Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase Ib/II, Open-Label Study of M7824 in Combination with Chemotherapy in Participants with Stage IV Non-small Cell Lung Cancer
Study Number:	MS200647_0024
Merck Compound Number:	M7824
Short Title:	M7824 in Combination with Chemotherapy in Stage IV NSCLC
Coordinating Investigator:	PPD PPD
Sponsor Name and Legal Registered Address:	For all countries, except the USA: Merck KGaA Frankfurter Str. 250 Darmstadt, Germany An affiliate of Merck KGaA, Darmstadt, Germany In the USA: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA, 01821, USA
Regulatory Agency Identifying Numbers:	IND: PPD EudraCT: 2018-004040-28
Protocol Version:	22 December 2021/Version 5.0

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	20 Nov 2018
2.0	Global Protocol Amendment 1.0	02 Jul 2019
3.0	Global Protocol Amendment 2.0	12 Nov 2019
4.0	Global Protocol Amendment 3.0	20 Oct 2020 (submitted to US FDA only and was later withdrawn)
5.0	Global Protocol Amendment 4.0	22 Dec 2021

Protocol Version [5.0] (22 December 2021)

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

Overall Rationale for the Amendment

The primary purpose of this amendment is to align with the current Investigator Brochure (Version 7.0) and to update the risk classification and minimization measures. In light of three of M7824 studies closing down prematurely, further pharmacokinetic/anti-drug antibody samples are no longer collected as communicated in the letter to the Investigators (dated 02 November 2021). In addition, the sequence of analysis is updated to remove the main analysis of efficacy endpoints 18 months after the last participant started treatment and no further analyses will be done except in the case of a new safety signal observation. The interim analysis data are considered mature and the prespecified main analysis is no longer needed.

Section# and Name	Description of change	Brief rationale
Title Page	Changed Name and Contact information of Coordinating Investigator Removed “Amendment Number”, “Replaces Version” and “Approval Date” rows Removed Medical Responsible and Medical Monitor’s names and contact information	Administrative change
1.1 Synopsis 1.3 Schedule of Activities 3 Objectives and Endpoints 8.5 Pharmacokinetics 8.10 Immunogenicity Assessments	A note is added to state that sample collection has been stopped as communicated in the Investigator letter dated as 2 November 2021	Collection of PK/ADA samples is no longer required and has been removed from the protocol

Section# and Name	Description of change	Brief rationale
2.2 Background 2.3 Benefit/Risk Assessment	Revised text to update the risk classification and to add the discontinuation of 3 randomized controlled studies	To update the risk classification and minimization measures and refer to the Investigator's Brochure V7.0 for full safety details
6.8.1.1 and 6.9.3.1 Infusion-related Reactions, Including Immediate Hypersensitivity	Clarified that signs or symptoms experienced by participants during the infusion or within 1 day thereafter should be evaluated as potential IRR. Infusion-related reactions are reclassified from "important identified risk" to "identified risk" for M7824. Clarified premedication If an investigator deems it necessary prior to M7824 infusion to a particular participant. The list of events has been updated accordingly.	The risk reclassification was based on in depth analysis of a pooled safety dataset of N = 765 participants who received bintrafusp alfa monotherapy at 1,200 mg Q2W as reflected in Investigator's Brochure V7.0
6.8.1.2 and 6.9.3.2 Immune-related Adverse Events	Risk reclassification has been done and the list of events has been updated accordingly Added a list of irAEs and clarified that they are important identified or important potential risks for M7824. Added a reference to the current NCCN guideline	
6.8.1.3 Skin Adverse Events 6.9.3.3 TGFβ Inhibition Mediated Skin Reactions Appendix 4	Potential TGFβ mediated skin AEs have been renamed as "TGFβ inhibition mediated skin reactions"	
6.8.1.4 Anemia 6.9.3.4 Anemia	The term "treatment-related anemia adverse events" have been revised to "anemia" and reclassified from "important potential risk" to "important identified risk" for M7824 Added recommendation for thorough investigations of new anemia cases of unspecified etiology as there could be many reasons for anemia in patients with advanced cancer General guidance for anemia management and evaluation was updated	
6.8.1.5 Bleeding Adverse Events 6.9.3.5 Management of bleeding events	Bleeding AEs have been reclassified from "potential risks" to "important identified risks" for M7824 Updated texts for management of bleeding events accordingly.	
6.8.2 Additional Important Potential Risks	Title updated to add Important	

Section# and Name	Description of change	Brief rationale
6.8.2.1 Impaired Wound Healing	The risk name “Alterations in Wound Healing or Repair of Tissue Damage” has been changed to “Impaired Wound Healing”	
6.8.2.3 Mild to Moderate Mucosal Bleeding Events (in Version 3.0 of the protocol)	Deleted previously present “Section 6.8.2.3” as bleeding AEs have been reclassified from “potential risks” to important identified risks	
6.9.3 Risk Management for M7824	Risk categorization has been revised and the list of events has been updated accordingly Updated the corresponding information for risk evaluation, risk management, and treatment modification guidance accordingly	
9.4.4 Sequence of Analysis	Sequence analysis is revised to remove prespecified main analysis (at 18 months after the last participant’s first dose. Text stating that further analyses may be performed, e.g., for publication purposes is removed. Specification that other interim analyses not specified in the protocol may be performed for internal planning purposes has been removed. Added text to state that if a new safety signal is observed an additional analysis will be done at the end of the study and included in the study report. No further analyses are planned for any other case.	The interim analysis data are considered mature and the prespecified main analysis is no longer needed

ADA = antidrug antibodies; AE = adverse event(s); irAE = immune-related AEs; IRR = infusion related reaction; NCCN = National Comprehensive Cancer Network; PK = pharmacokinetics; Q2W = once every 2 weeks; TGFβ = transforming growth factor beta; V = version.

Note: Minor changes have been performed throughout the protocol to address consistency pertaining to major changes made in the protocol or to add further clarity and precision.

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A Phase Ib/II, Open-Label Study of M7824 in Combination with Chemotherapy in Participants with Stage IV Non-small Cell Lung Cancer

Short Title: M7824 in Combination with Chemotherapy in Stage IV NSCLC

CCI [redacted]

[redacted]

Objectives and Endpoints:

Objectives	Endpoints (Outcome Measures)
Primary	
To evaluate the safety and tolerability of M7824 in combination with chemotherapy	• Occurrence of dose-limiting toxicities (DLTs) during the 3-week DLT observation period • Occurrence of treatment-emergent adverse events and treatment-related adverse events
Secondary	
To evaluate objective response rate (ORR) for M7824 in combination with chemotherapy	Confirmed objective response according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) assessed by Investigator
To evaluate progression-free survival (PFS) for M7824 in combination with chemotherapy	PFS according to RECIST 1.1 assessed by Investigator
To evaluate overall survival (OS) for M7824 in combination with chemotherapy	OS
To evaluate duration of response (DoR) for M7824 in combination with chemotherapy	DoR assessed from complete response (CR) or partial response (PR) until progression of disease (PD) or death
To characterize pharmacokinetic (PK) profile of M7824 (Sample collection has been stopped as communicated in the Investigator letter dated as 2 November 2021)	• PK profile of M7824 in terms of C_{eoi} and C_{trough} for all participants • PK profile of M7824 in terms of AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{½}$ (only for participants in the Safety part of the study)
To evaluate the immunogenicity of M7824 (Sample collection has been stopped as communicated in the Investigator letter dated as 2 November 2021)	Immunogenicity of M7824, as measured by antidrug antibody (ADA) assay, from Screening through the last Safety Follow-up Visit

Overall Design:

This is a Phase Ib/II, open-label study of M7824 in combination with chemotherapy in participants with Stage IV NSCLC regardless of programmed death (ligand) 1 (PD-[L]1) expression status. The dose for M7824 is 2,400 mg administered as an intravenous infusion once every 3 weeks. The study has 4 cohorts:

- Cohort A: cisplatin or carboplatin + pemetrexed + M7824 during induction followed by maintenance with M7824 + pemetrexed in participants with non-squamous Stage IV NSCLC (first-line [1L])
- Cohort B: carboplatin + paclitaxel or nab-paclitaxel + M7824 during induction followed by maintenance with M7824 in participants with non-squamous or squamous Stage IV NSCLC (1L)
- Cohort C: cisplatin or carboplatin + gemcitabine + M7824 during induction followed by maintenance with M7824 in participants with non-squamous or squamous Stage IV NSCLC (1L)
- Cohort D: docetaxel + M7824 during induction followed by maintenance with M7824 in participants with non-squamous or squamous Stage IV NSCLC who had disease progression on previous 1L treatment with PD-(L)1 inhibitors in combination with platinum-based chemotherapy, or 1L treatment with platinum-based chemotherapy followed by 2L treatment with PD-(L)1 inhibitors, or 1L PD-(L)1 inhibitor followed by 2L platinum-based chemotherapy.

This study is divided in 2 parts (safety and expansion parts) and includes:

Safety part - Cohorts A to D

- 28-day Screening period
- Treatment with M7824 in combination with chemotherapy for 4 cycles (each cycle is 21 days) followed by maintenance therapy for up to 31 cycles, or until unacceptable toxicities, confirmed disease progression, or death, whichever occurs first
- Safety Follow-up Visits are at 28 days (± 5 days) (or prior to starting a subsequent treatment) and 12 weeks (± 2 weeks) after the last dose of M7824 plus pemetrexed (Cohort A) or M7824 in maintenance (Cohorts B, C, and D)
- Long-term follow-up should be performed every 12 weeks (± 2 weeks) after last dose of M7824 plus pemetrexed (Cohort A) or M7824 in maintenance (Cohorts B, C, and D) up to 3 years after the last participant is included in the study according to Schedule of Activities. Long-term follow-up can be performed in person or by phone call, as clinically indicated
- For each cohort, 8 participants will be enrolled during the safety part of the study to evaluate the safety and tolerability of each combination treatment. The combination will be considered safe if DLTs are observed in ≤ 2 of 8 evaluable participants. If DLTs are observed in ≥ 3 of the 8 participants, the Safety Monitoring Committee (SMC) will give a recommendation regarding clearing the corresponding combination based on a review of all

relevant parameters including adverse events (AEs) and serious adverse event (SAEs) and benefit-risk assessment for that cohort.

Expansion part - Cohort A

- Additional 32 participants will be enrolled in the expansion part of Cohort A after the safety profile of the combination is cleared by the SMC. Cohort A will serve as pilot cohort to assess additional safety data and preliminary efficacy. Expansion of Cohorts B, C, and D may be considered at a later date based on the safety profile of each combination and on emerging data. If applicable, the information will be described in a future protocol amendment.

Number of Participants:

In total, approximately 64 participants will be enrolled in the study.

Study Intervention Groups and Duration:

Participants with Stage IV NSCLC regardless of PD-(L)1 expression status and who meet the study criteria will receive treatment with M7824 at a dose of 2,400 mg (intravenous) every 3 weeks in combination with chemotherapy for 4 cycles (each cycle is 21 days) followed by up to 31 cycles in maintenance with M7824 and pemetrexed (Cohort A) or M7824 alone (Cohort B, C, and D).

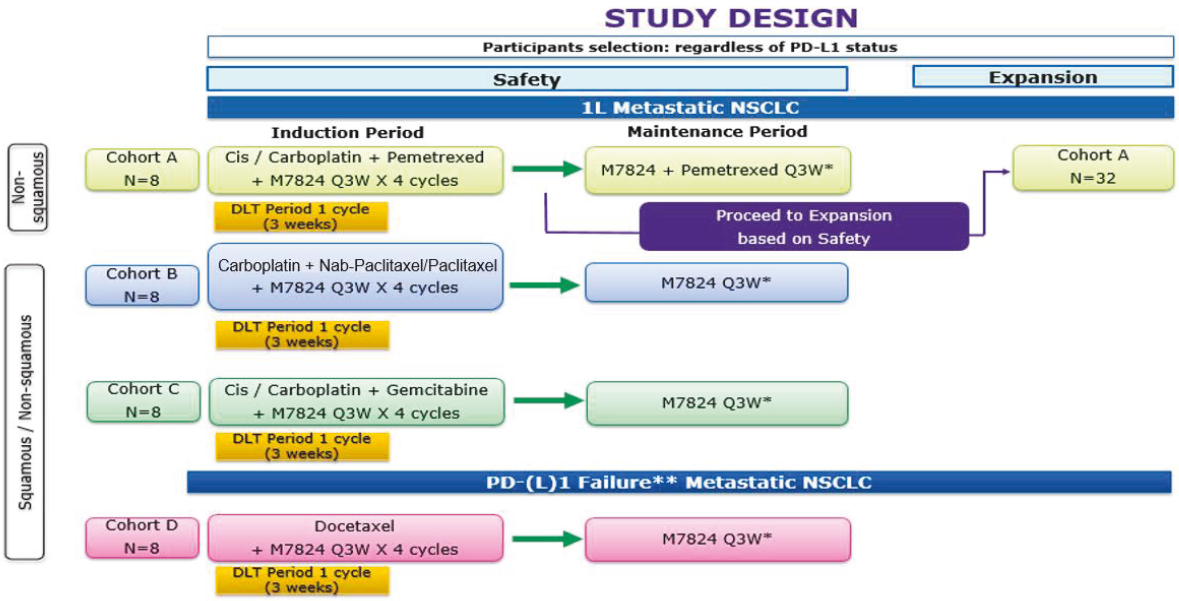
Involvement of Special Committee(s): Yes

Safety Monitoring Committee (SMC) will review the safety data periodically. The specific working procedures and frequency will be described in an SMC Charter.

Independent Review Committee (IRC) will assess tumor response according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and immune-related RECIST (irRECIST) retrospectively only if deemed appropriate. The IRC membership, assessment criteria details, mandate, and processes of the IRC are provided in the IRC Charter if the analysis are to be performed.

1.2 Schema

Figure 1 Study Design Diagram



* Up to 31 cycles (approximately 2 years), PD, or unacceptable toxicity.

** Participants who had disease progression on previous 1L treatment with PD-(L)1 inhibitors in combination with platinum-based chemotherapy, or 1L treatment with platinum-based chemotherapy followed by 2L treatment with PD-(L)1 inhibitors, or 1L PD-(L)1 inhibitor followed by 2L platinum-based chemotherapy are enrolled in Cohort D.

1L = first-line; 2L = second-line; DLT = dose-limiting toxicity; NSCLC = non-small cell lung cancer; PD = progression of disease; PD-(L)1 = programmed death (ligand) 1; Q3W = every 3 weeks.

