PK To characterize PK profile of M7824	PK profile of M7824 in terms of C_{eoi} PK profile of M7824 in terms of Ctrough	Predose samples at Weeks 1,3,5,7, then 6 weekly during treatment; postdose (within 30 min) samples at 6 weekly during treatment and up to study's Safety Follow-up Visit at 28 days after last study intervention administration.
• Immunogenicity To characterize the immunogenicity of M7824	Immunogenicity as measured by ADA assays at Baseline and on-treatment	From randomization up to study's Safety Follow-up Visit, defined as 28 days after last study intervention administration.
Tertiary/Exploratory		
• Exploratory efficacy objectives are to evaluate whether M7824 improves efficacy in terms of:		
- Immune-related tumor responses	- irBOR according to irRECIST assessed by IRC	From randomization to planned PFS primary analysis at approximately 37 months.
- Immune-related Progression-free survival (irPFS)	- irPFS according to irRECIST assessed by IRC	Time from randomization to planned assessment after 192 PFS events, expected at 37 months.
- Time to response	- Time to Response according to RECIST 1.1 assessed by IRC until CR or PR	From randomization until first observation of CR or PR, approximately 6 months
- Tumor shrinkage in target lesions	- Maximum shrinkage in sum of diameter of target lesions according to RECIST 1.1 assessed by IRC until PD, death due to advancing disease, or last tumor assessment	Time from randomization to planned assessment after 192 PFS events, expected at 37 months
- PFS2	- Time from randomization to investigator-assessed PD (radiographic and/or symptomatic) during first subsequent anticancer therapy or death (any cause) prior to the start of the second subsequent anticancer therapy, whichever occurs first	Time from randomization to the end of study approximately at 47 months.
- ORR on subsequent line (2L) of anticancer therapy	- BOR assessed by Investigator on subsequent line of therapy	Time from start of first subsequent anticancer therapy to the end of this study approximately at 47 months from randomization

Objectives	Endpoints (Outcome Measures)	Timeframe
- PFS on subsequent line of anticancer therapy (PFS2L)	- Time from start of first subsequent anticancer therapy to investigator-assessed PD (radiographic and/or symptomatic) during first subsequent anticancer therapy or death (any cause) prior to the start of the second subsequent anticancer therapy, whichever occurs first	Time from start of first subsequent anticancer therapy to the end of this study approximately at 47 months from randomization.
• To evaluate whether M7824 improved PRO endpoints compared with pembrolizumab	PROs as reported by EORTC-QLQ-C30, NSCLC-SAQ and EQ-5D-5L. (see Section 8.10)	Baseline, Weeks 1, 7, 13, 19 to last safety follow-up defined as 12 weeks (± 2 weeks) after last study intervention administration
• Biomarker To evaluate potential predictive markers of clinical response in blood, tumor, and tumor environment	- TMB based on liquid biopsies or in tumor tissue and correlation between mutation numbers and clinical outcome - PD-L1 expression by IHC in tumors - Genes or gene signatures in tumors	Baseline or Week 1 samples
• To compare 2 PD-L1 IHC assays and their relationship to clinical response	- Blood for pharmacogenetic testing	Baseline or Week 1 samples
• To evaluate changes in biomarkers in blood, tumor, and tumor environment and their relationships to drug exposure, clinical response, or other biologic response markers during the course of treatment	- PD-L1 expression in tumors as determined by the Dako PD-L1 IHC test (clone 73-10) and PD-L1 detection method. - Changes in TMB based on liquid biopsies or in tumor tissue during treatment or at End-of-Treatment - Changes in genes/gene signatures during treatment or at End-of-Treatment	Baseline tumor samples Week 7 and End-of-Treatment
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.		
ADA = anti-drug antibodies; AE = adverse event; BOR = best overall response; C_{eoi} = concentration at end of infusion; C_{trough} = concentration at the end of the dosing interval; CR = complete response; DOR = duration of response; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire Core-30; EQ-5D-5L = European Quality Of Life 5-dimensions 5-level questionnaire; IHC = immunohistochemistry; irBOR = immune-related best overall response; IRC = Independent Review Committee; irPFS = immune-related progression-free survival; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; NSCLC = non-small cell lung cancer; NSCLC-SAQ = non-small cell lung cancer symptom assessment questionnaire; ORR = objective response rate; OS = overall survival; PA = primary analysis; PD = progressive disease; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; survival; PFS2L = PFS on subsequent line of anticancer therapy; PK = pharmacokinetic; PR = partial response; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria in Solid Tumors; TEAE = treatment-emergent adverse event; TMB = tumor mutation burden. a At discretion of Sponsor, may extend survival analysis for all participants (see Section 4.4)		

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 3 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, 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. PD-L1 high is defined as ≥ 80% PD-L1 positive tumor cells as determined by the 73-10 assay. Participants with TPS ≥ 50% as determined by the PD-L1 IHC 22C3 pharmDx assay performed according to local laboratory regulations prior to study enrollment are also eligible. Approximately 300 participants who have not received previous treatment for their advanced NSCLC will be enrolled in this study for examination of the efficacy and safety of M7824 versus pembrolizumab. These participants must not have EGFR sensitizing mutation or ALK translocation, ROS1 mutation, or BRAF V600E mutation if targeted therapy is locally approved. 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 (ie, 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 5.2). 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 (Food and Drug Administration [FDA], European Medicines Agency [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 [3L]) 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 (for example, 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 ≤ 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 Scientific Rationale for Study Design

4.2.1 Requirement for PD-L1 High Status

All participants randomized in the study are expected to be PD-L1 high as defined by either ≥ 80% PD-L1 positive tumor cells based on the 73-10 assay or TPS ≥ 50% as determined by the PD-L1 IHC 22C3 pharmDx assay performed according to local laboratory regulations. The decision is made to target participants who may have a greater chance to respond to M7824 (ie, higher PD-L1 expression). The decision is supported by the preliminary data in the NSCLC 2L cohort from Study EMR200647-001 where an ORR at 85.7% (CI: 42.1, 99.6) in participants with PD-L1 high tumors dosed at 1200 mg was observed (Table 5); historically, response rates to PD-L1 monotherapy in 2L NSCLC with PD-L1 high tumors ranged from 29% to 41%. Additionally, as seen in other checkpoint inhibitor NSCLC studies, it is assumed that 1L ORR for M7824 will be higher than 2L M7824 data observed in EMR200647-001. In the KEYNOTE-024 study, the ORR of 1L monotherapy pembrolizumab in participants with advanced NSCLC and PD-L1 high expressing tumors was 44.8%. It is expected that the promising clinical activity of M7824 in participants with 2L NSCLC translates into efficacy in 1L participants.

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 ≥ 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 ≥ 50%) and were negative for EGFR and ALK genomic tumor aberrations (KEYNOTE-024 study) (Monotherapy for the 1L treatment of participants with metastatic NSCLC whose tumors had positive PD-L1 expression as determined by the 22C3 pharmDx assay (TPS ≥ 1%) is reported to have met its OS primary endpoint (KEYNOTE-042), and would support regulatory filing for this indication; however, there is no approval at the time of this protocol.)
- 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, but not approved in the EU.

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 (ie, approximately 1 week off every 6 weeks) and burden to 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 Independent Data Monitoring Committee (IDMC) and blinded Independent Review Committee (IRC) review will mitigate risk of bias by not double-blinding the study.

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 BOR as the Primary Endpoints

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

The BOR and PFS will be informative for Phase III and future clinical development and/or registration strategy. Furthermore, per the FDA and EMA guidance, in NSCLC PFS can be considered as a primary endpoint for demonstration of efficacy for drug approval based on magnitude of effect and risk benefit profile of the drug.

4.3 Justification for Dose

The RP2D for M7824 is 1200 mg administered as an iv 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 PBMCs 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), there was no apparent dose-dependency in observed toxicities.

Preclinical pharmacology and Phase I dose escalation PK and pharmacodynamics

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 preclinical pharmacology studies with M7824 supporting the RP2D of 1200 mg q2w are described in the Investigator's Brochure.

In brief, the dose of 1200 mg q2w (corresponding to approximately 17 mg/kg for a 70-kg participant and to 15 mg/kg for an 80-kg participant) is within the efficacious dose range predicted based on modeling of preclinical pharmacology data in tumor-bearing mice. In participants with solid tumors, full pharmacological activity on PD-L1 in PBMC on TGFβ1 and TGFβ3 (in blood) were observed at doses ≥ 3 mg/kg. It is important to consider that full pharmacological activity, including PD-L1 TO and TGFβ trapping is required at the tumor site, for which no data are available for M7824 in humans. It is likely that doses higher than 3 mg/kg q2w are required for full pharmacological activity at the tumor site (refer to the M7824 Investigator's Brochure).

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

Exposure-response and exposure-PFS assessments are based on data from 2L NSCLC 80 participants that were administered either 500 or 1200 mg of M7824 iv q2w) (n = 40 per cohort). As of the data cutoff of 25 October 2017, numerically higher confirmed ORR was observed in the 1200-mg cohort (25%), compared with the 500-mg cohort (20%) and the only CR was in the 1200-mg cohort. Similarly, there was a trend of longer PFS and OS in the 1200-mg cohort compared with the 500-mg cohort with a median PFS of 1.4 months in the

500-mg cohort versus 2.7 months in the 1200-mg cohort. Efficacy and PK data from the 500 and 1200-mg cohorts were combined for exposure-response and exposure-survival analyses.

Preliminary univariate analyses relating M7824 exposures (ie, pop PK- predicted AUC and C_{trough} after a single dose) to ORR in 500 and 1200 mg 2L NSCLC cohorts were unable to identify a relevant exposure-response relationship. However, the participants in the lowest exposure quartile (comprised of those in 500-mg cohort only) had a lower ORR than those in the higher exposure quartiles. Results of Kaplan-Meier analysis of PFS by exposure quartiles and preliminary results of exposure-PFS Cox regression modeling also support 1200 mg q2w as the RP2D in NSCLC participants. These preliminary exposure-ORR/PFS analyses combined with a trend of improved ORR, PFS, and OS in the 1200 mg q2w cohort compared with those in the 500 mg q2w cohort, suggest that 1200 mg q2w dose may be associated with a better response rate and survival compared with the 500 mg q2w dose.