1.3 Schedule of Activities

Table 1 Schedule of Activities – During Treatment

Assessments & Procedures	Screening Day -28 to W1D1	Induction Period (± 3 days/cycle)				Maintenance Period (- 3 / + 7 days)		EoT	Safety Follow-up Visit		Long-term Follow-up	Notes
		V1	V4 (DLT Visit)	V7	V10	V13	Until PD or EoT	On the Day of or Within 7 Days of Decision	28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment	Every 12 weeks (± 2 weeks)	DLT will be assessed for participants in the safety part of the study
		W1	W4	W7	W10	W13						
		D1	D22	D43	D64	D85						
Administrative Procedures												
Written informed consent	X											Screening tests performed prior informed consent signing as part of routine care will be accepted if they are within 28 days screening window.
Inclusion/ exclusion/ Enrollment (if eligible)	X	X[a]										a: Confirmation of eligibility via an abbreviated checklist is required prior to dosing on W1D1.
Demographic data	X											
Medical history	X											Medical history includes substance usage (tobacco and nicotine).
Documentation of concomitant medication and procedures	X	X	X	X	X	X	Every 3 weeks	X	X	X	X	Concomitant medication and procedures should be collected in accordance with the AE reporting period. See Sections 8.3.1, 8.3.2 and Appendix 4 for definition of the AE/SAE, reporting period, and follow-up.

Assessments & Procedures	Screening Day -28 to W1D1	Induction Period (± 3 days/cycle)				Maintenance Period (- 3 / + 7 days)		EoT	Safety Follow-up Visit		Long-term Follow-up	Notes
		V1	V4 (DLT Visit)	V7	V10	V13	Until PD or EoT	On the Day of or Within 7 Days of Decision	28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment	Every 12 weeks (± 2 weeks)	DLT will be assessed for participants in the safety part of the study
		W1	W4	W7	W10	W13						
		D1	D22	D43	D64	D85						
Prior anticancer drug/ radiotherapy/ procedures	X											
Subsequent anticancer therapy (any line)									X	X	X	
Survival follow-up											X	
Drug Administration - See Table 2												
Tumor Assessments												
CT scan (chest/abdomen/pelvis/other as clinically indicated)	X[b]			X (±7 days)		X (± 7 days)	Every 6 weeks up to 12 months, then every 12 weeks (± 7 days)					b: Ideally as close to W1D1 as possible (see Section 8.1). Confirmation of CR, PR, and PD is required as described in Section 8.1. If a participant cannot receive iodinated contrast, or if regional radiation regulations prevent full CT scan, CT scan of the chest without iodinated contrast is required. MRI of abdomen and pelvis area, using gadolinium enhancement (according to local practice) is permitted (see Section 8.1).
Brain MRI/CT	X[c]	As clinically indicated										c: Ideally as close to W1D1 as possible. Brain metastasis (untreated) should be followed at the tumor evaluation visits. Confirmation of CR, PR, and PD is required as described in Section 8.1.

Assessments & Procedures	Screening Day -28 to W1D1	Induction Period (± 3 days/cycle)				Maintenance Period (- 3 / + 7 days)		EoT	Safety Follow-up Visit		Long-term Follow-up	Notes
		V1	V4 (DLT Visit)	V7	V10	V13	Until PD or EoT	On the Day of or Within 7 Days of Decision	28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment	Every 12 weeks (± 2 weeks)	DLT will be assessed for participants in the safety part of the study
		W1	W4	W7	W10	W13						
		D1	D22	D43	D64	D85						
Bone scan	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.
Tumor Evaluation/Staging during follow-up												
Tumor evaluation/staging (CT Scan/MRI/other established methods)											X	CT scan should be performed every 12 weeks during follow-up up to progression or start of new treatment. Brain MRI should be done according to local practice. If a participant cannot receive iodinated contrast, or if regional radiation regulations prevent full CT scan, CT scan of the chest without iodinated contrast is required. MRI of abdomen and pelvis area, using gadolinium enhancement (according to local practice) is permitted (see Section 8.1). These evaluations should be documented by the Investigator and uploaded to the imaging repository, if available.
Response and progression on subsequent treatment											X	Investigators should follow local clinical practice for monitoring disease status on subsequent lines of therapy. Disease evaluations should be documented by the Investigator, and uploaded to the imaging repository, if available.

Assessments & Procedures	Screening Day -28 to W1D1	Induction Period (± 3 days/cycle)				Maintenance Period (- 3 / + 7 days)		EoT	Safety Follow-up Visit		Long-term Follow-up	Notes
		V1	V4 (DLT Visit)	V7	V10	V13	Until PD or EoT	On the Day of or Within 7 Days of Decision	28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment	Every 12 weeks (± 2 weeks)	DLT will be assessed for participants in the safety part of the study
		W1	W4	W7	W10	W13						
		D1	D22	D43	D64	D85						
Safety Assessment												
Documentation of AEs[d]	X	X	X	X	X	X	Every 3 weeks	X	X[e]	X[e,f]	X[e,f]	d: AE should be collected at every site visit during the AE reporting period irrespective of whether dosing took place or not. See Sections 8.3.1, 8.3.2, and Appendix 4 for definition of the AE/SAE, reporting period, and follow-up. e: Main questions include any new safety concerns, any new anticancer treatment started (details with dates), and participant death. f: 12-week and long-term AE follow-up may be conducted via phone call.
Physical examination	X	X[g]	X[g]	X[g]	X[g]	X[g]	Every 3 weeks	X	X			Complete PE at Screening. Subsequent focused PEs to be performed as per local standard practice and as clinically indicated. g: PE should be performed at each visit according to Table 2 during induction.
Skin Assessment	X			X		X	Every 6 weeks	X	X			See Section 0 for participants experiencing a dermatologic-related AE.
Vital signs	X[h]	X[i]	X[i]	X[i]	X[i]	X[i]	Every 3 weeks	X	X			h: Including weight and height (height at Screening only). i: Performed at each visit according to Table 2 during induction.
ECOG PS	X	X	X	X	X	X	Every 3 weeks	X	X			
12-lead ECG	X											12-lead ECG will be repeated if clinically indicated (See Section 8.2.3).

Assessments & Procedures	Screening Day -28 to W1D1	Induction Period (± 3 days/cycle)				Maintenance Period (- 3 / + 7 days)		EoT	Safety Follow-up Visit		Long-term Follow-up	Notes
		V1	V4 (DLT Visit)	V7	V10	V13	Until PD or EoT	On the Day of or Within 7 Days of Decision	28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment	Every 12 weeks (± 2 weeks)	DLT will be assessed for participants in the safety part of the study
		W1	W4	W7	W10	W13						
		D1	D22	D43	D64	D85						
Laboratory Assessments												
Viral serology (HBV and HCV)	X	As clinically indicated in participants with a history of HBV or HCV infection.										HIV testing is not mandated for study inclusion; 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. See Appendix 5 for detailed information of HBV and HCV serology.
Hematology	X	X[j]	X[j]	X[j]	X[j]	X	Every 3 weeks	X	X			j: Performed when either M7824 or chemotherapy or both are administered during induction. Details on blood tests under this category are listed in Appendix 5. Samples must also be drawn within 48 hours and results to be reviewed prior to dose administration.
Hemostaseology	X	Repeat only if clinically indicated										Details on blood tests under this category are listed in Appendix 5. Samples must also be drawn within 48 hours and results to be reviewed prior to dose administration.
Core chemistry						Every 3 weeks (not when chemistry Panel A is performed)						Core chemistry are listed in Appendix 5. Samples must also be drawn within 48 hours and results to be reviewed prior to dose administration.

Assessments & Procedures	Screening Day -28 to W1D1	Induction Period (± 3 days/cycle)				Maintenance Period (- 3 / + 7 days)		EoT	Safety Follow-up Visit		Long-term Follow-up	Notes
		V1	V4 (DLT Visit)	V7	V10	V13	Until PD or EoT	On the Day of or Within 7 Days of Decision	28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment	Every 12 weeks (± 2 weeks)	DLT will be assessed for participants in the safety part of the study
		W1	W4	W7	W10	W13						
		D1	D22	D43	D64	D85						
Full serum chemistry Panel A	X	X[k]	X[k]	X[k]	X[k]	X	Every 6 weeks until W24	X	X			k: Performed when either M7824 or chemotherapy or both are administered during induction. See Appendix 5 for individual tests in each laboratory panel. Samples must also be drawn within 48 hours and results to be reviewed prior to dose administration.
Full serum chemistry Panel B	X	As clinically indicated										See Appendix 5 for individual tests in each laboratory panel.
Urinalysis	X	As clinically indicated										Full urinalysis (dipstick plus microscopic evaluation) at the Screening visit and then as clinically indicated thereafter (see Appendix 5). If the urinalysis is abnormal, then a culture should be performed.
β-HCG pregnancy test (only applicable to WOCBP)	X	X	X	X	X	X	Every cycle		X			β-HCG must be determined from serum at Screening and from a urine or serum sample thereafter once every cycle and at the 28-day Safety Follow-up Visit. Results of the most recent pregnancy test should be available prior to dosing of study intervention.
T_4 and TSH	X			X		X	Every 6 weeks		X			

Assessments & Procedures	**Screening Day -28 to W1D1**	**Induction Period (± 3 days/cycle)**				**Maintenance Period (- 3 / + 7 days)**		**EoT**	**Safety Follow-up Visit**		**Long-term Follow-up**	**Notes**
		V1	**V4 (DLT Visit)**	**V7**	**V10**	**V13**	**Until PD or EoT**	**On the Day of or Within 7 Days of Decision**	**28 Days (± 5 days) after Last Treatment**	**12 Weeks (± 2 weeks) after Last Treatment**	**Every 12 weeks (± 2 weeks)**	DLT will be assessed for participants in the safety part of the study
		W1	**W4**	**W7**	**W10**	**W13**						
		D1	**D22**	**D43**	**D64**	**D85**						
PK, ADA, CCI [redacted]												
Blood sample for PK (Sample collection has been stopped as communicated in the Investigator letter dated as 2 November 2021)		X/X[l] (pre/ eoi) **See Note for D1, 2, 8 and 15 during the safety part only**	X/- (pre/ eoi)	X/X (pre/ eoi)	X/- (pre/ eoi)	X/- (pre/ eoi)	Pre-infusion sample at Weeks 19 and 25 and then every 12 weeks	X	X	X		Samples for PK analysis to be taken before (pre) M7824 infusion (as close to the start of the infusion as possible), immediately after the completion of M7824 infusion (eoi, 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 is defined by a sample not being drawn or time of collection not being recorded. l: Additional blood samples for PK for the safety part (only): Day 1: 4 hours after the start of the M7824 infusion; Day 2: 24 hours after Day 1 start of M7824 infusion; Day 8, and Day 15.

Assessments & Procedures	Screening Day -28 to W1D1	Induction Period (± 3 days/cycle)				Maintenance Period (- 3 / + 7 days)		EoT	Safety Follow-up Visit		Long-term Follow-up	Notes
		V1	V4 (DLT Visit)	V7	V10	V13	Until PD or EoT	On the Day of or Within 7 Days of Decision	28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment	Every 12 weeks (± 2 weeks)	DLT will be assessed for participants in the safety part of the study
		W1	W4	W7	W10	W13						
		D1	D22	D43	D64	D85						
Blood Sample for ADA (Sample collection has been stopped as communicated in the Investigator letter dated as 2 November	X[m]		X /- (pre/ eoi)	X /- (pre /eoi)	X / - (pre/e oi)	X /- (pre/ eoi)	Pre-dosing at Week 19 and 25 and then every 12 weeks	X	X	X		m: Blood samples can be at Screening or W1D1 prior to dose.

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	Screening Day -28 to W1D1	Induction Period (± 3 days/cycle)				Maintenance Period (- 3 / + 7 days)		EoT	Safety Follow-up Visit		Long-term Follow-up	Notes
Assessments & Procedures		**V1**	**V4 (DLT Visit)**	**V7**	**V10**	**V13**	**Until PD or EoT**	**On the Day of or Within 7 Days of Decision**	**28 Days (± 5 days) after Last Treatment**	**12 Weeks (± 2 weeks) after Last Treatment**	**Every 12 weeks (± 2 weeks)**	DLT will be assessed for participants in the safety part of the study
		W1	**W4**	**W7**	**W10**	**W13**						
		D1	**D22**	**D43**	**D64**	**D85**						
CCI [redacted]												

AE = adverse event; βHCG = β-human chorionic gonadotropin; CR = complete response; CT = computed tomography; D = Day; DLT = dose-limiting toxicity; CCI [redacted] ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eoi = end of infusion; EoT = end of treatment; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IRR = infusion-related reaction; iv = intravenous; MRI = magnetic resonance imaging; PD = progression of disease; PE = physical examination; PR = partial response; SAE = serious adverse event; T_4 = free thyroxine; CCI [redacted]; TSH = thyroid-stimulating hormone; V = visit; W = Week; WOCBP = Woman of childbearing potential.

Table 2 Study Intervention Administration Schedule

Assessments & Procedures	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Maintenance Period	EoT	Notes
	Cycle 1			Cycle 2			Cycle 3			Cycle 4			V13	Until EoT	On the Day of or Within 7 Days of Decision	
	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13			
	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85			
M7824	X			X			X			X			X	Every 3 weeks[a]		See Table 6 for dose and administration. M7824 should be administered prior to chemotherapy when given on the same day. Premedication prior to each dose is not mandatory. Steroids are not allowed as premedication for M7824. Allowed window: Induction period (± 3 days) and Maintenance Period (-3 / +7 days). a: Every 3 weeks for a total of 31 doses in maintenance.
Cisplatin	X			X			X			X						See Table 10 for predosing considerations for cisplatin. A corticosteroid-sparing approach for antiemetic prophylaxis should be preferred and evaluated on a case by case and chemotherapy regimen basis. See Section 6 for dose and administration. All the medications used as hydration (drugs and fluids) must be reported in the eCRF.
Carboplatin (immediately after paclitaxel or nab-paclitaxel, gemcitabine or pemetrexed)	X			X			X			X						Premedication should be administered as per standard practice. A corticosteroid-sparing approach for antiemetic prophylaxis should be preferred and evaluated on a case by case and chemotherapy regimen basis. See Section 6 for dose and administration.