In summary, efficacy, safety/tolerability, PK, and pharmacodynamic data from the Phase I studies, as well as preliminary pop PK and exposure-response modeling of the data support the selection of 1200 mg iv q2w as the RP2D in NSCLC participants.

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 date when 67% of participants have had an OS event. 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 benefitting is provisioned via a rollover study, expanded access, marketed product or another mechanism of access as appropriate.

The primary completion date is defined as the cutoff time point for the primary analysis of PFS; the study continues after the primary completion date.

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 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.

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 either tumor archival material (< 6 months old) or fresh biopsies collected within 28 days (excluding bone biopsies) before the first dose is mandatory to determine PD-L1 expression level prior to enrollment. If participant received local therapy (ie, 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. Fine needle aspirates, endobronchial ultrasound (EBUS), or cell blocks are not acceptable. Needle or excisional biopsies, or resected tissue is required.
   e. PD-L1 high status is required. PD-L1 high tumors are defined as having ≥ 80% PD-L1 positive tumor cells by the 73-10 assay Participants with a prior test of TPS ≥ 50% as determined by the PD-L1 IHC 22C3 pharmDx assay performed according to local laboratory regulations are allowed. 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 5.2 for exclusion criteria for participants with EGFR, ALK, ROS1, or BRAF V600E mutation.

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) $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin ≥ 9 g/dL
   b. Adequate hepatic function defined by a total bilirubin level $\leq$ the upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels $\leq 1.5 \times$ ULN and alkaline phosphatase $\leq$ 2.5 ULN. For participants with liver involvement in their tumor, AST $\leq$ 5.0 $\times$ ULN, ALT $\leq$ 5.0 $\times$ ULN, and bilirubin $\leq 3.0 \times$ ULN is acceptable
   c. Adequate renal function defined by creatinine $\leq$ 1.5$\times$ ULN or calculated creatinine clearance (CrCL) $\geq$ 30 mL/min for participant with Creatinine > 1.5$\times$ ULN (glomerular filtration rate [GFR] 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] $\times$ weight [kg] $\times$ [0.85 for females only]) / (72 $\times$ creatinine)
   d. Adequate coagulation function defined as international normalized ratio (INR) or prothrombin time (PT) $\leq$ 1.5$\times$ ULN unless the participant is receiving anticoagulant therapy, and activated partial thromboplastin time (aPTT) $\leq 1.5 \times$ ULN unless the participant is receiving anticoagulant therapy

Sex

5. Are:

- A male participant must agree to use and to have their female partners use a highly effective contraception (ie, methods with a failure rate of less than 1% per year) as detailed in Appendix 3 of this protocol 30 days before the first dose of study intervention (as appropriate), during the study intervention period, and for at least 4 months after the last dose of study intervention and refrain from donating sperm during this period.
- A male participant is eligible if they agree to the following during the intervention period and for at least 90 days (a spermatogenesis cycle) after the last dose of study intervention.
  - Refrain from donating sperm
  - Use contraception/barrier as detailed below:
    - A male condom and female partner use of an additional highly effective contraceptive method with a failure rate of < 1% per year as described in Appendix 3, when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
    - A male condom when engaging in any activity that allows for passage of ejaculate to another person that may result in pregnancy

- A female is eligible if she is not pregnant (i.e., after a negative serum or highly sensitive urine pregnancy test), not breastfeeding, and at least one of the following conditions applies:

  a. Is **not** a woman of childbearing potential (WOCBP), as defined in Appendix 3.

  OR

  b. Is a WOCBP who agrees to use a highly effective contraceptive method (ie, has a failure rate of less than 1% per year), as listed in Appendix 3, 30 days before the start of the first dose of study intervention (as appropriate), during the study intervention period and for at least 4 months after the last dose of study intervention. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, the treating physician should be informed immediately.

Informed Consent

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

5.2 Exclusion Criteria

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

Medical Conditions

1. The participant's tumor harbors an EGFR sensitizing (activating) mutation, ALK translocation, ROS1 rearrangement, or BRAF V600E mutation, if targeted therapy is locally approved. 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. Investigators must be able to produce the source documentation of the EGFR mutation and ALK translocation status in all participants with nonsquamous histologies AND for participants in whom testing is clinically recommended. ROS1 testing is required in participants with nonsquamous NSCLC, who have had negative EGFR/ALK testing if targeted therapy is locally approved. If an EGFR sensitizing mutation, ALK translocation, or ROS1 rearrangement, or BRAF V600E is not detected, additional information regarding the mutation status of the other molecules is not required. If unable to test for these molecular changes, formalin fixed paraffin embedded tumor tissue of any age should be submitted to a central laboratory designated by the Sponsor for such testing. Participants with nonsquamous histologies will not be randomized until the EGFR mutation status and/or ALK translocation, ROS1 rearrangement, and/or BRAF V600E mutation (if indicated) status is available in source documentation at the site. For participants enrolled who are known to have a tumor of predominantly squamous histology, molecular testing will not be required as this is not standard of care and is not part of current diagnostic guidelines.
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 4 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 (ie, 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 reactions to mAB (Grade ≥ 3 National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0), 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 (eg, corneal transplant, hair transplant)
9. Has interstitial lung disease (ILD) 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 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

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 6 months 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.

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; ie, over 50 to 80 minutes) once every 2 weeks. See Section 6.8 for special precautions.	200 mg over 30 minutes every 3 weeks. See Section 6.8 for special precautions.
Supplier/ Manufacturer:	M7824 will be supplied by the Sponsor and packaged, labeled, and distributed for clinical studies by a suitable service provider and finally released by a Sponsor qualified person under Good Manufacturing Practice conditions.	Depending on the local regulations, pembrolizumab may be either sourced from a local hospital pharmacy or supplied by the Sponsor and packaged, labeled, and distributed for clinical studies by a suitable service provider and finally released by a Sponsor qualified person under Good Manufacturing Practice conditions.
Packaging and Labeling	M7824 is formulated as a 10 mg/mL solution and is supplied by the Sponsor in USP/Ph Eur type I vials filled to allow an extractable volume of 60 mL (600 mg/60 mL) and closed with rubber stoppers in serum format complying with USP and Ph Eur with an aluminum crimp seal closure. Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.	Commercial product: Refer to pembrolizumab SmPC or Package Insert for more information. Investigational Medicinal Product: Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines

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

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 (ie, 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 stored in a refrigerator (2°C to 8°C) until use. M7824 must not be frozen and should be stored in the original packaging.

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

6.2.2 Pembrolizumab

Pembrolizumab drug product should be stored in a refrigerator (2°C to 8°C). The reconstituted vials and/or diluted iv bags may be stored for a cumulative time of up to 24 hours in a refrigerator (2°C to 8°C). Pembrolizumab must not be frozen and should be stored in the original carton in order to protect from light.

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.

Study using IVRS/IWRS	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 Voice/Web Response System (IVRS/IWRS) and per a computer-generated randomization list. The IVRS/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 telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site. The site will contact the IVRS/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.

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 > 1 cycle of study intervention for nonmedical reasons and barring any extenuating circumstances in the opinion of the Investigator. Extenuating circumstances should be documented, and when possible, discussed with the Sponsor in advance. If 1 cycle was missed and the interval between the subsequent treatment cycle and the last administered treatment cycle is longer than 4 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 (eg, medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including

any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

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

6.5.1 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 6.8 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 5.2, 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 (that is, 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 (that is, 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 (for example, inactivated influenza vaccines).

If the administration of a nonpermitted concomitant drug becomes necessary during the study, the participant will be withdrawn from study intervention (the Sponsor may be contacted to discuss whether 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

Bone-directed 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 (for example, 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.

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

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.

6.8.1 Infusion-related Reactions Including Immediate Hypersensitivity

Infusion-related reactions including immediate hypersensitivity are defined in Section 6.9.1 and are important identified risks for both M7824 and pembrolizumab.

Infusion reactions may vary in manifestation and timing, and signs and symptoms usually develop during or shortly after drug infusion which generally resolves completely within 24 hours of completion of infusion. Infusion reactions like cytokine release syndrome may manifest similar signs and symptoms of an immediate hypersensitivity/allergic reaction.

All study interventions will be administered on an outpatient basis. As a routine precaution, for the first 2 infusions, all participants enrolled in this study must be observed for 2 hours post end of infusion, in an area with resuscitation equipment and emergency agents. At all times during M7824 or pembrolizumab treatment, immediate emergency treatment of an IRR or a severe hypersensitivity reaction according to institutional standards must be assured. In order to treat possible hypersensitivity reactions like anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation. If no IRRs are observed during the first 2 infusions, the mandated 2-hour post infusion observation time is no longer required.

Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] iv or oral equivalent) approximately 30 to 60 minutes prior to each dose of M7824 is mandatory for the first 2 infusions, after which premedication is optional and at the discretion of the Investigator. Steroids as premedication are not permitted. If Grade $\geq$ 2 infusion reactions are seen during the first 2 infusions, premedication should not be stopped.

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 divided into reactions versus signs and symptoms.

- An IRR 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 any infusion-related reaction, drug hypersensitivity, anaphylactic reaction, hypersensitivity and/or 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. Signs and symptoms may include, but are not limited to: rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, fever, dyspnea, back pain, abdominal pain, and urticaria.

Table 9 Treatment Modification for Symptoms of Infusion-related Reactions

NCI-CTCAE v5.0 Grade	Treatment Modification
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Increased monitoring of vital signs as medically indicated, presuming these participants are deemed medically stable.
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
iv = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs. For Grade 3 or 4 infusion-related reactions, 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 9 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids and the infusion should be stopped for that day. At the next infusion, the Investigator may consider the addition of H2 blocker antihistamines (for example, famotidine or ranitidine), in addition to premedication, for select participants. However, prophylactic steroids are NOT permitted. At next dose, if the participant has a second IRR Grade ≥ 2 on the slower infusion rate, with the addition of further medication to premedication, the infusion should be stopped and the participant removed from treatment.