Assessments & Procedures	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Maintenance Period		EoT	Notes
	Cycle 1			Cycle 2			Cycle 3			Cycle 4			V13	Until EoT	On the Day of or Within 7 Days of Decision	
	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13			
	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85			
Pemetrexed (only for participants for Cohort A)	X			X			X			X			X	Every 3 weeks[b]		See Section 6 for dose and administration. In addition, all participants should receive the appropriate corticosteroid premedications as per the local practice and approved label. Additional premedications should be administered as per standard practice. A corticosteroid-sparing approach for antiemetic prophylaxis should be preferred and evaluated on a case by case and chemotherapy regimen basis. b: Every 3 weeks for a total of 31 doses in maintenance period. Acetaminophen and/or antihistamines may be administered as premedication per institutional standard at the discretion of the Investigator.
Folic acid 350-1000 µg (only for participants for Cohort A)	Starting at day -5 and continuing 21 days after the last dose of pemetrexed															
Vitamin B12 (only for participants for Cohort A)	IM injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter															
Nab-paclitaxel (Administered before carboplatin. Only for participants in Cohort B)	X	X	X	X	X	X	X	X	X	X	X	X				See Section 6 for dose and administration. All participants should be premedicated with oral or injectable steroids according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice. A corticosteroid-sparing approach for antiemetic prophylaxis should be preferred and evaluated on a case by case and chemotherapy regimen basis.

Assessments & Procedures	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Maintenance Period		EoT	Notes
	Cycle 1			Cycle 2			Cycle 3			Cycle 4			V13	Until EoT	On the Day of or Within 7 Days of Decision	
	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13			
	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85			
Paclitaxel (Administered before carboplatin. Only for participants in Cohort B)	X			X			X			X						See Section 6 for dose and administration. All participants should be premedicated with oral or injectable steroids according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice. A corticosteroid-sparing approach for antiemetic prophylaxis should be preferred and evaluated on a case by case and chemotherapy regimen basis.
Gemcitabine (only for participants in Cohort C)	X	X		X	X		X	X		X	X					See Section 6 for dose and administration. A corticosteroid-sparing approach for antiemetic prophylaxis should be preferred and evaluated on a case by case and chemotherapy regimen basis.
Docetaxel (only for participants in Cohort D)	X			X			X			X						See Section 6 for dose and administration. All participants should be premedicated with oral or injectable steroids according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice. A corticosteroid-sparing approach for antiemetic prophylaxis should be preferred and evaluated on a case by case and chemotherapy regimen basis.
eCRF = electronic case report form; D = day; EoT = end of treatment; V = visit; W = week.																

2 Introduction

M7824 (MSB0011359C, bintrafusp alfa) is a first-in-class, intravenously administered bifunctional fusion protein that combines an anti-programmed death ligand 1 (PD-L1) antibody and the soluble extracellular domain of the human transforming growth factor β (TGFβ) receptor II (RII) as a TGFβ neutralizing 'trap', into a single molecule. Specifically, the protein is a heterotetramer, consisting of the 2 immunoglobulin light chains of anti-PD-L1, and 2 heavy chains comprising the heavy chain of anti-PD-L1 genetically fused via a flexible glycine-serine linker to the extracellular domain of the human TGFβRII. Bintrafusp alfa is the proposed international nonproprietary name for M7824.

M7824 is being developed for the treatment of participants with Stage IV non-small cell lung cancer (NSCLC) in combination with chemotherapy.

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

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response (DoR) was not reached in the 1,200 mg every 2 weeks cohort, with responses ongoing in CCI

[redacted]

2.2 Background

Lung cancer is the leading cause of cancer death 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 in combination with chemotherapy have shown improved treatment outcome and manageable safety profile in patients with advanced or metastatic NSCLC. The responses of PD-(L)1 inhibitors in combination with chemotherapy as 1L treatment for NSCLC are summarized in Table 3.

Table 3 Summary Efficacy Results of PD-(L)1 Inhibitors in Combination with Chemotherapy as First-line Treatment for NSCLC

Study	Design	PD-(L)1 inhibitor chemo combo vs. chemo alone		
		ORR (%)	PFS	OS
KEYNOTE-021 (Cohort G)	Phase II randomized, open-label, study in chemotherapy-naive, Stage IIIB or IV, nonsq NSCLC (no sensitizing EGFR or ALK mutations) Pembrolizumab + carboplatin + pemetrexed followed by pembrolizumab and pemetrexed maintenance therapy vs Carboplatin and pemetrexed followed by pemetrexed maintenance therapy N = 123	56.7 vs. 30.2 (p = 0.0016)	HR: 0.53 (95% CI: 0.33-0.86, p = 0.0049)	HR: 0.56 (95% CI: 0.32-0.95, p = 0.0151)
KEYNOTE-189	Phase III double-blind controlled study in metastatic nonsq 1L NSCLC (no sensitizing EGFR or ALK mutations) Pembrolizumab + pemetrexed + platinum-based chemotherapy vs. Placebo + pemetrexed + platinum-based chemotherapy N = 616	47.6 vs. 18.9 (p <0.001)	HR: 0.52 (95% CI: 0.43-0.64, p < 0.001); Median 8.8 vs. 4.9 months	HR: 0.49 (95% CI: 0.38-0.64, p < 0.001); Median not reached vs. 11.3 months
KEYNOTE-407	Phase III double-blind controlled study in metastatic sq 1L NSCLC Pembrolizumab + carboplatin + paclitaxel or nab-paclitaxel vs. Placebo+ carboplatin + paclitaxel or nab-paclitaxel N = 560 (data reported on 204, cutoff April 2018)	58.4 vs. 35.0 (p = 0.0004)	HR: 0.56 (95% CI: 0.45-0.70, p < 0.0001); Median 6.4 vs. 4.8 months	HR: 0.64 (95% CI: 0.49-0.85, p = 0.0008); Median 15.9 vs. 11.3 months
IMpower131	Phase III study in advanced Sq NSCLC A: atezolizumab + carboplatin + paclitaxel vs. B: atezolizumab + carboplatin + nab-paclitaxel vs. C: carboplatin + nab-paclitaxel N = 1021	49 (B) vs. 41 (C)	HR: 0.71 (95% CI: 0.60-0.85, p = 0.0001); Median 6.3 (B) vs. 5.6 (C) months	HR: 0.96 (95% CI: 0.78-1.18, p = 0.6931); Median 14.0 (B) vs. 13.9 (C) months

Study	Design	PD-(L)1 inhibitor chemo combo vs. chemo alone		
		ORR (%)	PFS	OS
IMpower150	Phase III nonsq1L NSCLC A: chemotherapy + atezolizumab vs. B: chemotherapy + atezolizumab + bevacizumab vs. C: chemotherapy + bevacizumab. N = 1202	63.5 (B) vs. 48.0 (C)	HR: 0.62 (95% CI: 0.52-0.74, p < 0.001); Median 8.3 (B) vs. 6.8 (C) months	HR: 0.78 (95% CI: 0.64-0.96, p = 0.02); Median 19.2 (B) vs. 14.7 (C) months
Source: Borghaei 2018; Gandhi 2018; Paz-Ares 2018; Jotte 2018; Socinski 2018. 1L = first-line; ALK = anaplastic lymphoma kinase; CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; nonsq = non-squamous; nab-paclitaxel = nano-particle albumin-bound paclitaxel; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-(L)1 = programmed death (ligand) 1; PFS = progression-free survival; Sq = squamous, vs = versus.				

M7824 is a bifunctional fusion protein that combines the extracellular domain of TGFβRII, which acts as a TGFβ neutralizing 'trap', and an anti-PD-L1 antibody into a single molecule.

The novel design of M7824, which neutralizes TGFβ and simultaneously inhibits the anti-PD-L1 pathway in the tumor microenvironment, may be more effective than agents targeting PD-L1 and TGFβ separately. In preclinical studies, M7824 was shown to have full biological activity in vitro including the ability to block PD-L1 and neutralize TGFβ simultaneously. Experiments demonstrated 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). Importantly, in the MC38 model, M7824 showed significantly better efficacy than the combination of avelumab plus TGFβ Trap control, supporting the rationale of combining the 2 active moieties in 1 molecule (Lan 2018).

M7824 enhanced the antitumor effects of a number of chemotherapy agents including gemcitabine or cisplatin in experiments investigating the combination of M7824 with standard of care therapies in mouse tumor models (Lan 2018 and unpublished data).

The overall safety profile with treatment of M7824 in Phase I is considered well tolerated, can be adequately managed and is consistent across various tumor types (refer to IB). The highest dose for M7824 in EMR200647-001 was 30 mg/kg every 2 weeks, which corresponds to 2,100 mg for a 70 kg participant and to 2,400 mg for an 80 kg participant. Based on clinical observations, M7824 was well tolerated up to 30 mg/kg, and the maximum tolerated dose (MTD) was not reached. The interim safety analysis performed with participants from expansion cohorts from EMR200647-001 showed that most of the observed events were in line with those expected in participants with advanced solid tumors and within the spectrum of similar class effects of mAb blocking the PD-1/PD-L1 axis and anti-TGFβ targeting therapies (refer to M7824 IB). The risks for M7824 are updated based on the safety data from 765 patients treated with M7824 monotherapy at 1200 mg every-two-weeks dose in the IB Version 7.0 (April 2021). The risk classification and minimization measures are revised in this amendment, see Section 6.8 for specifics. In addition, M7824 was evaluated at 2 dose levels (500 mg and 1,200 mg every 2 weeks) in the 2L NSCLC cohort in EMR200647-001, the safety profiles were comparable at the 2 dose levels.

The dose for M7824 in this study is 2,400 mg administered as an intravenous infusion once every 3 weeks. Since most chemotherapies are administered every 3 weeks, the same dosing interval for M7824 is preferred for convenience and compliance (for dose rationale see Section 4.3).

M7824 monotherapy demonstrated promising clinical activity in participants who received M7824 at 1,200 mg every 2 weeks as the 2L treatment for NSCLC across PD-L1 expression levels and in participants who were PD-(L)1 failures as summarized in Table 4.

Table 4 Efficacy According to RECIST 1.1 of M7824 in EMR200647-001 NSCLC Cohorts

	Objective Response Rate		Disease Control Rate	
	ORR (%)	95% CI	DCR (%)	95% CI
2L 1,200 mg[a] N = 40, assessed by Independent review	25.0	(12.7, 41.2)	47.5	(31.5, 63.9)
2L 500 mg[a] N = 40, assessed by Independent review	17.5	(7.3, 32.8)	32.5	(18.6, 49.1)
PD-(L)1 Failure[b] **1,200 mg** N = 83, assessed by Investigator	2 (2.4)	(0.3, 8.4)	24.1	(15.4, 34.7)

a Paz-Ares 2018. The data presented reflect a database cutoff of 23 July 2018.

b Participants have received and failed platinum-based chemotherapy and anti-PD-1 or anti-PD-L1 as monotherapy with disease progression (Barlesi 2017). The data presented reflect a database cutoff date of 07 September 2017. Two additional PRs were reported by Investigator after the data cutoff.

2L = second-line; CI = confident interval; DCR = disease control rate; ORR = objective response rate.

2.3 Benefit/Risk Assessment

Preclinically, in combination with standard of care therapies in mouse tumor models, M7824 enhanced the antitumor effects of a number of chemotherapy agents including oxaliplatin, 5-fluorouracil, gemcitabine, and cisplatin (Lan 2018 and unpublished data). Measures of animal body weight indicated that the doses of M7824 and chemotherapeutic agents used in preclinical combination studies were well tolerated by the mice. Modulation of the immune response through PD-1 inhibition may be enhanced by the potential immunogenic effects of cytotoxic chemotherapy, such as increasing the potential for antigen cross presentation by dendritic cells after the destruction of tumor cells, inhibiting myeloid-derived suppressor cells, increasing the ratio of cytotoxic lymphocytes to regulatory T cells, and blocking the STAT6 pathway to enhance dendritic-cell activity (Bracci 2014; Roselli 2013; Lesterhuis 2011). It is hypothesized that 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 to be more effective than agents that target only a single pathway.

The safety profile of M7824 has been monitored in EMR200647-001, MS200647-0008 and MS200647-0047 in more than 700 participants, the safety risks of M7824 were manageable and consistent with prior therapies targeting PD-(L)1 or TGFβ, with no new safety signals emerged. Consistent with other PD-(L)1 inhibitors the IRR and irAE are risks for M7824 (refer to IB for details). The frequency and severity of irAEs were comparable in participants with NSCLC treated

with M7824 at 2 dose levels (500 mg and 1,200 mg), and the spectrum of irAE were similar to other PD-(L)1 targeting drugs. No increased irAE risk was observed with M7824 due to blocking 2 immunosuppressive pathways.

TGFβ inhibition mediated skin reactions due to M7824 (including rash with hyperkeratosis keratoacanthomas [KA] and cutaneous squamous cell cancers [cSCC]) are important identified risks with M7824. These lesions were similar to observed skin lesions in individuals with genetic mutations in the TGFβ receptor (i.e. Ferguson-Smith Syndrome), and participants treated with the TGFβ-targeting agent, fresolimumab (Goudie 2011; Morris 2014). These skin AEs were observed in approximately 10.8% of participants without requiring treatment discontinuation, they were adequately managed and some spontaneously regressed (refer to IB version 7.0).

The risks for M7824 are updated based on the pooled safety data from 765 patients treated with M7824 monotherapy in the IB Version 7.0 (April 2021). The risk classifications are revised in this amendment (Protocol version 5.0). The important identified risks include TGFβ inhibition mediated skin reactions, anemia, bleeding adverse events and events listed for immune related adverse events. see Section 6.8 for the risks of M7824.

M7824 has demonstrated promising antitumor activities in Phase I studies. In 2L patients with NSCLC the response rates of M7824 monotherapy were substantially better than other PD-(L)1 inhibitor approved (Borghaei 2015; Herbst 2016; Fehrenbacher 2016). The promising activity of M7824 observed as a 2L treatment is expected to translate in treatment-naïve patients with advanced NSCLC, as seen in other checkpoint inhibitor NSCLC studies (Borghaei 2018; Gandhi 2018; Paz-Ares 2018; Jotte 2018; Socinski 2018) and summarized in Table 3. The antitumor activity as well as the disease control were also observed with M7824 as monotherapy in patients who failed previous therapies with checkpoint inhibitors (Gulley 2017).