Hypersensitivity Reaction

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

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

Symptoms may include, but are not limited to:

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

Management of hypersensitivity includes:

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.

6.8.2 Immune-related Adverse Events

Immune-related AEs are specific to immunotherapies and vary by organ system. Immune-related AEs are important identified risks for both M7824 and pembrolizumab. In general, the spectrum of irAEs are similar for both M7824 and pembrolizumab.

Immune-related AEs should be documented as an 'Adverse Event of Special Interest,' (see Section 6.9.1) and it is recommended to involve the Medical Monitor at first incidence and as needed for follow-up. Details of the diagnostic work-up will be requested by the study team.

The recommendations for irAE management, in accordance with the joint American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines (Brahmer, 2018) and National Comprehensive Cancer Network (NCCN) (NCCN Guidelines®), are listed in Appendix 4. 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.

For organ/system specific management guidelines, review ASCO guideline tables in Appendix 4.

6.8.3 Potential TGFβ-mediated Skin Adverse Events

Skin AEs possibly due to TGFβ inhibition, including hyperkeratosis, KA and/or cutaneous squamous cell carcinomas (cSCC), are important identified risks for M7824 and are described in Section 6.9.1. Cases of KA and cSCC have also been reported for patients under treatment with other checkpoint inhibitors as well (Freites-Martinez, 2017; Bednarek, 2018).

Skin assessments are performed at Baseline and 6 weekly for all participants (see Section 1.3 [Schedule of Activities]). A detailed medical history of genetic or iatrogenic skin conditions, skin type, geographical location, occupational or environmental exposure to radiation or chemicals will be queried. For participants experiencing a dermatologic-related AE (hyperkeratosis, KA, or cSCC), initial biopsy with pathology report of initial AE is expected. Additional excisional biopsies of suspicious lesions should occur, and management discussed with the Medical Monitor as indicated. Dermatology consultation is encouraged for diagnosis, outcome and follow-up.

6.8.4 Anemia

Treatment-related anemia is an AESI (refer to the Investigator's Brochure and Section 6.9.1). Notably, there are many reasons for anemia in patients with advanced cancer, which is why a thorough investigation of new anemia cases of unspecified etiology is requested.

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

General Guidance for anemia management and evaluation:

- 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 (eg, < 8 g/dL), then the amount of blood to be drawn may be reduced by not taking blood at selected time points for pharmacodynamic biomarkers and TMB. The decision to reduce the time points for these biomarkers 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 treatment-related anemias is provided in Table 10.
- Discuss further management with Medical Monitor for clinically significant treatment-related anemias.

Table 10 Evaluation Guidance of Suspected Treatment-related Anemia Adverse Events

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

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

6.9 Management of Adverse Events of Interest

6.9.1 Specific Planned Assessments

6.9.1.1 Adverse Events of Special Interest

Adverse events of special interest are serious or nonserious AE specific to the known mechanism of action of the treatment drug. These events are of clinical interest, which require close monitoring and rapid communication for optimal management. The method of AESI recording and reporting will follow the guideline for AE recording and reporting (refer to Appendix 5). Safety measures to mitigate risks of AESIs include decisions for inclusion/exclusion criteria prior to study enrollment and guidance for prevention, monitoring, diagnostic work-up and management of potential risks, as well as guidance on study intervention interruption or discontinuation for study participants.

Infusion-related reactions, including immediate hypersensitivity

Any signs or symptoms experienced by participants during the infusion or any event occurring during or within 1 day of drug administration should be evaluated as a potential IRR. IRRs are common adverse drug reactions (ADRs) with mAbs that occur temporally related to drug administration. Reported signs/symptoms have included anaphylaxis, anaphylactoid reactions, and cytokine release syndrome, among others. IRRs are an AESI for M7824, and important identified risks for M7824 and pembrolizumab; precautions and management are discussed in Section 6.8.1.

Immune-related adverse events

Immune-related adverse events are defined as off-target immune-mediated side effect associated with exposure to an immunogenic drug. In the evaluation of irAEs, a full differential diagnosis should be considered in the diagnostic work-up, including possible etiologies such as neoplastic, infectious, metabolic, toxin, etc. Serologic, histologic (biopsy), and/or immunologic work-up should be performed as indicated to evaluate the differential diagnosis and/or support an immune-mediated cause. Immune-related AEs are AESIs for M7824 and important identified risks for M7824 and pembrolizumab; the precautions and management are discussed in Section 6.8.2.

Skin adverse events

Skin AEs are AESIs for M7824 and include 2 potential mechanisms:

1. Skin AEs possibly due to TGFβ inhibition are grouped as rash with hyperkeratosis, KA, and SCC of skin. Skin lesions with hyperkeratosis, KA, cutaneous squamous cell

carcinoma possibly due to TGFβ inhibition are important identified risks for M7824. These treatment-related skin AEs were well managed and did not require treatment discontinuation in Studies EMR200647-001 and MS200647-0008. Similar lesions have also been described with other immune checkpoint inhibitors; therefore, monitoring and diagnostic work-up is required for both treatment arms. For more information, refer to Section 6.8.3.

2. Immune-related skin AEs possibly mediated by PD-L1 inhibition (events in this category are also reported under irAE). For more information, see Section 6.8.3.

Treatment-related Anemia Adverse Events

Anemia is considered a potential risk based on toxicologic findings with M7824 in cynomolgus monkey indicating a decrease in hemoglobin, red blood cell count (RBC), and hematocrit which was fully reversible or showed a trend toward recovery after treatment discontinuation. Treatment-related anemia AEs are AESIs for M7824. A consistent clinical risk of treatment-related anemia on M7824 was not observed in Study EMR200647-001. As summarized in the Investigator's Brochure (Version 4), treatment-related anemia was reported in 6.1% of participants in pooled cohort data (n=23; 3.4% Grade 3+ (n=13). In the NSCLC 2L cohort of the study, treatment-related anemias were reported in 2 participants (2.5%), both of which were in the 500-mg cohort (data cutoff 12 March 2018). No consistent and/or specific etiology was identified for related anemia events. For more information, refer to Section 6.8.4 and the Investigator's Brochure.

6.9.1.2 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.

6.9.2 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, anemia, and potentially TGFβ-mediated skin AEs 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 6.8.2.
- For infusion-related reactions and hypersensitivity reactions guidance, see Section 6.8.1.
- For anemia guidance, see Section 6.8.4.
- For guidance and management for potentially TGFβ mediated skin AEs, see Section 6.8.3.

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 0 to 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.

See Section 6.8.2 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 (ie, 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 6.8.3 for management).

2. See Section 6.8.2 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 0 to 1 within 12 weeks after dose of treatment.

Grade 2 ADRs should be managed as follows:

a. If a Grade 2 ADR resolves to Grade ≤ 1 by the day before the next infusion, treatment may continue.

b. 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.

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 (ie, 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 6.9.2 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/biomarker 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 (ie, withdrawal of consent), and without giving a reason.
- The participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons (with reasons documented).

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, patient-reported outcomes (PRO) questionnaires, 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 (eg, 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. 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. Tumor responses to treatment assessed according to RECIST 1.1 by the Investigator will be documented in the eCRF (all measurements should be recorded in metric notation). The irRECIST will not be assessed by the Investigator.

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 BOR 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 performance status, and laboratory tests.

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

The AE reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of 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 6, 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 AE and a Serious Adverse Event (SAE) are in Appendix 5.

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

The AE reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the 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 5, 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 5.

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 and all nonserious AESI must be additionally documented and reported using the appropriate Report Form as specified in Appendix 5.

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 5 (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 comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) that approved the study.

In accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the Sponsor/designee will inform the Investigator of findings that could adversely affect

the safety of participants, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

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

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

8.3.5 Pregnancy

Only pregnancies the Investigator considers to be related to the study intervention (eg, 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 5, section on Reporting Serious Adverse Events and Adverse Events of Special Interest.

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 (eg, 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 above.

8.4 Treatment of Overdose

For this study, any dose of M7824 greater than 2 times more (ie, > 2400 mg) than the planned dose administered within a 24-hour time period will be considered an overdose. This is based on dose-escalation study data in which participants safely received up to 30 mg/kg M7824 every 2 weeks (including with doses > 2400mg) 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 5.

If an incidence of overdose occurs meeting the protocol-defined definition without any association of symptoms or laboratory abnormalities, then it should be reported as a nonserious AESI, 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 5, section on Reporting Serious Adverse Events and Adverse Events of Special Interest.

8.5 Pharmacokinetics

The following PK parameters will be calculated, when appropriate:

Table 11 Pharmacokinetic Parameters

Symbol	Definition
C_{eoi}	The concentration observed immediately at the end of infusion
C_{trough}	The concentration observed immediately before next dosing (corresponding to predose or trough concentration for multiple dosing)

- Blood samples of approximately 3.5 mL will be collected for measurement of serum concentrations of M7824 and ADA, as specified in Section 1.3 (Schedule of Activities). Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of M7824. Each serum sample will be divided into 2 aliquots (1 each for PK, and a back-up). Samples collected for analyses of M7824 serum

concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

The PK parameters will be summarized using descriptive statistics. Individual as well as mean concentration-time plots will be depicted. Unresolved missing data may be imputed when the analysis integrity is affected. The conservative principle will be used for data imputation.

8.6 Pharmacodynamics

- Venous blood samples of approximately 3.5 mL will be collected for measurement of potential pharmacodynamic markers as specified in Section 8.8

8.7 Genetics

- Where local regulations and IRB/IEC allow, a 6 mL blood sample will be collected for DNA analysis from consenting participants. Participation in genetic research is optional. Participants who do **not** wish to participate in the genetic research may still participate in the study.
- In the event of DNA extraction failure, a replacement genetic sample may be requested from the participant. Additional informed consent will not be required to obtain a replacement sample.