Immune checkpoint inhibitors in combination with chemotherapy have shown improved treatment outcome and manageable safety profile in patients with advanced or metastatic NSCLC. Improving response and survival in 1L patients and patients who failed previous therapies will be meaningful as responses to immunotherapy are durable, and therapeutic, non-cytotoxic treatment options are limited.

The dose for M7824 in this study is 2,400 mg administered as an intravenous infusion once every 3 weeks (see Section 4.3). The potential overlapping toxicities of M7824 in combination with chemotherapy is unknown, however, cannot be ruled out (Bracci 2014). Assessment of the safety profile of M7824 and the established safety profile of chemotherapies did not trigger any special consideration for overlapping toxicity assessment in this study. In addition, based on different clearance mechanisms for chemotherapy versus M7824, pharmacokinetic (PK) interactions are unlikely. Furthermore, based on mechanisms of action of M7824 or chemotherapy, there are no expectations of exaggerated immune response (e.g. cytokine release) in M7824 and chemotherapy in combination.

Risks of M7824 in combination with chemotherapy, including chemotherapy associated myelotoxicity, will be closely monitored and assessed during the dose-limiting toxicity (DLT) period before Expansion part of the study. Additionally, participants who experienced irAEs with prior immunotherapy will be closely monitored for any enhanced risk due to immune response. A

general guidance on management of toxicities has been addressed with precautionary measures in terms of an AE monitoring strategy and treatment modification plan with other appropriate risk mitigation measures in the protocol (Section 6.8 and 6.9).

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of M7824 may be found in Section 4.2 and the IB.

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In the course of 2021, the data review outcome from the 3 randomized controlled studies in NSCLC and BTC (MS200647_0037 [NCT03631706], MS200647_0055 [NCT04066491] and MS200647_0005 [NCT03840902], which have been discontinued in the course of 2021, appears to indicate, consistently across 2 indications, either poorer observed hazard ratios for PFS and OS in the experimental arms with bintrafusp alfa or low likelihood for bintrafusp alfa to add benefits compared to standard of care. No new safety signal has been identified. The data review also showed that cases of early progression and death (i.e., within 60 days after start of treatment) were observed more frequently with bintrafusp alfa: 16 patients (10.6%) versus 9 patients (5.9%) in NSCLC Stage IV first line (bintrafusp versus pembrolizumab, MS200647-0037); 11 patients (7.5%) versus 2 patients (1.3%) in BTC first line (bintrafusp in combination with chemotherapy versus placebo plus chemotherapy, MS200647-0055); immature data with 3 patients (4.1%) versus 2 patients (2.6%) in NSCLC Stage III (bintrafusp plus concurrent chemoradiation followed by bintrafusp maintenance versus chemoradiation followed by durvalumab, MS200647-0005). Early deaths were due to progressive disease, signs and symptoms of progressive disease, or known treatment toxicities.

3 Objectives and Endpoints

The objectives and endpoints are defined in Table 5. Endpoint assessments are in Section 8.

Table 5 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)
Primary	
To evaluate the safety and tolerability of M7824 in combination with chemotherapy	• Occurrence of DLTs during the 3-week DLT observation period • Occurrence of TEAEs and treatment-related AEs
Secondary	
To evaluate objective response rate (ORR) for M7824 in combination with chemotherapy	Confirmed objective response according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) assessed by Investigator
To evaluate PFS for M7824 in combination with chemotherapy	PFS according to RECIST 1.1 assessed by Investigator
To evaluate overall survival (OS) for M7824 in combination with chemotherapy	OS

Objectives	Endpoints (Outcome Measures)
To evaluate DoR for M7824 in combination with chemotherapy	DoR assessed from complete response (CR) or partial response (PR) until progression of disease (PD) or death
To characterize pharmacokinetic (PK) profile of M7824 (Sample collection has been stopped as communicated in the Investigator letter dated as 2 November 2021)	• PK profile of M7824 in terms of C_{eoi} and C_{trough} for all participants • PK profile of M7824 in terms of AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{½}$ (only for participants in the Safety part of the study)
To evaluate the immunogenicity of M7824 (Sample collection has been stopped as communicated in the Investigator letter dated as 2 November 2021)	Immunogenicity of M7824, as measured by antidrug antibody (ADA) assay, from Screening through the last Safety Follow-up Visit
CCI [redacted]	

ADA = antidrug antibody; AE = adverse event; AUC_{0-t} = area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification calculated using the mixed log-linear trapezoidal rule (linear up, log down); $AUC_{0-\infty}$ = AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last}, as estimated using the linear regression from λz determination; $AUC_{0-\infty} = AUC_{0-t} + C_{last}$ pred/ λz; C_{eoi} = concentration immediately at the end of infusion; C_{max} = maximum serum concentration observed postdose; CR = complete response; CCI [redacted]; C_{trough} = concentration immediately before next dosing; DLT = dose-limiting toxicity; DoR = duration of response; IHC = immunohistochemistry; IRC = Independent Review Committee; irPFS = immune-related progression-free survival; CCI [redacted] ORR = objective response rate; OS = overall survival; PD = progression of disease; CCI [redacted]; PFS = progression-free survival; CCI [redacted] to progression on first subsequent anticancer therapy or death; PK = pharmacokinetic; PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; TEAE = treatment-emergent adverse event; t_{max} = time at which the C_{max} occurs; CCI [redacted]; $t_{½}$ = elimination half-life determined as 0.693/ λz; λz = terminal first order (elimination) rate constant.

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 Section 1.3 (Table 1 and Table 2) for the M7824 in combination with chemotherapy treatment cohorts. See Section 6.7 for details of study intervention after the end of the study.

This is a Phase Ib/II, open-label study of M7824 in combination with chemotherapy in participants with Stage IV NSCLC regardless of PD-(L)1 expression status. The dose for M7824 is 2,400 mg iv every 3 weeks. The study has 4 cohorts:

- Cohort A: cisplatin or carboplatin + pemetrexed + M7824 during induction followed by maintenance with M7824 + pemetrexed in participants with non-squamous Stage IV NSCLC (1L)
- Cohort B: carboplatin + paclitaxel or nab-paclitaxel + M7824 during induction followed by maintenance with M7824 in participants with non-squamous or squamous Stage IV NSCLC (1L)
- Cohort C: cisplatin or carboplatin + gemcitabine + M7824 during induction followed by maintenance with M7824 in participants with non-squamous or squamous Stage IV NSCLC (1L)
- Cohort D: docetaxel + M7824 during induction followed by maintenance with M7824 in participants with non-squamous or squamous Stage IV NSCLC who had disease progression on previous 1L treatment with PD-(L)1 inhibitors in combination with platinum-based chemotherapy, or 1L treatment with platinum-based chemotherapy followed by 2L treatment with PD-(L)1 inhibitors, or 1L PD-(L)1 inhibitor followed by 2L platinum-based chemotherapy.

Participants in Cohorts A, B, and C must not have received any previous treatment for their metastatic NSCLC. In addition, participants must not have epidermal growth factor receptor (EGFR) sensitizing mutation or anaplastic lymphoma kinase (ALK) translocation, and if tested, ROS1 mutation, or BRAF V600E mutation if targeted therapy is locally approved.

For each cohort, 8 participants will be enrolled during the safety part of the study to evaluate the safety and tolerability of each combination treatment. The combination will be considered safe when DLTs are observed in ≤ 2 of the 8 evaluable participants (See Table 17). If DLTs are observed in ≥ 3 of the 8 participants, the Safety Monitoring Committee (SMC) will give a recommendation regarding clearing the corresponding combination based on a review of all relevant parameters including AEs and serious adverse event (SAEs) and risk benefit assessment for that cohort. Furthermore, if deemed appropriate by SMC, additional participants could be enrolled to further evaluate the safety of a specific cohort.

Additional 32 participants will be enrolled in the expansion part of Cohort A after the safety profile of the combination is cleared by the SMC. Cohort A will serve as pilot cohort to assess additional safety data and preliminary efficacy.

Expansion of Cohorts B, C, and D may be considered at a later date based on the safety profile of each combination and on emerging data. Additional cohorts may be added to this study at a later date based on emerging data to evaluate the potential of M7824 in combination with anticancer agents. If applicable, the information will be described in a future protocol amendment.

The most frequently used chemotherapies in USA and Europe are chosen for this Phase Ib/II study. Investigator may choose cisplatin or carboplatin for participants in Cohorts A and C based on participant profile and accessibility to the drug. Investigator may choose paclitaxel or nab-paclitaxel for participants in Cohort B based on participant profile and accessibility to the drug. Participants who experience toxicities from the selected chemotherapy regimen will be allowed to switch to the other chemotherapy regimens permitted in this study if clinically indicated and after discussion with Medical Monitor. During the safety part of the study, if a participant will switch to a different chemotherapy treatment, this participant will be replaced.

This study includes:

- 28-day Screening period
- Treatment with M7824 in combination with chemotherapy for 4 cycles (each cycle is 21 days) followed by maintenance therapy for up to 31 cycles, or until unacceptable toxicities, confirmed disease progression, or death, whichever occurs first.
  - An extension of up to 3 days for each cycle is allowed during the induction period in case of technical or logistical issue.
  - The DLT observation period will be 3 weeks from the participant's Week 1 Day 1 (W1D1) visit. DLTs are as defined in Section 6.9.1. Participants who received < 90% of the M7824 infusion during the DLT observation period (e.g. because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be considered in the assessment of the overall DLT rate for the particular cohort and will be replaced.
  - On the DLT visit, participants who did not experience DLTs will receive study interventions as planned according to the Schedule of Activities (Table 1). Otherwise study interventions must be delayed until toxicities recover to Grade 1. Dose modifications should be applied to the following cycle(s) according to Section 6.9.
  - Participants who have interruption of chemotherapy due to toxicity related to chemotherapy agents are allowed to continue treatment with M7824 (and pemetrexed in Cohort A if clinically indicated) until progression, unacceptable toxicity or up to 31 cycles.
  - Participants who interrupted M7824 due to immune-related toxicity are allowed to continue treatment with chemotherapy (and pemetrexed) until progression, unacceptable toxicity or up to 4 cycles (or 31 cycles with pemetrexed).
  - Maintenance treatment with M7824 plus pemetrexed (Cohort A) or M7824 (Cohorts B, C, and D) until confirmed progression of disease (PD) per RECIST 1.1, unacceptable toxicity, or 31 cycles. 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 Section 4.1.1.

- Participants who experience stable disease (SD), partial response (PR), or complete response (CR) should continue treatment until the completion of 31 cycles (approximately 2 years) with M7824 (and pemetrexed in Cohort A) in the maintenance period. If the Investigator believes that a participant will benefit from treatment beyond 31 cycles, it may be permissible after discussion with the Medical Monitor and the Sponsor Medical's Responsible.

- Safety Follow-up Visits are at 28 days (± 5 days) (or prior to starting a subsequent treatment) and 12 weeks (± 2 weeks) after the last dose of M7824 plus pemetrexed (Cohort A) or M7824 in maintenance (Cohorts B, C, and D).
- Long-term follow-up should be performed every 12 weeks (± 2 weeks) after last dose of M7824 plus pemetrexed (Cohort A) or M7824 in maintenance (Cohorts B, C, and D) up to 3 years after the last participant is included in the study according to Schedule of Activities (Table 1). Long-term follow-up can be performed in person or by phone call, as clinically indicated.
- Participants who start first subsequent treatment should be monitored for a response to that treatment (Table 1). 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 12 weeks, if feasible, in addition to a scan within 28 days prior to starting the subsequent treatment. These evaluations should be documented by the Investigator and uploaded to the imaging repository, if available. A participant's progression may involve the following: objective radiological, symptomatic progression, or death due to advancing disease. This should be documented every 12 weeks until progression on first subsequent treatment, initiation of next subsequent treatment, withdrawal of consent, or death.

See Section 4.4 for the end of study definition.

4.1.1 Study Intervention Beyond Progression

Participants will receive M7824 and chemotherapy during the induction period and M7824 plus pemetrexed or M7824 during the maintenance period as outlined in Section 1.3 (Schedule of Activities) until disease progression or unacceptable toxicity or up to 31 cycles in maintenance. Study intervention may be continued 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 study intervention is ongoing
- No new unacceptable toxicity related to treatment or disease
- Tolerance of study interventions
- Stable ECOG PS
- Study intervention beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g. central nervous system [CNS] metastases).

A radiographic assessment should be performed within 4 to 6 weeks of initial PD to determine whether there has been a decrease in the tumor size, or confirmed 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 chemotherapy combination in the induction period and M7824 alone or in combination with pemetrexed in the maintenance period.

4.1.2 Study Intervention Beyond Confirmed Progression

After confirmed PD, if the Investigator feels that the participant continues to achieve clinical benefit by continuing study intervention, the participant may remain on the study and continue to receive study intervention and monitoring according to the Schedule of Activities (Section 1.3). The decision to continue study intervention 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 every 6 weeks up to 12 months, then every 12 weeks up to 24 months as per the Schedule of Activities (Section 1.3). Study intervention 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. If the study intervention is continued beyond PD, it will be discontinued once any other criteria for withdrawal are met (see Section 7.1).

4.1.3 Continuation of Study Intervention After Local Treatment of Disease Progression

If disease progression is due to brain metastasis, participants may continue study interventions after 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 continuation 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.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.2.3 Selection of Chemotherapy

Chemotherapy regimens are selected based on histology. Most non-squamous Stage IV NSCLC are treated with chemotherapy regimens such as cisplatin (or carboplatin) plus pemetrexed followed by pemetrexed as maintenance, carboplatin plus paclitaxel (or nab-paclitaxel) or cisplatin (or carboplatin) plus gemcitabine. Patients with Stage IV squamous NSCLC are treated with carboplatin plus paclitaxel (or nab-paclitaxel) or cisplatin (or carboplatin) plus gemcitabine.

Among the provided choices, the chemotherapy regimen will be decided by the Investigator with regards to tumor histology, participant's performance status, and preexisting comorbidities. Participants with disease control after treatment with M7824 in combination with chemotherapy during induction will continue to maintenance with M7824 plus pemetrexed (Cohort A) or M7824 (Cohorts B, C, and D) for up to 31 cycles, or until unacceptable toxicities, or confirmed disease progression, or death.

4.2.4 Open-label Design

This study will use an open-label design to fully assess the safety and tolerability of M7824 in combination with chemotherapy.

4.3 Justification for Dose

The dose for M7824 in this study is 2,400 mg administered as an intravenous infusion once every 3 weeks. Since most chemotherapies are administered every 3 weeks, the same dosing interval for M7824 is preferred for convenience and compliance.

The 2,400 mg every 3 weeks dose selection was based on the following:

1. Phase I data and population PK and exposure-response modeling and simulations were used to select 1,200 mg every 2 weeks for M7824 monotherapy trials and estimate target efficacious $C_{trough,ss}$ (refer to the IB). Specifically, the following data from Phase 1 Study EMR200647-001 and Study MS200647-0008 were used: safety/tolerability, and PK, CCI [redacted] Modeling and simulation were used to select 2,400 mg every 3 weeks dose as the dose that maintains target efficacious $C_{trough,ss}$ of M7824. Available safety/tolerability data at 2,400 mg dose and exposures associated with 2,400 mg dose in monotherapy Phase I studies were evaluated.

2. Assessment of potential of PK interactions and overlapping toxicities with chemotherapies was conducted to support 2,400 mg every 3 weeks dose of M7824 in this combination study.

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

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 last scheduled procedure shown in Section 1.3 (Schedule of Activities).

The end of the study is defined as 3 years after treatment start of the last participant or until all the participants in the study experienced PD to the subsequent treatment, whichever occurs first.

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

5 Study Population

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

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

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative 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 histologically confirmed diagnosis of Stage IV NSCLC International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology (IASLC Staging Manual in Thoracic Oncology, V8) and:
    a. Participants in Cohort A, B, and C must not have received prior systemic therapy treatment for their Stage IV NSCLC. Completion of treatment with cytotoxic chemotherapy, biological therapy, and/or radiation as part of neoadjuvant/adjuvant/unresectable locally advanced therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease.
    b. Resolution of toxic effects of previous chemotherapy to Grade ≤ 1 must be confirmed prior to enrollment. For radiation toxicity or prior major surgeries, participants should have recovered from side effects and/or complications.

c. Participants who had disease progression on previous 1L treatment with PD-(L)1 inhibitors in combination with platinum-based chemotherapy, or 1L treatment with platinum-based chemotherapy followed by 2L treatment with PD-(L)1 inhibitors, or 1L PD-(L)1 inhibitor followed by 2L platinum-based chemotherapy are enrolled in Cohort D, as long as therapy was completed at least 28 days of the first study intervention.

d. Have measurable disease based on RECIST 1.1.

e. Have a life expectancy of at least 3 months.

f. Availability of fresh biopsies or archived tumor material (< 6 months old) (excluding bone biopsies) adequate for biomarker analysis is mandatory at Screening, central laboratory confirmation is required. If participant received systemic therapy after the archival biopsy was taken, a fresh biopsy will be required prior to study entry if clinically feasible. Archived tumor material should be collected only if fresh biopsies material is not available.

g. See Section 5.2 for exclusion criteria for participants with EGFR mutation, ALK positive, ROS1 rearrangement, 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 (Hgb) ≥ 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 (ALP) ≤ 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) $\geq$ 50 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] × weight [kg] × [0.85 for females only]) / (72 × 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. Contraceptive use by males or females will be consistent with local regulations on contraception methods for those participating in clinical studies.

a. Male participants:

Contraceptive measures should be continued as per guidance specified in labeling document for approved chemotherapies. If not specified, continue measures similar to investigational agent i.e. agree to the following during the study intervention period and for at least 4 months after the last dose of study intervention or as per guidance specified in labeling document for approved chemotherapies.

- Refrain from donating sperm

PLUS, either:

- Abstain from intercourse with a WOCBP female

OR

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

b. Female participants:

- Are not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Not a WOCBP, as defined in Appendix 3

  OR

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

      OR

      - Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay.
    - During the intervention period
    - Contraceptive measures should be continued as per guidance specified in labeling document for approved chemotherapies. If not specified, continue measures similar to investigational agent i.e. after the study intervention period (i.e. after the last dose of study intervention is administered or as per guidance specified in labeling document for approved chemotherapies) for at least 2 months after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period.

- Have a negative pregnancy test, as required by local regulations on W1D1 before the first dose of study intervention.

- Additional requirements for pregnancy testing during and after study intervention are in Schedule of Activities (Section 1.3).
- The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.

Informed Consent

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, ROS1 rearrangement, BRAF V600E mutation or is ALK positive, if targeted therapy is locally approved.

   For participants with non-squamous histology:

   a. EGFR mutation status and/or ALK positive, ROS1 rearrangement, and/or BRAF V600E mutation (if indicated) status must be available at the site.

   b. Investigators must be able to produce the source documentation of the EGFR mutation and/or ALK positive status.

   c. ROS1 testing is required in participants who have had negative EGFR/ALK testing if targeted therapy is locally approved.

   d. BRAF V600E mutation is required if targeted therapy is locally approved

   e. If unable to provide source documentation nor 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.

   f. If an EGFR sensitizing mutation, ALK positivity, or ROS1 rearrangement, or BRAF V600E is not detected, additional information regarding other mutation status is not required.

   For participants enrolled who are with NSCLC of predominantly squamous histology, molecular testing will not be required as this is not standard of care and is not mandated by the current National Comprehensive Cancer Network (NCCN) guidelines.

2. Mixed small cell with NSCLC cancer histology.
3. Has received major surgery within 4 weeks prior to the first dose of study intervention; received thoracic radiation therapy (RT) of > 30 Gy within 6 months prior to the first dose of study intervention.

4. 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, ductal 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.
5. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are clinically stable for at least 2 weeks after the end of the RT and have no evidence of new or enlarging brain metastases evaluated by imaging, preferably brain magnetic resonance imaging (MRI). In addition, any steroids administered as part of this therapy must be completed at least 3 days prior to study intervention. Stable brain metastases by this definition should be established prior to the first dose of study medication and after at least 2 weeks from the last dose of RT. Participants with known untreated, asymptomatic brain metastases (i.e. no neurological symptoms, no requirements for corticosteroids, no or minimal surrounding edema, and no lesion >1.5 cm) may participate after discussion with the Medical Monitor and will require regular imaging of the brain as a site of disease, preferably by MRI.
6. Active autoimmune disease that has required systemic treatment in the past 1 year (e.g. 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 (M7824, cisplatin, carboplatin, pemetrexed, paclitaxel, nab-paclitaxel, gemcitabine, or docetaxel) 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. 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.
7. Known severe hypersensitivity (Grade ≥ 3 National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] V5.0) to study intervention or any components in their formulations, or uncontrolled asthma (i.e. 3 or more features of partially controlled asthma). Occurrence of irAEs during previous treatment with checkpoint inhibitors could potentially constitute an exclusion criterion in participants candidate for treatment in Cohort D. Investigator must carefully evaluate benefit-risk assessment on a case basis and discuss it with the Medical Monitor and the Sponsor's Medical Responsible prior participant's enrollment.
8. Receipt of any organ transplantation, including allogeneic stem-cell transplantation, but with the exception of transplants that do not require immunosuppression (e.g. corneal transplant, hair transplant).
9. Has interstitial lung disease (ILD) OR has had a history of pneumonitis that has required oral or intravenous steroids. Participants with a history of radiation pneumonitis which has clinically and radiologically resolved and not requiring treatment with steroids may be eligible. Investigator must carefully evaluate benefit-risk assessment on a case basis and

discuss it with the Medical Monitor and the Sponsor's Medical Responsible prior to participant's enrollment.

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 deoxyribonucleic acid (DNA), or HBV core antibody positive alone with reflex to positive HBV DNA, or positive HCV antibody with reflex to positive HCV ribonucleic acid (RNA) at Screening. 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 (e.g. 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 (LFT) or hematologic abnormalities (must meet criteria below) and with planned monitoring and management according to appropriate labeling guidance. HBV and/or HCV viral serology must be monitored according to Schedule of Activities in these participants.
    c. Participants with active tuberculosis (history of exposure or history of positive tuberculosis test; plus, presence of clinical symptoms, physical, or radiographic findings).
11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with participation for the full duration of the study, or is not in the best interest of the participant, in the opinion of the treating Investigator. Participants with history of bleeding diathesis or recent major bleeding events considered by the Investigator as high risk for investigational drug treatment are also excluded.

Prior/Concomitant Therapy

12. For participants in Cohorts A, B and C: Has received prior systemic therapy for Stage IV NSCLC, including 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 28 days of the first dose of study intervention.

Diagnostic Assessments

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

Other Exclusions

19. Known active alcohol or drug abuse.
20. Any psychiatric condition that would prohibit the understanding or rendering of informed consent or consistent participation in study procedures.
21. Legal incapacity or limited legal capacity.

5.3 Lifestyle Considerations

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

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened within 2 weeks. Rescreened participants will be assigned a new participant number and are required to sign a new ICF. 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

6.1.1 Administration of M7824

Table 6 Administration of M7824

Study Intervention Name:	M7824
Dose Formulation:	Sterile concentrate solution for infusion
Unit Dose Strength(s)/Dosage Level(s):	10 mg/mL in single-use glass vials
Route of Administration:	Intravenous infusion
Dosing Instructions:	2,400 mg q3w. The administration has to be conducted within 60 minutes (-10/+20 minutes) by intravenous infusion (the total infusion time must not exceed 2 hours (-10/+20 minutes). See Section 6.9.3.1 for special precautions. M7824 should be administered prior to chemotherapy when given on the same day. Premedication prior to each dose is not mandatory. Steroids are not allowed as premedication for M7824.
Supplier/Manufacturer:	Merck KGaA/Baxter Oncology GmbH
Packaging and Labeling:	Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

q3w = every 3 weeks.

6.1.2 Administration of Chemotherapy

Investigators can select the chemotherapy regimen from the following standard options according to NCCN guidelines. Refer to each chemotherapy agent Summary of Product Characteristics (SmPC) or package insert for more information.

Chemotherapy agent(s) will be sourced from a local hospital pharmacy and packaged, labeled, and distributed for clinical studies according to local requirements. Chemotherapy should be administered according to the guidelines provided below or to the local standard practice.

Depending on the chemotherapy regimen, all participants should receive the appropriate corticosteroid premedication as per the local practice and approved label. A corticosteroid-sparing approach for antiemetic prophylaxis should be preferred and evaluated on a case by case and chemotherapy regimen basis (NCCN Guideline for Patients® - Antiemesis). Additional premedication should also be administered as per standard practice.

Cisplatin or Carboplatin (AUC 5) + Pemetrexed (Cohort A)

Cisplatin is administered intravenously at a dose of 75 mg/m^2 over 60 minutes every 3 weeks. All the medications used as hydration (drugs and fluids) must be reported in the electronic case report form (eCRF).

Carboplatin is administered at AUC 5 when combined with pemetrexed over 30 to 60 minutes every 3 weeks, immediately after pemetrexed. Premedication should be administered as per standard practice.

Pemetrexed is administered intravenously at a dose of 500 mg/m^2 over 10 minutes every 3 weeks. All participants should receive the appropriate supplementation of vitamin B12 and folic acid as per Table 2 assessment.

Carboplatin (AUC 6) + Paclitaxel or Nab-paclitaxel (Cohort B)

Carboplatin is administered intravenously at AUC 6 when combined with paclitaxel or nab-paclitaxel over 30 to 60 minutes every 3 weeks immediately after paclitaxel or nab-paclitaxel.

Paclitaxel is administered intravenously at a dose of 200 mg/m^2 over 3 hours every 3 weeks (Table 2).

Nab-paclitaxel is administered intravenously at a dose of 100 mg/m^2 over 30 minutes in a 3-week cycle on Days 1, 8, and 15, in each cycle (Table 2).

Cisplatin or Carboplatin (AUC 5) + Gemcitabine (Cohort C)

Cisplatin is administered intravenously at a dose of 75 mg/m^2 over 60 minutes every 3 weeks. All the medications used as hydration (drugs and fluids) must be reported in the eCRF.

Carboplatin is administered intravenously at AUC 5 when combined with gemcitabine over 30 to 60 minutes every 3 weeks, immediately after gemcitabine.

Gemcitabine is administered intravenously at a dose of 1250 mg/m^2 over 30 minutes in a 3-week cycle on Days 1 and 8, in each cycle (Table 2).

Docetaxel (Cohort D)

Docetaxel is administered intravenously at a dose of 75 mg/m^2 over 60 minutes every 3 weeks.

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

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

- Upon receipt of the study intervention(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported

and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the Pharmacy Manual.

- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused study intervention(s).
  - Dates, quantities, batch numbers, vial numbers, expiry dates, formulations, and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and 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.
- 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.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Pharmacy Manual.
- M7824 drug product should be stored CCI [redacted] until use. CCI [redacted]
- Additional instructions for the preparation, handling, storage, and disposal of M7824 will be provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Participants will be assigned to one of the 4 cohorts based on the eligibility criteria and the Investigator's assessment. The allocation of participants to cohorts per determination by the Investigator will be recorded in the Interactive Web Response System (IWRS). Enrollment will be controlled by IWRS to ensure that over enrollment into a single cohort does not occur.

The IWRS will be used to assign a unique participant identifier number to eligible participants at the time of informed consent signature. Participant identifiers will be comprised of digits representing the study number, the site number, and the participant number, which is allocated sequentially.

6.3.2 Blinding

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

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 for each study intervention administration including the date, time, and dose of study intervention will be recorded on the eCRF. The Investigator will make sure that the information entered into the eCRF regarding drug administration is accurate for each participant. Any reason for noncompliance should be documented.

Noncompliance is defined as a participant missing > 1 infusion of study intervention for nonmedical reasons and barring any extenuating circumstances in the opinion of the Investigator. Extenuating circumstances should be documented and when possible, discussed with the Sponsor in advance. If 1 infusion is missed and the interval between the subsequent infusion and the last administered treatment is longer than 4 weeks for nonmedical reasons, the criteria of insufficient compliance are 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 CRF all concomitant therapies (e.g. medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

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

Concomitant medication and procedures should be collected in accordance with the AE reporting period. See Sections 8.3.1, 8.3.2, and Appendix 4 for definition of the AE/SAE, reporting period, and follow-up.

6.5.1 Permitted Medicines

The only permitted medications are the following:

1. 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.
2. Other drugs to be used for prophylaxis, treatment of hypersensitivity reactions, and treatment of fever or flu-like symptoms are described in Section 6.9 as part of precautions.
3. Erythropoietin is allowed if clinically indicated per Investigator assessment.
4. Secondary prophylaxis with granulocyte-colony stimulating factor (G-CSF) is allowed if clinically indicated per Investigator assessment.
5. Corticosteroids use on study as a premedication for iv contrast allergies/reactions (related to scans).
6. Corticosteroids use for hormonal replacement and at low doses (typically $\leq$ 10 mg of prednisone or equivalent per day).
7. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intraocular, or inhalation) is acceptable.