Appendix 7 provides further information on genetic research.

8.8 Biomarkers

- Collection of participant samples for biomarker research is also part of this study and is governed by the appropriate ICF.
- The following participant samples for exploratory biomarker research are required and will be collected from all participants in this study, as specified in Section 1.3 (Schedule of Activities):
  - Blood for plasma samples to determine TMB will be collected prior to infusion at Week 1 Day 1, Week 7, and at the End-of-Treatment Visit for participants receiving M7824 and for participants receiving pembrolizumab. TMB will be analyzed using circulating tumor DNA isolated from plasma to evaluate the association between the numbers of tumor-specific mutations and the observed clinical responses.
  - Blood for serum samples will be collected for the assessment of exploratory pharmacodynamic biomarkers, such as soluble PD-L1. Predose samples prior to infusion will be collected at Baseline and Weeks 1, 3, and 5 for M7824, and at Baseline and Weeks 1, 4, and 7 for pembrolizumab. Postdose samples within 30 minutes post end of infusion will be collected at Weeks 1 and 3 for M7824, and Weeks 1 and 4 for pembrolizumab.
  - Either tumor archival material (< 6 months old) or fresh biopsies collected within 28 days (excluding bone biopsies) before first dose is mandatory to determine PD-L1 protein expression levels using the 73-10 assay prior to enrollment. If participant received local

therapy (ie, RT or CRT) after the archival biopsy was taken, a fresh biopsy will be required prior to study entry. Tumor samples obtained during the Screening period will be tested for PD-L1 expression using the IHC 22C3 pharmDx assay post-enrollment to allow comparison of the 2 assays (73-10 and 22C3) in our participant population and to further evaluate the association of PD-L1 protein expression obtained from each assay with the observed clinical responses to M7824 or pembrolizumab. Participants enrolled based on previous results from a 22C3 assay will need to provide tumor material for post-enrollment testing with the 73-10 assay.

- **Optional** samples for biomarker research may be collected from the participants when possible, and when consent was given are the following:
  - Fresh biopsies (excluding bone biopsies) at Week 7 and at End-of-Treatment will be used to study the mechanism of action of each treatment. It is optional to collect tissue procured outside of specified procedures at the discretion of Investigator (eg, unplanned emergent surgery).
  - In addition, tissue and/or blood samples may be analyzed for biomarker variants which could play a role in the biology of the drug targets, the tumor or the tumor microenvironment including, but not limited to, specific gene mutations, genome-wide analysis for RNA, or protein biomarkers to evaluate their association with observed clinical responses to M7824 or pembrolizumab.
  - Optional collection of tissue procured outside of specified procedures at the discretion of Investigator (eg, skin biopsies or tumors obtained as part of unscheduled interventions) may be analyzed for biomarker variants thought to play a role in the biology of the drug targets, the tumor or the tumor microenvironment including, but not limited to, specific gene mutations, genome-wide analysis for RNA, or protein biomarkers to evaluate their association with observed clinical responses to M7824 or pembrolizumab.
  - In addition, participant samples and/or radiographic scans may be used for additional research (eg, to develop methods, assays, prognostics, and/or companion diagnostics) related to, but not limited to the drug targets (PD-L1 and TGFβ), disease process, pathways associated with disease state, and/or mechanism of action of the study intervention, as specified in the ICF.

Samples will be tested as described in Table 12 to evaluate the association with the observed clinical responses to study intervention.

Table 12 Biomarker Overview

Sampling	Biomarker	Biomarker Assay	Biomarker type	Purpose (Exploratory Endpoints)	Time Points[a]
Blood	Pharmacogenetics	DNA sequencing	Predictive (exploratory)	Effect of genetics on drug or drug effect	W1D1
	TMB	DNA sequencing	Predictive (exploratory)	To evaluate association with observed clinical responses to M7824 or	W1D1

Sampling	Biomarker	Biomarker Assay	Biomarker type	Purpose (Exploratory Endpoints)	Time Points[a]
				pembrolizumab.	
	TMB	DNA sequencing	MoA (exploratory)	Drug effect on tumor	W7, End-of-Treatment
	Pharmacodynamic biomarkers	Immuno-assay	Pharmaco-dynamic (exploratory)	To evaluate association with PK or observed clinical responses to M7824 or pembrolizumab.	Predose samples prior to infusion at Baseline (optional) and Weeks 1, 3, 5 for M7824; and at Baseline (optional) and Weeks 1, 4, 7 for pembrolizumab. Postdose samples within 30 minutes post end of infusion at Week 3 for M7824; and Week 4 for pembrolizumab
Tumors	PD-L1 protein	IHC 73-10 IHC 22C3	Predictive Predictive	Participant selection biomarker Assay comparison	Baseline Baseline sample tested post-enrollment
	Immune biomarkers	IHC and/or RNAseq	Predictive MoA (exploratory)	To evaluate association with observed clinical responses to M7824 or pembrolizumab Drug effect on TME	Baseline W7, at End-of-Treatment, or unscheduled intervention
	Tumor biomarkers	IHC and/or RNAseq	Predictive MoA (exploratory)	To evaluate association with observed clinical responses to M7824 or pembrolizumab Drug effect on tumor	Baseline W7, at End-of-Treatment, or unscheduled intervention

D = Day; IHC = immunohistochemistry; MoA = mechanism of action; PK = pharmacokinetic; TMB = tumor mutational burden; TME = tumor micro environment; W = Week.

a: Tumor samples at W7, at End-of-Treatment, or unscheduled intervention are optional.

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

8.8.1 Ribonucleic Acid Transcriptome Research

Transcriptome studies may be conducted using microarray, and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of ribonucleic acid (RNA) species resulting in a transcriptome profile for each blood

and tumor sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to the tumor or its microenvironment or the action of M7824 or pembrolizumab.

The same samples may also be used to confirm findings by application of alternative technologies.

8.8.2 Ribonucleic Acid Expression Research of a Subset of Ribonucleic Acid Species

Not applicable.

8.8.3 Proteome Research

Not applicable.

8.8.4 Metabolomic Research

Not applicable.

8.9 Immunogenicity Assessments

Antibodies to M7824 will be evaluated in serum samples collected from all participants per Section 1.3 (Schedule of Activities). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to M7824 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to M7824 and/or further characterize the immunogenicity of M7824.

The detection and characterization of antibodies to M7824 will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to M7824 may also be evaluated for M7824 serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for a maximum of 10 years or per local regulations following the last participant’s last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to M7824.

8.10 Patient-reported Outcomes

Patient-reported outcomes will be collected using the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire Core-30 (EORTC-QLQ-C30), NSCLC symptom assessment questionnaire (NSCLC-SAQ) and European Quality of Life 5-dimensions 5-level questionnaire (EQ-5D-5L). The PROs should be performed in the same sequence at each visit.

The EORTC-QLQ-C30 is a cancer specific health-related quality of life questionnaire that has been widely used in clinical studies and investigations using PROs for individual participant management. It includes 5 function domains (physical, emotional, social, role, cognitive), 8 symptoms (fatigue, pain, nausea/vomiting, constipation, diarrhea, insomnia, dyspnea, and appetite loss), as well as global health/quality of life and financial impact. Participants respond on a 4-point scale from "not at all" to "very much" for most items. Most items use a "past week" recall period. Raw scores can be linearly converted to a 0 to 100 scale with higher scores reflecting higher levels of function and higher levels of symptom burden. The EORTC also includes an item library from which items can be selected to supplement the core instrument. Items measuring rash, pruritus, and trouble by side effects will be added to the items on the C30 for a total of 33 EORTC items.

The NSCLC-SAQ is a 7-item PRO questionnaire created to measure the cardinal symptoms of NSCLC. Items measure cough (1 item), pain (2 items), dyspnea (1 item), fatigue (2 items), and appetite (1 item). Each of these items is rated in terms of symptom severity or frequency on a 5-point response scale (1 = none or never, 5 = very severe or always).

The EQ-5D-5L is a 6-item instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D-5L consists of a descriptive system (5 items) and a single item EQ Visual Analog Scale (VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale. The EQ-5D-5L has 5 response categories: no problems, slight problems, moderate problems, severe problems and extreme problems. The participant is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. The responses (ranging from 1 to 5) to the 5 dimensions are summarized into a 5-digit profile. This profile can be converted into a preference-weighted index value.

The PRO assessments will be administered and completed by the participants prior to any study-related procedures at the indicated visits in Section 1.3. The Baseline PRO assessments should be conducted at Screening; in the event the Screening assessments are missed, they can be done at Visit 1 (Day 1) prior to the first treatment. The PRO questionnaires should be completed by the participants prior to any of the other study-related assessments being performed, that is, physical examinations, blood draws, and study intervention administrations. Whenever possible, the PRO assessments will be completed by the participant prior to a health care invention of any nature, regardless of whether it is study-related or not, and should be performed in the same sequence when performed.

9 Statistical Considerations

9.1 Statistical Hypotheses

The following hypotheses on the primary endpoints, BOR and PFS will be tested.

Primary endpoint BOR

Objective tumor response is evaluated by the ORR, defined as the number of participants having reached a BOR of CR or PR divided by the number of participants in the analysis population. Treatment groups will be compared in terms of difference of ORR ($\Delta^{\mathrm{ORR}} = ORR_M - ORR_P$), between the treatment groups, with *M* for M7824 and *P* for pembrolizumab.

The following null hypothesis will be tested:

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

Primary endpoint PFS

Progression-free survival 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.

The following null hypothesis will be tested:

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

Where $\lambda_{\cdot}^{PFS}(t)$ represents the hazard at time t and θ the unknown constant of proportionality of hazards in the treatment groups *M* (M7824) and *P* (pembrolizumab).

Secondary endpoint OS

The OS is defined as the date from randomization to death due to any cause. For participants alive, the OS will be censored at the last date known to be alive.

The following null hypothesis will be tested confirmatory if and only if at least one of the hypotheses H_0^{PFS} or H_0^{ORR} could be rejected at the corresponding local significance level:

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

Where $\lambda_{\cdot}^{OS}(t)$ represents the hazard at time t and θ the unknown constant of proportionality of hazards in the treatment groups *M* (M7824) and *P* (pembrolizumab).

9.2 Sample Size Determination

The sample size calculation is driven by the PFS endpoint and based on the following assumptions:

- Exponential distribution of PFS in each arm and stratum
- 1:1 randomization
- Local significance level α^{PFS}=0.044

- Hazard ratio (HR) of $0.\overline{66}$ corresponding to an increase in median PFS from 10 months in the pembrolizumab arm to 15 months in the M7824 arm in all strata
- Accrual over a period of 20 months, with a ramp-up phase of 9 months with 9 recruited participants per month and 20 per months from month 10 onwards
- An expected overall drop-out rate of 15%
- An interim analysis for efficacy after 72.9% of the planned PFS events have been observed, applying alpha-spending according to Lan-DeMets with O'Brian-Fleming-like boundaries
- Local power of 85.7% for rejecting H_0^{PFS} in a group sequential testing procedure

A sample size of 300 randomized participants is planned in order to observe 192 events (tumor progression or death due to advancing disease) at the primary analysis, which is projected for 37 months after the first participant randomized. Assuming a PD-L1 high proportion of around 20%, the screening failure rate is at least 80% and 1500 participants need to be screened. Calculations were performed using EAST version 6.4, Cytel Inc.

The BOR analysis is based on the following assumptions

- 1:1 randomization
- Local $\alpha^{ORR} = 0.006$ (one-sided)
- $ORR_P = 0.45$ and $ORR_M = 0.60$ for pembrolizumab and M7824, respectively, $\Delta^{\mathrm{ORR}} = 0.15$
- Sample size of 100 participants (50 in each arm).

With a sample size of 100 randomized participants, the null hypothesis H_0^{ORR} can be rejected at alpha = 0.006 (one-sided) when exceeding the critical value of $\Delta_{crit}^{\mathrm{ORR}} = 0.25$. The power is 16%. The used critical value depends on the standard error calculation as described in Section 9.4.1. Calculations were performed using EAST version 6.4, Cytel Inc.

Further considerations on sample size

At the time of central review of enrollment scans, if there is a relevant number of participants with unmeasurable disease by RECIST 1.1 potentially compromising the assessment of primary endpoints, additional participants may be randomized at the discretion of the Sponsor to facilitate completing the specified analyses.

If during the study, high discordance of PD-L1 status is found between 22C3 and the 73-10 assay used at enrollment, additional participants may be randomized.

In addition, the number of participants enrolled with prior PD-L1 test results (as opposed to having tested performed centrally via the 73-10 assay) will be monitored and a decision may be made to limit the number of participants allowed to enter based on prior testing.

Alternatively, with a significance level of 2.5% one-sided, the study will have the operating characteristics as described in Table 13.

Table 13 Operating Study Characteristics for Different Global α Values

Significance Level			Critical values testing H_0^{ORR} and H_0^{PFS}			(local) power for rejecting H_0^{ORR} or H_0^{PFS}		
Global α	(Local) α^{ORR}	(Local) α^{PFS}	Δ_{crit}^{ORR}	$HR_{crit}^{PFS\ IA}$	$HR_{crit}^{PFS\ PA}$	H_0^{ORR}	H_0^{PFS}	any
5%	0.6%	4.4%	0.25	0.702	0.774	16%	79%	81%
2.5%	0.6%	1.9%	0.25	0.654	0.737	16%	70%	74%

Calculated under the same assumptions as in the sample size part. Last column shows the global power for rejecting at least one of both null hypotheses under assuming independence for both primary endpoints.
ORR = objective response rate; PFS = progression-free survival.

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 14.

Table 14 Analysis Populations

Analysis Population	Description
SCR	All participants, who provided informed consent, regardless of the participant's randomization and study intervention status in the study.
ITT	All participants, who were randomized to study intervention. Analyses performed on the ITT population will consider participants' allocation to study intervention groups as randomized.
SAF	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.
PK	All participants who complete at least 1 infusion of M7824, and who provide at least 1 sample with a measurable concentration of M7824.
Subgroup Analysis Set	Analysis of efficacy variables will also be performed on subgroup of interest, which will be specified in the IAP.

IAP = Integrated Analysis Plan; ITT = Intention-to-Treat; PK = Pharmacokinetic; SAF = Safety; SCR = Screening;

9.4 Statistical Analyses

Full details of all planned analyses will be described in the study Integrated Analysis Plan (IAP). Major modifications of planned analyses will be reflected in a protocol amendment or in the clinical study report.

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.

The family-wise error rate for testing the one-sided hypotheses listed in Section 9.1 is strictly controlled at a level of 5%. A hierarchical closed testing procedure will be used with weighted Bonferroni tests according to Hommel, Bretz, Maurer (2007) to account for multiplicity. Any further statistical test or analysis would be regarded as being fully exploratory. Details on the applied testing procedures are given in the following section.

Data collected after reinitiation of treatment will not be included for safety and efficacy analyses except for OS and disposition.

9.4.1 Efficacy Analyses

The 2 primary endpoints of this study are BOR and PFS. The study will be considered positive if either the BOR analysis results and/or the PFS analysis results are statistically significant.

A hierarchical testing strategy will be applied to test superiority of either M7824 versus pembrolizumab regarding the 2 primary endpoints, BOR and PFS, in the first level and OS in the second level. The global α (one-sided) is split into $\alpha^{ORR} = 0.006$ and $\alpha^{PFS} = \alpha - \alpha^{ORR}$ for testing the hypotheses on hierarchy level one. If and only if one of the hypotheses H_0^{ORR} or H_0^{PFS} was rejected at local α level the second hierarchy level hypothesis H_0^{OS} will be tested at the sum of the local α levels for the rejected hypotheses in hierarchy level one. For instance, if only H_0^{PFS} could be rejected, the local α level for testing H_0^{OS} would be $\alpha^{OS} = \alpha^{PFS}$. If both first hierarchy level hypotheses could be rejected it would be $\alpha^{OS} = \alpha$. The test for H_0^{OS} will be regarded as exploratory if none of the first hierarchy level hypotheses could be rejected.

BOR analysis

H_0^{ORR} is tested only once by an unblinded IDMC on the subset of size 100 from the Intention-to-Treat (ITT) population, which is randomized since at least 6 months. The asymptotically normal distributed test statistic:

$$T^{ORR} = \left(ORR_{obs}^{M} - ORR_{obs}^{P}\right) \Big/ \sqrt{\left(ORR_{obs}^{M} * \left(1 - ORR_{obs}^{M}\right)/n^{M} * ORR_{obs}^{P} * \left(1 - ORR_{obs}^{P}\right)/n^{P}\right)}$$

will be tested at a local significance level of $\alpha^{ORR} = 0.006$. The terms, n^M and n^P, describe the actual number of participants randomized to M7824 or pembrolizumab in the analyzed population.

The following additional descriptive analyses will be performed at this time point and at the time point of primary PFS analysis. ORR, ie, the rate of participants having an unconfirmed BOR of

CR or PR according to RECIST 1.1 evaluated by IRC will be calculated along with the corresponding two-sided exact Clopper-Pearson 95% CI per treatment group. The difference Δ^{ORR} will be estimated by the crude rate difference and complemented by a 95% Miettinen-Nurminen CI.

The difference in ORR is estimated based on the Cochran-Mantel-Haenszel method (taking into account the randomization strata) as additional sensitivity analysis at the time point of primary PFS analysis. Logistic models for BOR will be fitted with the endpoint as dependent variable, subgroup, treatment, and with and without the treatment by subgroup interaction as explanatory variables at the same time point.

Futility analysis

The BOR analysis will also include a nonbinding futility analysis using a threshold of $\Delta^{\mathrm{ORR}} \leq 0$, ie, the observed M7824 and pembrolizumab ORR are identical. Assuming true $ORR_P = 0.45$ and $ORR_M = 0.60$ for pembrolizumab and M7824, respectively, $\Delta^{\mathrm{ORR}}_{observed} \leq 0$ would only occur in 8% of cases. If on the other hand, the true $\Delta^{\mathrm{ORR}}_{true} = 0$, an observed $\Delta^{\mathrm{ORR}}_{observed} \leq 0$ would occur in 50% of cases; and if the true $\Delta^{\mathrm{ORR}}_{true} = 0.10$, an observed $\Delta^{\mathrm{ORR}}_{observed} \leq 0$ would occur in 18% of cases. Details for the decision study conduct will be described in the IDMC charter.

PFS analysis

A one-sided stratified (same strata as used for randomization) log rank test at the local $\alpha^{PFS} = \alpha - \alpha^{ORR}$ will be used for testing H_0^{PFS} sequentially in an interim analysis (at least 140 PFS events observed as assessed by IRC for RECIST 1.1) and in the primary analysis, which is conducted when 192 events are observed.

Lan-DeMets alpha spending with O'Brien-Fleming-like boundaries will be adopted for the currently observed event size at cut-off date.

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

The following sensitivity analyses of PFS will also be performed

1. Considering events after start for new anticancer treatment.

2. Clinical progression will be considered as event

3. PFS based on Investigator assessment.

Additional sensitivity analyses may be provided, details will be documented in the IAP.

The PFS treatment effect (HR θ) is estimated by a Cox proportional hazards model, which is stratified by randomization strata (each stratum defines separate baseline hazard function). Ties are handled by replacing the proportional hazards model by the discrete logistic model. 95% CIs for the HR will be calculated.

Sensitivity analyses taking other factors and analysis populations into account will be specified in the IAP. The proportional hazards assumption will be checked graphically.

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.

Subgroup analyses will be defined in the IAP.