6.5.2 Prohibited Medicines

As stated for the exclusion criteria in Section 5.2, participants enrolled in this study to receive study intervention indicated for 1L therapy (Cohorts A, B, and C), 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.

For all participants in this study the following concurrent treatment are prohibited:

- Cytoreductive therapy other than the described chemotherapy regimens
- Radiotherapy delivered for non-palliative indications (see Section 5.2)
- Use of any investigational drug different from study intervention
- Immunotherapy, immunosuppressive drugs (i.e. chemotherapy or systemic corticosteroids), or other experimental pharmaceutical products. Short-term administration of systemic steroid for allergic reactions or the management of irAEs is allowed.

- Vaccine administration within 30 days before M7824 administration. Vaccination with live vaccines while on study is prohibited. Administration of inactivated vaccines is allowed (i.e. inactivated influenza vaccines).
- Herbal remedies with immune-stimulating properties (i.e. mistletoe extract) or known to potentially interfere with major organ function (i.e. hypericin).

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); (see Section 7.1). The participant should complete the End of Treatment Visit and be followed for safety and survival (see Schedule of Activities, Section 1.3).

6.5.2.1 Medicines to Use with Caution

Caution should be exercised if any of the following is administered concomitantly with **cisplatin**:

- Allopurinol, colchicine, probenecid, sulfinpyrazone (increase in serum uric acid concentration)
- Cephalosporins, aminoglycosides, amphotericin B (increase nephrotoxic and ototoxic effects of cisplatin in these organs)
- Cyclosporine (excessive immunosuppression, with risk of lymphoproliferation)
- Cyclizine, phenothiazines (may mask ototoxicity symptoms)
- Furosemide (high-doses), hydralazine, diazoxide and propranolol (intensify nephrotoxicity)
- Oral anticoagulants (require an increased frequency of the INR monitoring)
- Penicillamine (may diminish the effectiveness of cisplatin)
- Phenytoin (reduced epilepsy control)
- Nephrotoxic drugs (intensify nephrotoxicity)

According to the label, no drug interaction studies have been conducted with **nab-paclitaxel**, but caution should be exercised when administering nab-paclitaxel concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4. Refer to the following **paclitaxel** drug interactions for detailed list of specific drugs to use with caution:

- Known substrates of CYP3A4 (e.g. midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam)
- Known inhibitors of CYP3A4 (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin)
- Known inducers of CYP3A4 (e.g. rifampin and carbamazepine)
- Known substrates of CYP2C8 (e.g. repaglinide and rosiglitazone)
- Known inhibitors of CYP2C8 (e.g. gemfibrozil)
- Known inducers of CYP2C8 (e.g. rifampin)

Caution should be exercised when administering **docetaxel** concomitantly with compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4:

- Known substrates of CYP3A4 (e.g. midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam)
- Known inhibitors of CYP3A4 (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin)
- Known inducers of CYP3A4 (e.g. rifampin and carbamazepine)

Caution should be exercised when administering **pemetrexed** concomitantly with ibuprofen due to increased risk of pemetrexed toxicity in patients with mild to moderate renal impairment.

Caution should be exercised when administering **carboplatin** with nephrotoxic compounds due to increased risk of nephrotoxicity.

6.5.3 Other Interventions

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

- Major surgery (excluding prior diagnostic biopsy) is prohibited within 28 days before the start of the study or during the study.
- Discuss with Medical Monitor if unplanned major surgery is required on study to plan for timing of next dose.

6.6 Dose Selection and Modification

See Section 4.3 for the dose justification for M7824 used in this study and Section 6.1.2 for chemotherapy regimens.

In case a dose reduction is necessary, the study interventions will be administered as described in Section 6.9 and subsections for the study interventions.

There will not be dose reductions of M7824.

6.7 Study Intervention after the End of the Study

After a participant has completed the study or has withdrawn early, additional study intervention will not be provided, unless in the opinion of the Investigator and after discussion with the Medical Monitor, the participant may benefit from additional study interventions. 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.

The Sponsor may terminate the study at any time once access to M7824 for participants still benefitting from treatment is made available via a rollover study, expanded access, marketed product or another mechanism of access as appropriate.

6.8 Special Precautions

6.8.1 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are serious or nonserious AEs specific to the known mechanism of action of the study intervention. Safety measures to mitigate the 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.

6.8.1.1 Infusion-related Reactions, Including Immediate Hypersensitivity

Any signs or symptoms experienced by participants during the infusion or within 1 day thereafter should be evaluated as a potential IRR. Infusion-related reactions are common adverse drug reactions (ADRs) with mAbs that are temporally related to drug administration. Reported signs/symptoms have included anaphylaxis, anaphylactoid reactions, and cytokine release syndrome, among others.

Infusion-related reactions are an AESI for M7824 and considered an identified risk for M7824; precautions and management are discussed in Section 6.9.3.1. See Section 6.9.4 for details on IRR due to immediate hypersensitivity associated with chemotherapy agents.

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

The following irAEs are important identified risks for M7824:

- Immune-related pneumonitis
- Immune-related hepatitis

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

The following irAEs are important potential risks for M7824:

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

The precautions and management are discussed in Section 6.9.3.2.

6.8.1.3 Skin Adverse Events

Several Skin AEs are AESIs, considered as important identified risk for M7824 and include 2 potential mechanisms:

- TGFβ Inhibition Mediated Skin Reactions are grouped as rash with hyperkeratosis, KA, and cSCC of skin. These treatment-related skin AEs were well managed and did not require study intervention discontinuation in Studies EMR200647-001 and MS200647-0008. Monitoring and diagnostic work-up is required (see Section 6.9.3.3).
- Immune-related skin AEs possibly mediated by PD-L1 inhibition (AEs in this category are reported under irAE, see Section 6.9.3.2).

6.8.1.4 Anemia

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

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

Anemia induced by chemotherapy mainly due to myelosuppression is not considered an AESI. See Section 6.9.3.4 for anemia risk management.

6.8.1.5 Bleeding Adverse Events

Bleeding AEs are AESIs and considered important identified risk (see Section 6.9.3.5 for more details).

6.8.2 Additional Important Potential Risks

6.8.2.1 Impaired Wound Healing

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

6.8.2.2 Embryo-fetal Toxicities

Embryo-fetal toxicities are a known risk of the PD-1/PD-L1 targeting class and are considered important potential risk. 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 mAb 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 Management of Adverse Events of Interest

6.9.1 Definition of Dose-limiting Toxicity

All toxicities will be graded using NCI-CTCAE V5.0. The DLT observation period will be 3 weeks from the W1D1 visit. The occurrence of any of the following toxicities will be considered a DLT, if judged by the Investigator and confirmed by the SMC to be related to study intervention:

- Grade 4 nonhematologic toxicity (not laboratory)
- Grade 4 hematologic toxicity lasting ≥ 7 days despite of medical intervention
- Grade 3 nausea, vomiting and diarrhea lasting ≥ 3 days despite optimal supportive care
- Any Grade 3 or Grade 4 nonhematologic laboratory value if:
    - The abnormality leads to hospitalization, or
    - The abnormality persists for ≥ 7 days
- Febrile neutropenia Grade 3 or Grade 4:
    - Grade 3 is defined as ANC < 1,000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour

  - Grade 4 is defined as ANC < 1,000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.

- Thrombocytopenia < 25,000/mm^3 if associated with:
  - A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or
  - A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit.
- Prolonged delay (> 2 weeks) in initiating Cycle 2 due to treatment-related toxicity
- Grade 5 toxicity.

The following are NOT considered DLT:

- Grade 3 IRRs resolving within 6 hours from the end of infusion and controlled with medical management.
- Transient (< 3 days) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1.
- Transient (< 2 days) Grade 3 flu-like symptoms or fever, which is controlled with medical management.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor that resolve to Grade ≤ 2 within 7 days.
- Skin lesion related to TGFβ inhibition (i.e. KA, squamous cell carcinoma) that is local and can be resected with negative resection margins.
- Grade 3 skin toxicity that resolves to ≤ Grade 1 in less than 7 days after medical management (e.g. immunosuppressant treatment) has been initiated.
- Grade 3 asymptomatic increases in LFTs, AST, ALT, ALP that resolves to ≤ Grade 1 within 7 days after medical management (e.g. immunosuppressant treatment) has been initiated.
- Single laboratory values out of normal range that are assessed as unrelated to study intervention according to the Investigator and/or do not have any clinical correlate and resolve to ≤ Grade 1 within 7 days with adequate medical management.
- Grade 3 diarrhea persisting < 3 days after initiation of medical management
- Isolated Grade 4 lymphopenia without clinical correlate
- Any Grade 4 neutropenia of < 7 days duration not associated with any clinical symptoms
- Any Grade 3 autoimmune thyroid-related toxicity that clinically resolves to ≤ Grade 2 within 7 days of initiating therapy
- Any death due to the underlying disease or extraneous causes.

6.9.2 Adverse Drug Reactions Requiring Study Intervention 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 TGFβ inhibition mediated skin reactions are managed and followed-up in their respective sections as indicated below. Permanent study intervention discontinuation may be recommended, so the relevant section must be reviewed:

- For management and guidance of suspected irAEs, (see Section 6.9.3.2).
- For IRRs and hypersensitivity reactions guidance, (see Section 6.9.3.1).
- For anemia guidance, (see Section 6.9.3.4).
- For guidance and management for TGFβ inhibition mediated skin reactions, (see Section 6.9.3.3).

General guidance:

- In any case, if ≥ 2 consecutive doses of M7824 are missed due to AEs, 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 study intervention 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 study intervention discontinuation.

Grade 4 ADRs:

Participants with any Grade 4 ADRs require permanent study intervention discontinuation except:

- Isolated laboratory values out of normal range that do not have any clinical correlation. Discuss with the Medical Monitor regarding work-up, management, and treatment continuation versus hold versus discontinuation for isolated Grade 4 laboratory abnormalities.
- Endocrinopathies controlled with hormone replacement therapy.
- Grade 4 AEs related to chemotherapy (i.e. neutropenia). Please refer to Section 6.9.4 for risk management for chemotherapy.

See Section 6.8.1.2 for other suspected Grade 4 irAEs, as most require permanent study intervention discontinuation.

Grade 3 ADRs:

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:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management.
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to ≤ Grade 1 or baseline.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Grade 3 Hgb decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor.
- Increases in ECOG PS ≥ 3 that resolves to ≤ 2 by Day 1 of the next infusion (i.e. infusions should not be given if the ECOG PS is ≥ 3 on the day of treatment and should be delayed until ECOG PS ≤ 2).
- Keratoacanthomas and/or cSCC (see Section 0 for management).
- See Section 6.9.3.2 for suspected Grade 3 irAEs as many require permanent study intervention discontinuation, including pneumonitis and nephritis.
- AST or ALT > 5 times ULN or total bilirubin greater than 3 times ULN must be permanently discontinued, except for participants with liver metastases (e.g. who begin study intervention 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.
- 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 study intervention.
- Endocrinopathies controlled with hormone replacement therapy.
- Grade 3 AEs related to chemotherapy. Please see Section 6.9.4 for risk management for chemotherapy.

Grade 2 ADRs:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the day before the next infusion, study intervention may be continued.
- If a Grade 2 ADR does not resolve to Grade ≤ 1 by the day before the next infusion, but it is manageable and/or not clinically relevant, the Medical Monitor should be consulted to assess if it is clinically reasonable to administer the following infusion.
- Grade 2 AEs related to chemotherapy. Please refer to Section 6.9.4 for risk management for chemotherapy.

6.9.3 Risk Management for M7824

6.9.3.1 Infusion-related Reactions Including Immediate Hypersensitivity

Infusion-related reactions (including immediate hypersensitivity) are defined in Section 6.8.1.1 and are AESIs and identified risks for M7824.

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 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 1:1,000 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 is not mandatory in this study. If an investigator deems necessary to administer a premedication prior to M7824 infusion to a particular participant, an antihistamine (e.g., 25 to 50 mg diphenhydramine) and paracetamol (acetaminophen, 500 to 650 mg intravenously or equivalent oral dose) is recommended. Premedication should be administered based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic glucocorticoids.

An assessment for possible IRR should be triggered based upon the development of specific symptoms by participants during study intervention administration or within 1 day thereafter. 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:

- Infusion-related reaction 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 PTs Infusion-Related Reaction, drug hypersensitivity, anaphylactic reaction, hypersensitivity, and Type 1 hypersensitivity.
- Signs and symptoms of IRRs and hypersensitivity/allergic reactions should be considered if the onset occurs during or within 1 day after an infusion and resolves within 2 days. Signs and symptoms include pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain and urticaria.

Management of symptoms should follow the guidelines shown in

Table 7.

Table 7 M7824 Treatment Modification Guidance for Symptoms of Infusion-related Reactions Including Immediate Hypersensitivity

NCI-CTCAE V5.0 Grade	M7824 Modification
Grade 1 – mild Mild transient reaction; in general, infusion interruption not indicated; intervention not indicated.	Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator. Hold infusion if deemed necessary by the Investigator.
Grade 2 – moderate Therapy or infusion interruption indicated but if responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics, iv fluids); prophylactic medications indicated for ≤ 24 hours.	Stop M7824 infusion. Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator. If symptoms resolve quickly, resume infusion at 50% of original rate with close monitoring of any worsening otherwise dosing held until resolution of symptoms with 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 infusion immediately and disconnect infusion tubing from the participant with additional appropriate medical measures and closely monitor until deemed medically stable by the attending Investigator. Hospitalization and/or close monitoring is recommended Administration of glucocorticoids may be required For Grade 3 or 4 IRRs, permanent discontinuation of M7824 is mandated.
Once the infusion is interrupted or rate reduced to 50% of previous infusion rate, it must remain decreased for all subsequent infusions. For all types and grades of infusion reactions, details about drug physical constitution, method of preparation, and infusion must be recorded. Participants should be instructed to report any delayed reaction immediately. IRR = infusion-related reactions; IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.	