OS analysis

H_0^{OS} will be tested confirmatory only if H_0^{ORR} or H_0^{PFS} are rejected before. The sequential stratified log-rank test uses then a local α^{OS} (one-sided) as described at the beginning of Section 9.4.1. If confirmatory testing is not possible the test is conducted exploratory at a local $\alpha^{OS} = 0.025$ (one-sided).

The OS interim analysis uses the same data cutoff as the PFS primary analysis. Lan-DeMets alpha spending with O'Brien-Fleming-like boundaries will be adopted for the currently observed event size at cut-off date. The primary analysis is conducted when two thirds of the randomized participants have died.

The same descriptive analyses as for the PFS endpoint will be used for OS, whereas the OS rates will be estimated at 12, 18, 24, 30, 36, 42, and 48 months.

Other efficacy endpoints

The analysis of other secondary or exploratory efficacy endpoints will be specified in the IAP.

9.4.2 Safety Analyses

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

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

Table 15 Safety Endpoints and Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary Occurrence of TEAEs and treatment-related AEs per NCI-CTCAE v5.0 assessed by	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.

Investigators	The incidence of TEAEs, regardless of attribution, will be summarized by preferred term and system organ class for each treatment arm, and described in terms of intensity and relationship to treatment. 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 will be provided in the IAP.
Tertiary/Exploratory	Will be specified in the IAP finalized before database lock.

AE = adverse event; AESI = adverse event of special interest; IAP = Integrated Analysis Plan; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event.

9.4.3 Other Analyses

Estimation of Individual PK Parameters:

- Pharmacokinetic parameters will be calculated by the PK/PD Data Processing Group of QPD, Merck, Darmstadt, Germany, or by a CRO selected by the Sponsor.
- PK parameters will be calculated using the actual elapsed time since dosing. When the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data.
- The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.4 or higher) may be used to produce tables, listings and figures and in the calculation of PK Parameters, if appropriate.

PK analysis (C_{eoi} and C_{trough} as outlined in Section 8.5), and biomarker exploratory analyses will be specified in the IAP finalized before database lock. The pop PK analysis and exposure-response may be performed using combined data from several M7824 clinical studies and will be specified in a separate IAP. Population PK, exposure-response, and biomarker analyses will be presented separately from the main clinical study report.

9.4.4 Sequence of Analyses

There will be 4 data cutoff time points in this study:

I – Analysis of BOR using the first 100 participants with minimum follow-up time for all participants of 4 regular post-baseline tumor assessments, approximately 17 months after the first participant is randomized; the decision to stop for futility if the ORR is observed to be higher in the pembrolizumab arm than in the M7824 arm is made nonbinding based on this interim analysis.

II – PFS interim analysis at the time of 73% information fraction when 140 PFS events have been reached and the last randomized participant in the study has reached at least 12 months follow-up time, expected at 26 months from randomization.

III – PFS primary analysis at the time when 192 PFS events have occurred, expected at approximately 37 months after the first participant is randomized. The same cutoff is used for the OS interim analysis.

IV – OS primary analysis at the time when two thirds of randomized participants have died, expected at approximately 49 months after the first participant is randomized or when the minimum follow-up time has reached 4 years, if that is reached earlier.

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11 Appendices

Appendix 1 Abbreviations

ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BOR	Best overall response
β-hCG	Beta human chorionic gonadotropin
CR	Complete response
CrCL	Creatinine clearance
CRT	Chemoradiotherapy
CNS	Central nervous system
CRO	Contract Research Organization
cSCC	Cutaneous squamous cell carcinomas
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
EBUS	Endobronchial ultrasound
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire Core-30
EQ-5D-5L	European Quality of Life 5-dimensions 5-level questionnaire

FDA	Food and Drug Administration
1L	First-line
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
IAP	Integrated Analysis Plan
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
ILD	Interstitial lung disease
INR	International normalized ratio
irAE	Immune-related AE
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-related reactions
ITT	Intention-to-Treat
iv	Intravenous
IVRS/IWRS	Interactive Voice/Web Response System
KA	Keratoacanthomas
mAb	Monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drug

NSCLC	Non-small cell lung cancer
NSCLC-SAQ	Non-small cell lung cancer symptom assessment questionnaire
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetics
pop PK	Population pharmacokinetic
PR	Partial response
PRO	Patient-reported outcomes
PT	Prothrombin time
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
SUSAR	Suspected unexpected serious adverse reactions
TGFβ	Transforming growth factor β
3L	Third-line
TMB	Tumor mutational burden
TPS	Tumor proportion score
ULN	Upper limit of normal
VAS	Visual analog scale
WOCBP	Woman of childbearing potential

Appendix 2 Study Governance

Financial Disclosure

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

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions on the study.
- Participants must be informed that their participation is voluntary.
- Participants or their legally-authorized representative defined as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research 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.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.
- 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) and Merck KGaA, Darmstadt, Germany, for sites outside the USA.

The study will be conducted at approximately 100 centers in North and South America, EU, and Asia-Pacific. Approximately 20 to 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.

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
  - Applicable laws and regulations
- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (eg, advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.

- Any protocol amendments (ie, 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 (eg, 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

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 (eg, 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 (eg, QoL and pain assessments), ePRO 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, 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, and weight
  - Medical history and concomitant diseases
  - Prior and concomitant therapies (including changes during the study)
  - Study identifier (ie, the Sponsor's study number) and participant's study number.
  - Dates of entry into the study (ie, 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 (eg, 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 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

Woman of Childbearing Potential (WOCBP)

A woman is of childbearing potential (ie, fertile), following menarche and until either:

1) Becoming postmenopausal; or,
2) is permanently sterile by means of a hysterectomy, bilateral salpingectomy, tubal occlusion, or bilateral oophorectomy.

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

Highly Effective Contraceptive Methods (as specified in the CTFG recommendations)

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

These methods are further classified into user-independent and user-dependent methods. Because user-independent methods do not depend on the participant's ability to use them consistently and correctly, they are preferred when contraception is introduced as a condition for study participation.

Caution should be taken for hormonal contraception, as it may be susceptible to interaction with the study intervention(s), which may reduce the efficacy of the contraception method. In this case, a second highly effective method of contraception should be used during the treatment period and for at least 4 months after the last dose of study treatment.

User-Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable

User-Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device (IUD)

- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner: This is a highly effective contraception method only if the partner is the sole sexual partner of the WOCBP and he has received medical assessment of the surgical success.
- Sexual abstinence: This is a highly effective method only if the WOCBP refrains from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Appendix 4 The Recommendations for irAE Management, in Accordance with the Joint American Society of Clinical Oncology Clinical Practice Guidelines and National Comprehensive Cancer Network

Reproduced from:
Brahmer JR.
Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

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Table A1 Management of Skin irAEs in Patients Treated With ICPis

1.0 Skin Toxicities	
1.1 Rash/inflammatory dermatitis	
Definition: Erythema multiforme minor (a targetoid reaction in the skin and mucous membranes usually triggered by infections, such as herpes simplex viruses, but can be associated with an immune-related drug eruption and if progresses to erythema multiforme major, it and can be a harbinger of SCAR, such as SJS), lichenoid (resembling the flat-topped, polygonal, and sometimes scaly or hypertrophic lesions of lichen-planus), eczematous (inflammatory dermatitis characterized by pruritic, erythematous, scaly, or crusted papules or plaques on the skin, which is vulnerable to superinfection, psoriasiform [resembling the well-demarcated, erythematous, and scaly papules and plaques of psoriasis], morbilliform [a nonpustular, nonbullous measles-like exanthematous rash of the skin often referred to as “maculopapular” and without systemic symptoms or laboratory abnormalities, excluding occasional isolated peripheral eosinophilia, palmoplantar erythrodysesthesia [hand-foot syndrome; redness, numbness, burning, itching, and superficial desquamation of the palms and soles], neutrophilic dermatoses [eg, Sweet syndrome], and others)	
Diagnostic workshop	
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 equires 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	Immediately hold ICPi and consult dermatology to determine appropriateness of resuming ICPi therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) ≤ 10 mg Systemic corticosteroids: IV (methyl)prednisolone (or

1.0 Skin Toxicities	
	equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves Monitor closely for progression to severe cutaneous adverse reaction Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology Consider alternative antineoplastic therapy over resuming ICPis if the skin irAE does not resolve to G1 or less; if ICPIs are the patient's only option, consider restarting once these adverse effects have resolved to a G1 level
1.2 Bullous dermatoses	
Definition: Including bullous pemphigoid or other autoimmune bullous dermatoses, bullous drug reaction Diagnostic work-up Physical examination Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease If needed, a biologic 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 (eg, herpes simplex, herpes zoster, bullous impetigo, bullous insect bite, friction or pressure blister) Consider skin biopsy (both hematoxylin and eosin evaluation of lesional skin and direct immunofluorescence evaluation of perilesional skin)	
Grading	Management
G1: Asymptomatic, blisters covering < 10% BSA and no associated erythema	If blisters are < 10% BSA, asymptomatic, and noninflammatory (such as the case with friction blisters or pressure blisters), cessation of ICPi is not necessary, and only observation and/or local wound care is warranted. When symptomatic bullae or erosions, which are deroofed vesicles or bullae, are observed on the skin or mucosal surfaces, the cutaneous irAE is by definition considered at least G2 See G2 management recommendations
G2: Blistering that affects quality of life and requires intervention based on diagnosis not meeting criteria for Grade > 2 Blisters covering 10%-30% BSA	Hold ICPi therapy and consult with dermatology for work-up and to determine appropriateness of resuming Attention given to general local wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions, which are left over on the skin after the blister has popped or if the roof of the blister easily sloughs off Counsel patients to avoid skin irritants and overexposure to sun, wear protective clothing, use sunscreens Work-up for autoimmune bullous disease as above Initiate Class 1 high-potency topical corticosteroid (eg, clobetasol, betamethasone or equivalent) and reassess every 3 days for progression or improvement Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg dosing and taper over at least 4 weeks Monitor patients with G2 irAEs closely for progression to involvement of greater BSA and/or mucous membrane

1.0 Skin Toxicities	
	involvement. Consider following patients closely using serial photography Primer on monitoring for complicated cutaneous adverse drug reactions:
	Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements
	Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN
G3: Skin sloughing covering > 30% BSA with associated pain and limiting self-care ADL	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming 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	

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

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

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

Table A2 Management of GI irAEs in Patients Treated With ICPis

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

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

2.0 GI Toxicities	
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

2.0 GI Toxicities	
	option in the situation of immune-mediated hepatitis given the potential risk of liver failure (Note: No clear evidence shows that the liver toxicity from infliximab from other studies); alternatives include non–TNF-a agents as systemic immunosuppressants If no improvement is achieved with corticosteroids or for patients on combination therapy with a novel agent, with standard chemotherapy, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis Corticosteroid taper can be attempted around 4-6 weeks; re-escalate if needed; optimal duration unclear
G4: Decompensated liver function (eg, ascites, coagulopathy, encephalopathy, coma; AST or ALT > 20 x ULN and/or total bilirubin > 10 x ULN)	Permanently discontinue ICPi Administer 2 mg/kg/d methylprednisolone equivalents If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil 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.	