In the event of a Grade 2 IRR that does not improve or worsens after implementation of the dose modifications indicated in

Table 7 (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 subsequent infusions, the same reduction of infusion rate by 50% should occur and the Investigator may consider premedication and if needed the addition of H_2 blocker antihistamines (e.g. famotidine or ranitidine), for select participants. However, prophylactic steroids are NOT permitted. At the next dose, if the participant has a second IRR Grade ≥ 2 on the slower infusion rate, with the use of premedication and addition of further medication to premedication, the infusion should be stopped, and the investigator may consider withdrawal of this participant from the study.

Immediate Hypersensitivity Reaction

If a hypersensitivity reaction occurs, the participant must be treated according to the best available medical practice. Hypersensitivity reactions may require immediate intensive care. M7824 should be administered in a setting that allows immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Potent steroids (e.g. dexamethasone), catecholamines (e.g. epinephrine), allergy medications (IV antihistamines), bronchodilators, or equivalents and oxygen should be available for immediate access.

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), e.g. ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each intravenous infusion.

6.9.3.2 Immune-related Adverse Events

Immune-related AEs are specific to immunotherapies and vary by organ system. Immune-related AEs are important identified risks for M7824.

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), NCCN, and FDA recommendations are listed in Appendix 6. These irAEs include, but are not limited to, pneumonitis, colitis, hepatitis, endocrinopathies (including hypophysitis, thyroid disorders, Type 1 diabetes mellitus), and nephritis.

General management by NCI-CTCAE V5.0 grading, as per ASCO, is listed below:

- Grade 1: study intervention should be continued with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities.
- Grade 2: study intervention may be suspended for most Grade 2 toxicities, with consideration of resuming when symptoms revert to Grade 1 or less. Corticosteroids may be administered (initial dose of 0.5 to 1 mg/kg/d of prednisone or equivalent).
- Grade 3: study intervention 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 intervention is recommended, with the exception of endocrinopathies that have been controlled with hormone replacement therapy.

For organ/system specific management guidelines, review ASCO guideline tables in Appendix 6. Recommended guidance and management for specific irAEs are provided in the current NCCN guideline available at http://www.nccn.org.

Requirements in addition to NCCN guidelines:

- Permanent treatment discontinuation is required in case of immune-related Grade 4 rash/inflammatory dermatitis, nephritis, autoimmune hemolytic anemia, hemolytic uremic syndrome, aplastic anemia, immune thrombocytopenia, acquired thrombotic thrombocytopenic purpura, inflammatory arthritis, myositis, and polymyalgia-like syndrome.
- For Grade 4 immune-related lymphopenia, permanent treatment discontinuation will be required, if lymphopenia is considered immune-related in nature, no clear alternative explanation exists for the event, and Grade 4 lymphopenia does not resolve within 14 days. Permanent treatment discontinuation is not required when the AE is manifest by a single laboratory value out of normal range without any clinical correlates. In this case, treatment should be held until the etiology is determined. If the event is not considered immune related and resolves to Grade ≤ 1, restarting treatment may be considered.
- For Grade 1 immune-related pneumonitis: continue treatment. If clinically indicated, monitor participants weekly or more frequently as needed with history, physical examination, and pulse oximetry. If symptoms appear and/or changes in the physical examination are noted, treat as Grade 2.
- For myositis: in case of management with rituximab, treatment should be discontinued.

6.9.3.3 TGFβ Inhibition Mediated Skin Reactions

TGFβ inhibition mediated skin reactions, including hyperkeratosis, KA and/or cSCC, are important identified risks for M7824 and are described in Section 6.8.1.3.

Skin assessments are performed at Baseline and 6 weekly for all participants (see Schedule of Activities in Section 1.3). 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.

Management guidelines for TGFβ inhibition mediated skin reactions are:

- Discontinuation or interruption is not required in most cases. Continuation of treatment should be evaluated by the Investigator.
- Emollients may continue to be used.
- Diagnostic and treatment plan should be developed in collaboration between Investigator and dermatologist. In general, treatment of TGFβ inhibition mediated skin lesions such as hyperkeratosis, KA and cSCC should be based on local guidelines/standard of care. Lesion evaluation should include excision biopsy of one representative lesion to confirm diagnosis.
- Treatment and follow-up for KA and cSCC will depend on number and localization of lesions.
  - For single lesions:
    - Full excision may be recommended.
  - In case of multiple lesions or location not suitable for full excision:
    - Other treatment options may be offered by the dermatologist, such as:
      - Mohs surgery, cryotherapy, or other standard treatment options depending on the pathology.
      - Use of retinoids if recommended by dermatologist, may be considered after discussion with Medical Monitor.
- Close clinical follow-up for re-evaluation, resolution, or potential recurrence should be implemented.
- Spontaneous resolution of KA lesions without surgical intervention has been observed, typically occurring within weeks after discontinuing M7824.
- The number and localization of lesions, diagnosis (including histopathological diagnosis), treatment, and outcome should be appropriately documented in the eCRF.

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

6.9.3.4 Anemia

<u>General Guidance for anemia management and evaluation:</u>

- Participants must enter the study with Hgb values at least 9 g/dL; routine blood test parameters are specified in Table 8.
- Transfusion should be performed at the discretion of the Investigator based on clinical assessment and considered when the participant experiences severe anemia. An attempt should be made to initiate work-up (as specified below) for the cause of anemia prior to transfusion, if clinically feasible, to not confound this work-up. In general, blood transfusions and erythroid growth factors are permitted as clinically indicated. Guidance for evaluation of suspected treatment-related anemias is provided in Table 8.

Table 8 Evaluation Guidance of Suspected Anemia

Basic Anemia Evaluation	
1. CBC with emphasis on red cell indices (e.g., Hgb, hematocrit, MCV, RDW, MCH, MCHC, reticulocytes counts). 2. If indicated and at clinical discretion, the following should be considered: a. Iron studies (TIBC, Ferritin, Fe) b. Serum Folate and Vitamin B12 values c. Coagulation factors (PT, PTT, INR) d. Fecal occult blood testing e. Urinalysis f. Hormone panel: TSH, Erythropoietin g. Peripheral blood smear for cell morphological assessment	
Further Recommendation Based on Suspected Etiology (in Addition to Basic Anemia Testing)	
Suspected hemolysis:	Bilirubin level, LDH, Coombs test, fibrinogen, haptoglobin, D-dimer Consider Hematology consultation.
Suspected bleeding:	Consider imaging/interventional radiology consultation as indicated Consider endoscopy, as clinically indicated. Consider imaging, as clinically indicated.
Suspected aplastic anemia:	Hematology consultation. Consider bone marrow aspiration/morphologic evaluation.

CBC = complete blood count; Hgb = hemoglobin; INR = international normalized ratio; LDH = lactate dehydrogenase; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RDW = red cell distribution width; TIBC = total iron binding capacity; TSH = thyroid-stimulating hormone.

6.9.3.5 Management of Bleeding Events

Bleeding AEs are AESIs and considered important identified risk.

Mucosal/Non-tumor Bleeding

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

If a Grade 2 treatment-related treatment-emergent adverse event (TEAE) improves to Grade ≤ 1 or completely resolves by the day before the next infusion, study intervention may be continued.

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

For Grade ≥ 3 non-tumor bleeding, study treatment must be permanently discontinued unless an alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic event, etc.). In case of alternative explanations for the Grade ≥ 3 bleeding event, study treatment should be held until the event recovers to Grade ≤ 1.

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

Tumor Bleeding

Participants treated with bintrafusp alfa were reported in lower frequencies, with Grade ≥ 3 hemorrhages including tumor bleeding. For Grade ≥ 2 tumor bleeding, study treatment must be held until the event recovers to Grade ≤ 1. Treatment should be permanently discontinued if the Investigator considers the participant to be at risk for additional severe bleeding.

6.9.4 Risk Management for Chemotherapy

Refer to the respective label for a full list of adverse reactions for each of the chemotherapy agent used in this study.

The Investigator should consider chemotherapy discontinuation for any of the following:

- Any drug-related AE which recurs after 2 prior dose reductions for the same drug-related AE requires discontinuation of the chemotherapy agent(s) which was/were previously dose reduced.
- Any Grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the chemotherapy agent(s) assessed as causing the reaction. The other study intervention(s) assessed as not related to the hypersensitivity reaction or infusion reaction may be continued.
- Any Grade 4 drug-related AE deemed by the Investigator as inappropriate to be managed by dose reduction(s) requires discontinuation of chemotherapy agent(s) assessed as causing the event. The other study intervention(s) assessed as not related to the event may be continued.
- Any event that leads to delay in dosing of any study intervention(s) for > 2 weeks from the previous dose requires discontinuation of the chemotherapy agent(s) with the following exception:
  - Dosing delays lasting > 2 weeks from the scheduled administration that occur for non-drug-related reasons may be allowed after discussion with Medical Monitor.

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued chemotherapy dosing. Investigators should consult the local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose discontinuation.
- If the participant experienced Grade 3 or 4 nonhematological toxicity (except for fatigue, transient arthralgia, and myalgia), treatment with chemotherapy should be withheld until the participant recovers completely or to Grade 1 toxicity. If recovery to Grade 1 toxicity does not occur within 2 weeks, chemotherapy should be discontinued. At the discretion of the Investigator, administration of M7824 could be continued according to the treatment schedule. A discussion between the Investigator and Sponsor's Medical Responsible should take place. Dose delays outside the allowed window (± 3 days) and dose reductions for M7824 are not permitted.

Dose modifications (dose delays) and dose reductions for toxicities should be made according to the tables listed below, approved product label and/or standard practice. Discontinuation of chemotherapy due to AEs should also be done in accordance with the approved product label and/or standard practice and discussed with the Sponsor

- See Table 9 for chemotherapy dose modification for hematologic toxicities.
- See Table 10 for predosing considerations for cisplatin.
- See Table 11 for dose modifications for cisplatin (or carboplatin)/pemetrexed.
- See Table 12 for dose modifications for carboplatin plus paclitaxel or nab-paclitaxel.
- See Table 13 for dose modifications for gemcitabine plus cisplatin or carboplatin.
- See Table 14 for dose modifications for docetaxel.

Table 9 Chemotherapy Dose Modification for Hematologic Toxicities

Platelets	Absolute neutrophil count	Chemotherapy Agent[a]
≥ 50,000/mcL AND	≥ 500/mcL	No change
≥ 50,000/mcL AND	< 500/mcL	Reduce 25%
< 50,000/mcL without bleeding AND	ANY	Reduce 25%
< 50,000/mcL with Grade ≥ 2 bleeding AND	ANY	Reduce 50%
ANY AND	< 1,000/mcL + fever ≥ 38.5°C (101°F)	Reduce 25%

ASCO = American Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network.

a Any chemotherapy agent allowed in this study.

Growth factors may be used in lieu of a dose reduction for neutropenic fever or Grade 4 neutropenia in accordance with ASCO and NCCN guidelines (Smith 2006). Upon recovery, dose adjustments at the start of a subsequent cycle will be based on the lowest platelet and neutrophil values from the previous cycle.

Table 10 Predosing Consideration for Cisplatin

Issue/Indication	Recommended Steps
Pre-emesis	Follow current MASCC/ESMO[a] or NCCN[b] guidelines for chemotherapy-induced nausea and vomiting for a "high risk" regimen
Hydration/ nephrotoxicity	Per package insert/SmPC for cisplatin[c]. Cisplatin causes severe cumulative nephrotoxicity. A urine output of 100 mL/hour or greater will tend to minimize cisplatin nephrotoxicity. Adequate hydration must therefore be maintained to cause sufficient diuresis prior to, during and after treatment with cisplatin. Next to intravenous infusion, forced diuresis may be required and moreover participants are to be requested to drink appropriate quantities of liquids for 24 hours after cisplatin infusion to ensure adequate urine secretion. Some institute may provide inpatient planned hydrated to reduce the risk of renal toxicity due to cisplatin; such planned hospital admission will not be considered for SAE reporting criteria.
Myelosuppression/ neutropenia	Refer to the current package insert/SmPC for modifications in dose and schedule of cisplatin[c]. First dose of cisplatin should be withheld if platelet count is less than 100,000 cells/mm^3 or neutrophil count is less than 1,500 cells/mm^3. Dose modifications for subsequent administrations will be based on the neutrophil and platelet nadir from the preceding cycle (see Table 9). According to NCI-CTCAE V5.0 febrile neutropenia (FN) is defined as ANC < 1000/mm^3 and a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour. FN treatment should be done per local practice and reported in eCRF. FN Prophylaxis: Primary prophylaxis with G-CSF in order to reduce the risk of FN is not recommended, according to NCCN guidelines for the use of myeloid growth factors (v1.2018)[d]. Secondary prophylaxis with G-CSFs should be considered and the benefit-risk associated with their use must be carefully evaluated. Investigators must be aware that the use of G-CSF during chemoradiation is associated with increased of increased incidence of severe thrombocytopenia and anemia. Participants receiving G-CSF during chemoradiation must be closely monitored for these adverse events. The dosage instructions should follow the local guidelines or the NCCN guidelines.
Ototoxicity/ neurotoxicity	Per SmPC for cisplatin[c]. Cisplatin is proven to be cumulative ototoxic and neurotoxic. Neurologic examination and monitoring of potential ototoxicity are to be performed prior to each cisplatin dosing and during the treatment.

ANC = Absolute neutrophil count; ASCO = American Society of Clinical Oncology; CSF = colony stimulating factor; eCRF = electronic case report form; ESMO = European Society for Medical Oncology; FN = febrile neutropenia; G-CSF = granulocyte-colony stimulating factor; MASCC = Multinational Association of Supportive Care in Cancer; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; NCCN = National Comprehensive Cancer Network; OS = overall survival; SmPC = summary of product characteristics.

a Annals of Oncology 21 (Supplement 5): v232–v243, 2010

b NCCN Guideline for Patients® - Antiemesis version 1/2019

c https://www.medicines.org.uk/emc/medicine/25944

d NCCN guidelines Myeloid growth factors version 1, 2018

Table 11 Dose modifications for Cisplatin (or Carboplatin)/Pemetrexed

Event	Grade (CTCAE V5.0)	Pemetrexed	Cisplatin	Carboplatin
Diarrhea	Grade 3 or 4	Reduce 25%	Reduce 25%	No change
Mucositis	Grade 3 or 4	Reduce 50%	No change	No change
Neurotoxicity	Grade 2	No change	Reduce 50%	No change
Neurotoxicity	Grade 3 or 4	Reduce 25%	Discontinue	Reduce 25%
Transaminase elevation	Grade 3	Reduce 25%	Reduce 25%	Reduce 25%
Transaminase elevation	Grade 4	Discontinue	Discontinue	Discontinue
Other non-hematological toxicity	Grade 3 or 4	Reduce 25%	Reduce 25%	Reduce 25%

Reference: Gandhi 2018.
CTCAE = Common Terminology Criteria for Adverse Events.

CrCL must be ≥ 50 mL/min prior to the administration of chemotherapy. Pemetrexed and/or platinum may be delayed for up to 2 weeks to allow the participant time to recover from the toxicity. If a participant's CrCL value has not returned to ≥ 50 mL/min within 2 weeks after the previous dose, platinum and/or pemetrexed must be discontinued.

Table 12 Dose Modifications for Carboplatin plus Paclitaxel or Nab-paclitaxel

Event	Grade (CTCAE V5.0)	Carboplatin	Paclitaxel/Nab-Paclitaxel
Diarrhea	Grade 3 or 4	Reduce 25%	Reduce 25%
Nausea and/or vomiting[a]	Grade 3 or 4	Reduce 25%	Reduce 25%
Mucositis[b]	Grade 3 or 4	Reduce 25%	Reduce 25%
Neurotoxicity	Grade 2	No change	Hold treatment until participant recovers to Grade 1 toxicity, then resume treatment at a 25% reduction
Neurotoxicity	Grade 3 or 4	No change	Hold treatment until participant recovers to Grade 1 toxicity, then resume treatment at a 50% reduction
Transaminase elevation/ Bilirubin elevation[c]	Grade 3/ Grade 2 or 3	No change	Reduce 25% if AST elevation G3 and Bilirubin elevation G2. Reduce 50% if both increase to G3
Transaminase elevation/ Bilirubin elevation[c]	Grade 4	No change	Discontinue
Other non-hematological toxicity	Grade 3 or 4	Resume at 75% for Grade 3 and 50% of dose (permanent dose reduction) for Grade 4 toxicities.	Resume at 75% for Grade 3 and 50% of dose (permanent dose reduction) for Grade 4 toxicities.

Reference: IMPower150 (Socinski 2018).

AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events.

a Nausea and/or vomiting should be controlled with adequate anti-emetics. If Grade 3 or 4 nausea/vomiting occurs despite of anti-emetics, the dose should be reduced by 25% for the next course. If tolerated, the dose should be increased back to 100% as soon as possible.

b If, on Day 1 of any treatment cycle, until the oral mucositis/stomatitis is cleared. If the oral mucositis/stomatitis has not cleared in 3 weeks, the participant's chemotherapy will be discontinued. If acute Grade 3 oral mucositis occurs at any time, a 75% dose should be given when the oral mucositis is completely cleared. This is a permanent dose reduction. If the participant has oral mucositis/stomatitis, the treatment should be withheld.

c For participants who develop hepatic toxicity, paclitaxel/nab-paclitaxel dose should be held until hepatic toxicity resolves to Grade ≤ 1 prior to subsequent dosing. If paclitaxel/nab-paclitaxel is withheld because of hepatic toxicity, carboplatin should also be withheld and administered when the paclitaxel/nab-paclitaxel is resumed. If paclitaxel/nab-paclitaxel is withheld, hepatic values must recover to Grade ≤ 1 within 3 weeks or the participant's paclitaxel/nab-paclitaxel treatment will be discontinued.

Cardiac rhythm disturbances have occurred infrequently in patients treated with paclitaxel or nab-paclitaxel in clinical studies; however, most patients were asymptomatic, and cardiac monitoring is not required. Cardiac events should be managed as follows:

- Asymptomatic bradycardia: no treatment required

- Symptomatic arrhythmia during infusion: stop paclitaxel/nab-paclitaxel infusion, manage arrhythmia according to standard practice. Paclitaxel/nab-paclitaxel treatment will be discontinued.
- Chest pain and/or symptomatic hypotension (< 90/60 mmHg or requires fluid replacement): stop paclitaxel/nab-paclitaxel infusion. Perform an electrocardiogram (ECG). Administer iv diphenhydramine and dexamethasone if hypersensitivity is considered. Also consider epinephrine or bronchodilators if chest pain is not thought to be cardiac. Paclitaxel/nab-paclitaxel treatment will be discontinued, and cardiovascular support should be given as appropriate. If appropriate, the advice of a cardiologist should also be sought.

Patients who had a mild to moderate hypersensitivity reaction to paclitaxel/nab-paclitaxel have been successfully rechallenged, but the administration of prophylactic medication and intensive monitoring of vital signs is recommended:

- Mild symptoms: complete paclitaxel/nab-paclitaxel infusion. Supervise at bedside. No treatment required.
- Moderate symptoms: stop paclitaxel/nab-paclitaxel infusion. Administer iv diphenhydramine 25 to 50 mg and dexamethasone 10 mg. Resume paclitaxel/nab-paclitaxel infusion after recovery of symptoms at a low rate, 20 mL/hour for 15 minutes, then 40 mL/hour for 15 minutes, then if no further symptoms, at full-dose rate until infusion is complete. If symptoms recur, stop paclitaxel/nab-paclitaxel infusion. Paclitaxel/nab-paclitaxel treatment will be discontinued.
- Severe life-threatening symptoms: stop paclitaxel/nab-paclitaxel infusion. Administer iv diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. Paclitaxel/ab-paclitaxel treatment will be discontinued.
- Moderate or severe hypersensitivity reactions should be recorded as an AE.

Table 13 Dose Modifications for Gemcitabine Plus Cisplatin or Carboplatin

Event	Grade (CTCAE V5.0)	Cisplatin	Carboplatin	Gemcitabine
Diarrhea	Grade 3 or 4	No change	No change	Reduce 25%
Neurotoxicity	Grade 2	Reduce 25%	No change	No change
Neurotoxicity	Grade 3 or 4	Discontinue	Discontinue	Discontinue
Calculated Creatinine Clearance < 50 mL/min		Discontinue	No change	No change
Allergic reaction [a]	Grade 3 or 4	Discontinue	Discontinue	Discontinue
Other Grade ≥ 3 toxicity (except for fatigue and transient arthralgia and myalgia)		Adjust as clinically indicated	Adjust as clinically indicated	Adjust as clinically indicated

Reference: Hellmann 2018.

CTCAE = Common Terminology Criteria for Adverse Events.

a Only the drug(s) causing the hypersensitivity reaction or acute infusion reaction (≥ Grade 3) require(s) discontinuation. All other drugs may be continued.

Note that participants receiving gemcitabine plus cisplatin who discontinue cisplatin alone may, at the Investigator's discretion, be switched to gemcitabine/carboplatin for the remainder of the platinum-doublet cycles (up to 4 cycles in total). Participants receiving pemetrexed/cisplatin who discontinue cisplatin alone may, at the Investigator's discretion, be switched to pemetrexed/carboplatin for the remainder of the platinum-doublet cycles (up to 4 cycles in total).

Table 14 Dose Modifications for Docetaxel

Event	Grade (CTCAE V5.0)	Docetaxel
Diarrhea	Grade 3 or 4	Reduce 25%
Transaminase elevation[a]	Grade 3 or 4	Reduce 50%
Bilirubin elevation	Grade 3 or 4	Reduce 25%
Neurotoxicity	Grade 2	Reduce 25%
Neurotoxicity	Grade 3 or 4	Discontinue
Allergic reaction	Grade 3 or 4	Discontinue
Other Grade ≥ 3 toxicity including nausea/vomiting while receiving optimal antiemetic therapy		Reduce 25%

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit normal.

a For participants with baseline AST/ALT values > 2.5 x ULN due to liver metastases, dose reduction guidelines based on CTC toxicity grading will be voided. Instead, dose reductions will be undertaken only if test results exceed 2x baseline values.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

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

- A participant may withdraw from the study at any time, at his/her own request (i.e. withdrawal of consent), and without giving a reason.
- Occurrence of an exclusion criterion, which is clinically relevant and affects the participant's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor.
- The participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- Confirmed PD per RECIST 1.1 with the exception that participants receiving treatment may continue past PD if the participant's ECOG PS has remained stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment (see Section 4.1).
- Some ADRs require withdrawal from study intervention. See Section 6.9.2 for additional details.
- Occurrence of pregnancy.

- Use of a prohibited 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.

The Schedule of Activities (Table 1) specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed.

7.1.1 Temporary Discontinuation

See Section 6.9 for information on temporary study intervention discontinuation.

7.1.2 Rechallenge

One reinitiation or rechallenge of treatment including M7824 alone or M7824 and chemotherapy at the same dose and schedule up to 2 years is allowed unless a new anticancer treatment has been initiated 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 cohort 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.

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

Prior to reinitiation of the study intervention, malignant disease must be radiologically restaged within 28 days of dosing to assess all known disease sites. Additionally, relevant safety laboratory assessments, including both full hematology and full chemistry results within 2 weeks, must be available and verified. The clinical Investigator will determine whether additional evaluation and work-up are required on a case-by-case basis. A discussion with the study team is warranted to determine if repeating PK/biomarker testing is indicated upon restarting treatment.

The participants should reinitiate treatment at the treatment phase visit where they left off according to the Schedule of Activities (Section 1.3). The participants may reinitiate treatment with M7824 alone or M7824 and chemotherapy, as clinically indicated. Participants who reinitiate treatment should stay on study and should be monitored according to the Schedule of Activities (Section 1.3) for the rest of the study. A rollover protocol may accommodate M7824 participants if available at the time of reinitiation.

7.2 Participant Discontinuation/Withdrawal from the Study

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

In case of participant discontinuation/ withdrawal from the study:

- The appropriate eCRFs for the End of Treatment Visit must be completed.
- Participants will be asked to sign a withdrawal consent to continue safety and survival follow-up, which includes the collection of data on survival, and subsequent anticancer therapy. After completion of the Follow-up period or after the End of Treatment Visit, whatever is applicable, the appropriate eCRF section for Study Termination must be completed.
- If 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.

7.3 Lost to Follow-up

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

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

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed “lost to follow-up”, the Investigator or designee will make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant’s last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant’s general practitioner or caretaker (where allowed by local regulations) for information. These contact attempts should be documented in the participant’s medical record. 4) if proper consent is obtained, continue to collect health status through public data.

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

8 Study Assessments and Procedures

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

8.1 Efficacy Assessments and Procedures

Contrast-enhanced CT of the chest/abdomen and pelvis covering the area from the superior extent of the thoracic inlet to the symphysis pubis is the first choice of imaging modality. If a participant 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 practice) 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. If local practice prohibits imaging of the full scanning of the asymptomatic pelvis, scans must at least include the entire inferior extent of the liver tip.

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 metastases cannot be selected 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).

Investigators will read and interpret all CT/MRI data; and make treatment decisions. Response will be evaluated according to RECIST 1.1. 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). If deemed appropriate by the Sponsor, evaluation of efficacy by RECIST 1.1 and immune-related RECIST (irRECIST, Bohnsack 2014) will be done retrospectively and assessed by an IRC.

Baseline scans are taken within 28 days, and preferably within 14 days, prior to W1D1. 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 with radiographic imaging to assess response to treatment every 6 weeks up to 12 months, then every 12 weeks of the participant's first dose up to 24 months, then every 6 to 12 weeks according to local practice.

In the case of a PR or CR, a confirmatory CT or MRI scan should be performed at the next regularly scheduled 6 weekly assessment intervals, or no sooner than 4 weeks after the initial documentation. After PD, confirmation of PD is also required and should be performed preferably and if clinically feasible, at the next regularly scheduled assessment, but no sooner than 4 weeks after the initial documentation.

8.2 Safety Assessments and Procedures

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

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 the Schedule of Activities (Section 1.3).

8.2.1 Physical Examinations

A complete physical examination at Screening will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Subsequent focused physical examinations to be performed as per local standard practice and as clinically indicated. A brief physical examination (at all other scheduled visits other than Screening) will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses and to emerging AEs.

General status, such as asthenia or appetite, should be evaluated at Baseline, as these are usually affected. Preexisting symptoms of underlying conditions and/or signs of infection should be investigated as clinically indicated.

Abnormal findings are to be reassessed at subsequent visits.

8.2.2 Vital Signs

Vital signs include:

- Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Height and weight (height at Screening visit only) will also be measured and recorded.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate. Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF.

8.2.3 Electrocardiograms

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

8.2.4 Clinical Safety Laboratory Assessments

Clinical Safety Laboratory Assessments include:

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 5, at the time points listed in the Schedule of Activities. 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 Sponsor or designated organization.
- 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 CRF. The laboratory reports must be filed with the source documents.

- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at the time points specified in the Schedule of Activities, Section 1.3, including at the end of relevant systemic exposure of the study intervention.

8.2.5 Suicidal Risk Monitoring

Not applicable.

8.3 Adverse Events and Serious Adverse Events

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

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

The AE reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the 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 4, whenever it occurs, irrespective of the time elapsed since the last administration of study intervention.

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

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

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

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

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

Adverse events are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) and are assessed for their outcome at the 12-week Safety Follow-up Visit.

All SAEs ongoing at the 12-week Safety Follow-up Visit must be monitored and followed-up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is given in Appendix 4.

Monitoring of Specific Adverse Events

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

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

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

The Investigator must 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 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 (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 (e.g. resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 must be recorded in the AE

page/section of the eCRF for both pregnancies in female participants and pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Appendix 4, section on Reporting Serious Adverse Events and Dose-Limiting Toxicities.

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 AE Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 8.3.1, while normal outcomes must be reported within 45 days after delivery.

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

8.4 Treatment of Overdose

For this study, any dose of M7824 greater than 2 times more than the recommended dose for each infusion (i.e. > 4,800 mg) 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 > 2,400 mg) with no observed DLT at 30 mg/kg and not reaching MTD (refer to the IB). Safety at significantly higher doses has not been clinically evaluated.

For chemotherapeutic agents used in this study, any single dose exceeding 20% of recommended chemotherapy dose regimen will be considered overdose.

In the event of an overdose with clinical correlation, symptomatic treatment must be used; there are no known antidotes for the compound. The Investigator should use his or her clinical judgment when treating an overdose of the study intervention. In the event of an 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 an overdose, it should follow SAE reporting criteria as indicated in Appendix 4.

Even if it not associated with an AE or SAE, any overdose is recorded in the CRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 4, section on Reporting Serious Adverse Events and Dose-Limiting Toxicities.

8.5 Pharmacokinetics

Sample collection has been stopped as communicated in the Investigator letter dated as 2 November 2021.