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	Hold ICPi with radiographic evidence of pneumonitis progression May offer one repeat CT in 3-4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as G2 Monitor patients weekly with history and physical examination and pulse oximetry; may also offer CXR
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 6 transbronchial biopsy Patients should be hospitalized for further management
Additional considerations GI and Pneumocystis prophylaxis with PPI and Bactrim may be offered to patients on prolonged corticosteroid use (> 12 weeks), according to institutional guidelines Consider calcium and vitamin D supplementation with prolonged corticosteroid use The role of prophylactic fluconazole with prolonged corticosteroid use (> 12 weeks) remains unclear, and physicians should proceed according to institutional guidelines Bronchoscopy + biopsy; if clinical picture is consistent with pneumonitis, no need for biopsy All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

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

Table A4 Management of Endocrine irAEs in Patients Treated With ICPis

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

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

4.0 Endocrine Toxicity	
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.	

4.0 Endocrine Toxicity	
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 6 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

4.0 Endocrine Toxicity	
	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 ofnormal.

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 6 MRI of affected joints if clinically indicated (eg, persistent arthritis unresponsive to treatment, suspicion for differential diagnoses such as metastatic lesions or septic arthritis) Consider early referral to a rheumatologist, if there is joint swelling (synovitis) or if symptoms of arthralgia persist > 4 weeks G3-4 As for G2 Seek rheumatologist advice and review Monitoring: Patients with inflammatory arthritis should be monitored with serial rheumatologic examinations, including inflammatory markers, every 4-6 weeks after treatment is instituted.	
Grading	Management
All Grades	Clinicians should follow reports of new joint pain to determine whether inflammatory arthritis is present; question whether symptom new since receiving ICPi
G1: Mild pain with inflammation, erythema, or joint swelling	Continue ICPi Initiate analgesia with acetaminophen and/or NSAIDs
G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling, limiting instrumental ADL	Hold ICPi and resume upon symptom control and on prednisone ≤ 10 mg/d Escalate analgesia and consider higher doses of NSAIDS as needed If inadequately controlled, initiate prednisone or prednisolone 10-20 mg/d or equivalent for 4-6 weeks If improvement, slow taper according to response during the next 4-6 weeks; if no improvement after initial 4-6 weeks, treat as G3 If unable to lower corticosteroid dose to < 10 mg/d after 3 months, consider DMARD Consider intra-articular corticosteroid injections for large joints Referral to rheumatology
G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL	Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to G1 or less Initiate oral prednisone 0.5-1 mg/kg If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD

5.0 Musculoskeletal Toxicities	
	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

5.0 Musculoskeletal Toxicities	
	(elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy)
G3-4: Severe weakness with or without pain, limiting self-care ADL	Hold ICPi until G1 or less while off immune suppression and permanently discontinue if any evidence of myocardial involvement 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
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	Hold ICPi and may resume, in consultation with rheumatology, if recover toG1 or less; however, note that cases of toxicity returning upon rechallenge have been reported. Referral to rheumatology Should initiate prednisone 20 mg/d or equivalent. If no improvement or need for higher dosages for prolonged

5.0 Musculoskeletal Toxicities	
	time, may offer a corticosteroid-sparing agent such as methotrexate or IL-6 inhibition with tocilizumab (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis or GI metastases). Consider admission for pain control
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

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

Table A6 Management of Renal irAEs in Patients Treated With ICPis

6.0 Renal Toxicities	
Nephritis and renal dysfunction: diagnosis and monitoring For any suspected immune-mediated adverse reactions, exclude other causes Monitor patients for elevated serum creatinine prior to every dose Routine urinalysis is not necessary, other than to rule out UTIs, etc; nephrology may consider further If no potential alternative cause of AKI identified, then one should forego biopsy and proceed directly with immunosuppressive therapy Swift treatment of autoimmune component important	
6.1 Nephritis	
Definition: Inflammation of the kidney affecting the structure	
Grading	Management
G1: Creatinine level increase of > 0.3 mg/dL; creatinine 1.5-2.0 3 over baseline	Consider temporarily holding ICPi, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status) and baseline renal function. A change that is still < 1.5 ULN could be meaningful
G2: Creatinine 2-3 x above baseline	Hold ICPi temporarily Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc); if other etiologies ruled out, administer 0.5-1 mg/kg/d prednisone equivalents If worsening or no improvement: 1 to 2 mg/kg/d prednisone equivalents and permanently discontinue treatment If improved to G1 or less, taper corticosteroids over 4-6 weeks If no recurrence of chronic renal insufficiency, discuss resumption of ICPI with patient after taking into account the risks and benefits.
G3: Creatinine > 3 x baseline or > 4.0 mg/dL; hospitalization indicated	Permanently discontinue ICPi
G4: Life-threatening consequences; dialysis indicated	Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc) Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent)
Additional considerations Monitor creatinine weekly Reflex kidney biopsy should be discouraged until corticosteroid treatment has been attempted	
6.2 Symptomatic nephritis: follow-up	
Grading	Management
G1	Improved to baseline, resume routine creatinine monitoring
G2	If improved to G1, taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring If elevations persist > 7 days or worsen and no other cause found, treat as G3
G3	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist 3-5 days or worsen, consider additional immunosuppression (eg, mycophenolate)

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

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

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

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

7.0 Nervous System Toxicities	
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	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 (eg, facial neuropathies/Bell palsy) may be present. Numbness and paresthesias may be painful or painless. Hypo- or areflexia or sensory ataxia may be present.	
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	

7.0 Nervous System Toxicities	
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 (ie, 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 (ie, 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	

7.0 Nervous System Toxicities	
Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits Consider empirical antiviral (IV acyclovir) and antibacterial therapy until CSF results Once bacterial and viral infection are negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg or IV methylprednisolone 1 mg/kg if moderate/severe symptoms
7.6 Encephalitis	
Definition: As for aseptic meningitis, need to exclude infectious causes, especially viral (ie, HSV). Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality Diagnostic work-up	
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 (ie, pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits As above for aseptic meningitis, suggest concurrent IV acyclovir until PCR results obtained and negative Trial of methylprednisolone 1-2 mg/kg If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids methylprednisolone 1 g IV daily for 3-5 days plus IVIG 2 g/kg over 5 days If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab or plasmapheresis in consultation with neurology
7.7 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 (ie, pain but no weakness or gait	Permanently discontinue ICPi Methylprednisolone 2 mg/kg Strongly consider higher doses of 1 g/d for 3-5 days Strongly consider IVIG

7.0 Nervous System Toxicities	
limitation) G3-4: Severe, limiting self-care and aids warranted	
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, cytogenetic analysis to evaluate for myelodysplastic syndromes Evaluation for viral/bacterial (mycoplasma, etc) causes of hemolysis studies Protein electrophoresis, cryoglobulin analysis Work-up for bone marrow failure syndrome if refractory, including B12, folate, copper, parvovirus, FE, thyroid, infection Glucose-6-phosphate dehydrogenase Evaluation of common drug causes (ribavirin, rifampin, dapsone, interferon, cephalosporins, penicillins, NSAIDs, quinine/quinidine, fludarabine, ciprofloxacin, lorazepam, diclofenac, etc) Assessment of methemoglobinemia	
Grading	Management
G1: Hgb < LLN to 10.0 g/dL; < LLN to 6.2 mmol/L; < LLN to 100 g/L	Continue ICPi with close clinical follow-up and laboratory evaluation
G2: Hgb < 10.0 to 8.0 g/dL; < 6.2to4.9mmol/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

8.0 Hematologic Toxicities	
	rituximab, IVIG, cyclosporin A, and mycophenolate mofetil RBC transfusion per existing guidelines; discuss with blood bank team prior to transfusions that a patient with possible ICPi serious AE is in house.
Additional considerations: Monitor Hgb levels on a weekly basis until the corticosteroid tapering process is complete; thereafter, less-frequent testing is needed	
8.2 Acquired TTP	
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities, and neurologic abnormalities, such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.	
Diagnostic work-up History with specific questions related to drug exposure (eg, chemotherapy, sirolimus, tacrolimus, opana ER antibiotics, quinine) Physical examination, peripheral smear ADAMTS13 activity level and inhibitor titer LDH, haptoglobin, reticulocyte count, bilirubin, urinalysis to rule out other causes PT, activated PTT, fibrinogen Blood group and antibody screen, direct antiglobulin test, CMV serology Consider CT/MRI brain, echocardiogram, ECG Viral studies Note: This disorder is usually associated with a severe drop in platelets and hemolysis/anemia precipitously	
Grading	Management
All grades	The first step in the management of TTP is a high index of suspicion for the diagnosis and timely recognition; hematology consult should immediately be called, as delay in identification is associated with increased mortality/morbidity. Initially, the patient should be stabilized and any critical organ dysfunction stabilized
G1: Evidence of RBC destruction (schistocytosis) without anemia, renal insufficiency, or thrombocytopenia clinically G2: Evidence of RBC destruction (schistocytosis) without clinical consequence with G2 anemia and thrombocytopenia	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting ICPi therapy Hematology consult Administer 0.5-1 mg/kg/d prednisone
G3: Laboratory findings with clinical consequences (G3 thrombocytopenia, anemia, renal insufficiency > 2) G4: Life-threatening consequences (eg, CNS hemorrhage or thrombosis/embolism or renal failure)	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 In conjunction with hematology, initiate PEX according to existing guidelines with further PEX dependent on clinical progress Administer methylprednisolone 1 g IV daily for 3 days, with the first dose typically administered immediately after the first PEX May offer rituximab
8.3 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	

8.0 Hematologic Toxicities	
Abdominal pain, vomiting, and occasionally fever Pallor Small, unexplained bruises or bleeding from the nose and mouth Fatigue and irritability Confusion or seizures High blood pressure Swelling of the face, hands, feet, or entire body	
Diagnostic work-up History and physical examination (special consideration for new history of high-risk drugs, hypertension, or cardiac causes) CBC with indices Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis. Serum creatinine ADAMTS13 (to rule out TTP) Homocysteine/methylmalonic acid Complement testing C3, C4, CH50 (complement inhibitory antibodies for suspected familial) Evaluate reticulocyte count and mean corpuscular volume Evaluation of infectious cause, including screening for EBV, CMV, HHV6 Evaluation for nutritional causes of macrocytosis (B12 and folate) Pancreatic enzymes Evaluation for diarrheal causes, shiga toxin, Escherichia coli 0157, etc Direct antibody test (Coombs test), haptoglobin, LDH, and other etiologies of anemia Evaluation for common drugs causing hemolysis (tacrolimus, cyclosporine, sirolimus, etc) Evaluation for concurrent confusion	
Grading	Management
G1-2: Evidence of RBC destruction (schistocytosis) without clinical consequences of anemia, thrombocytopenia Grade 2 G3: Laboratory findings with clinical consequences (eg, renal insufficiency, petechiae) G4: Life-threatening consequences (eg, CNS thrombosis/ embolism or renal failure)	Continue ICPi with close clinical follow-up and laboratory evaluation Supportive care Permanently discontinue ICPi Begin therapy with eculizumab therapy 900 mg weekly for four doses, 1,200 mg week 5, then 1,200 mg every 2 weeks Red blood transfusion according to existing guidelines
8.4 Aplastic anemia	
Definition: Condition in which the body stops producing enough new blood cells	
Diagnostic work-up 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	Hold ICPi and provide growth factor support and close

8.0 Hematologic Toxicities	
following: ANC < 500, peripheral platelet < 20,000, and reticulocyte < 20,000	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%	Hold ICPi and monitor weekly for improvement; if not resolved, discontinue treatment until AE has reverted to G1 Hematology consult, growth factor support Horse ATG plus cyclosporine If no response, repeat immunosuppression with rabbit ATG plus cyclosporine, cyclophosphamide For refractory patients, consider eltrombopag plus supportive care
8.5 Lymphopenia	
Definition: An abnormally low level of lymphocytes in PB; for adults, counts of < 1,500/mm^3	
Diagnostic work-up History and physical examination (special attention for lymphocyte-depleting therapy such as fludarabine, ATG, corticosteroids, cytotoxic chemotherapy, radiation exposure, etc, as well as history of autoimmune disease, family history of autoimmune disease) Evaluation of nutritional state as cause Spleen size CBC with differential, peripheral smear and reticulocyte counts CXR for evaluation of presence of thymoma Bacterial cultures and evaluation for infection (fungal, viral, bacterial specifically CMV/HIV)	
Grading	Management
G1-2: 500-1,000 PB lymphocyte count G3: 250-499 PB lymphocyte count G4: < 250 PB lymphocyte count	Continue ICPi Continue ICPi, checking CBC weekly for monitoring, initiation of CMV screening Consider holding ICPi Initiate *Mycobacterium avium* complex prophylaxis and *Pneumocystis jirovecii* prophylaxis, CMV screening. HIV/hepatitis screening if not already done May consider EBV testing if evidence of lymphadenopathy/hepatitis, fevers, hemolysis consistent with lymphoproliferative disease
8.6 Immune thrombocytopenia	
Definition: An autoimmune disorder characterized by immunologic destruction of otherwise normal platelets	
Diagnostic work-up History and physical examination (special attention for lymphocyte-depleting therapy, such as fludarabine, ATG, corticosteroids, cytotoxic therapy) Family history of autoimmunity or personal history of autoimmune disease History of viral illness CBC Peripheral blood smear, reticulocyte count Bone marrow evaluation only if abnormalities in the above test results and further investigation is necessary for a diagnosis Patients with newly diagnosed immune thrombocytopenia should undergo testing for HIV, hepatitis C virus, hepatitis B virus, and Helicobacter pylori Direct antigen test should be checked to rule out concurrent Evan syndrome Nutritional evaluation Bone marrow evaluation if other cell lines affected and concern for aplastic anemia	
Grading	Management

8.0 Hematologic Toxicities	
G1: Platelet count < 100/µL G2: Platelet count < 75/µL	Continue ICPi with close clinical follow-up and laboratory evaluation Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1 Administer prednisone 1 mg/kg/d (dosage range, 0.5-2 mg/kg/d) orally for 2-4 weeks after which time this medication should be tapered over 4-6 weeks to the lowest effective dose IVIG may be used in conjunction with corticosteroids if a more-rapid increase in platelet count is required.
G3: Platelet count < 50/µL	Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1
G4: Platelet count < 25/µL	Hematology consult Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue treatment IVIG used with corticosteroids when a more-rapid increase in platelet count is required 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 6 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

8.0 Hematologic Toxicities	
	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) 6 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, paroxusmal nocturnal hemoglobinuria; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell count; TTP, thrombotic thrombocytopenic purpura.

Table A9 Management of Cardiovascular irAEs in Patients Treated With ICPis

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

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

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

Table A10 Management of Ocular irAEs in Patients Treated With ICPis

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

10.0 Ocular Toxicities	
	intravitreal/periocular/topical corticosteroids per ophthalmologist opinion
Additional considerations: Consider use of infliximab or other TNF-a 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 5 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 Nov 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 (eg, 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 (eg, 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 (eg, 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, AESIs and DLTs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (eg, 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 (ie, 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

Adverse events of special interest can be serious or nonserious events; however, must always be reported on the SAE/AESI Report Form, and will follow the procedure described below for reporting SAEs and AESIs.

Categories of AESIs related to M7824 include:

- Infusion-related reactions including immediate hypersensitivity
- Immune-related adverse events
- Potential TGFβ-mediated skin adverse events
- Treatment-related anemia 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 and Adverse Events of Special Interest

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 (eg, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (eg, laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow-up information (eg, 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.

Adverse Events of Special Interest

In the event of a nonserious AESI, the Investigator will notify the Sponsor/designee by completing the AESI Report Form in the eCRF within 24 hours. Serious AESIs must be reported in an expedited manner as SAEs as outlined above.

Reporting of nonserious AESIs 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.

Appendix 6 Clinical Laboratory Tests

Table 16 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments [a]	Parameters			
Hematology	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	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 [b]	Iron Panel: TIBC, iron, ferritin, serum folate/B12	TST (if positive history of tuberculosis exposure)	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 [c]	• 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).			

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 Performed at Screening only.

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

Appendix 7 Genetics

Use/Analysis of DNA

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

  DNA samples will be analyzed for genetic research. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

- In addition, DNA samples will be used for research related to M7824 or NSCLC and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to M7824 and/or treatments of this drug class and NSCLC. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

- The results of genetic analyses may be reported in the CSR or in a separate study summary.

- Details on processes for collection and shipment of these samples can be found in the Laboratory Manual. The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- Retention time and possible analysis of DNA sample after the study ends are specified in the respective ICF.

Appendix 8 Sponsor Signature Page

Study Title:	A Phase II, Multicenter, Randomized, Open-Label, Controlled Study of M7824 versus Pembrolizumab as a First-line Treatment in Patients with PD-L1 Expressing Advanced Non-small Cell Lung Cancer
Regulatory Agency Identifying Numbers:	US IND 124757 EudraCT 2018-001517-32
Clinical Study Protocol Version:	23 May 2018/Version 1.0

I approve the design of the clinical study:

Signature

24 May 2018
Date of Signature

Name, academic degree:	Laureen Ojalvo, MD, PhD
Function/Title:	Medical Responsible
Institution:	EMD Serono Research & Development Institute, Inc., an affiliate of Merck KGaA
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Appendix 9 Coordinating Investigator Signature Page

Study Title:	A Phase II, Multicenter, Randomized, Open-Label, Controlled Study of M7824 versus Pembrolizumab as a First-line Treatment in Patients with PD-L1 Expressing Advanced Non-small Cell Lung Cancer
Regulatory Agency Identifying Numbers:	US IND 124757 EudraCT 2018-001517-32
Clinical Study Protocol Version:	23 May 2018/Version 1.0
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

May 24th 2018
Date of Signature

Name, academic degree:	Luis Paz-Ares Rodriguez, MD
Function/Title:	
Institution:	Hospital Universitario 12 de Octubre Servicio de Oncologia
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Appendix 10 Principal Investigator Signature Page

Study Title:	A Phase II, Multicenter, Randomized, Open-Label, Controlled Study of M7824 versus Pembrolizumab as a First-line Treatment in Patients with PD-L1 Expressing Advanced Non-small Cell Lung Cancer
Regulatory Agency Identifying Numbers:	US IND 124757 EudraCT 2018-001517-32
Clinical Study Protocol Version:	23 May 2018/Version 1.0
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 Conference on 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:	Give only highest academic degree
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: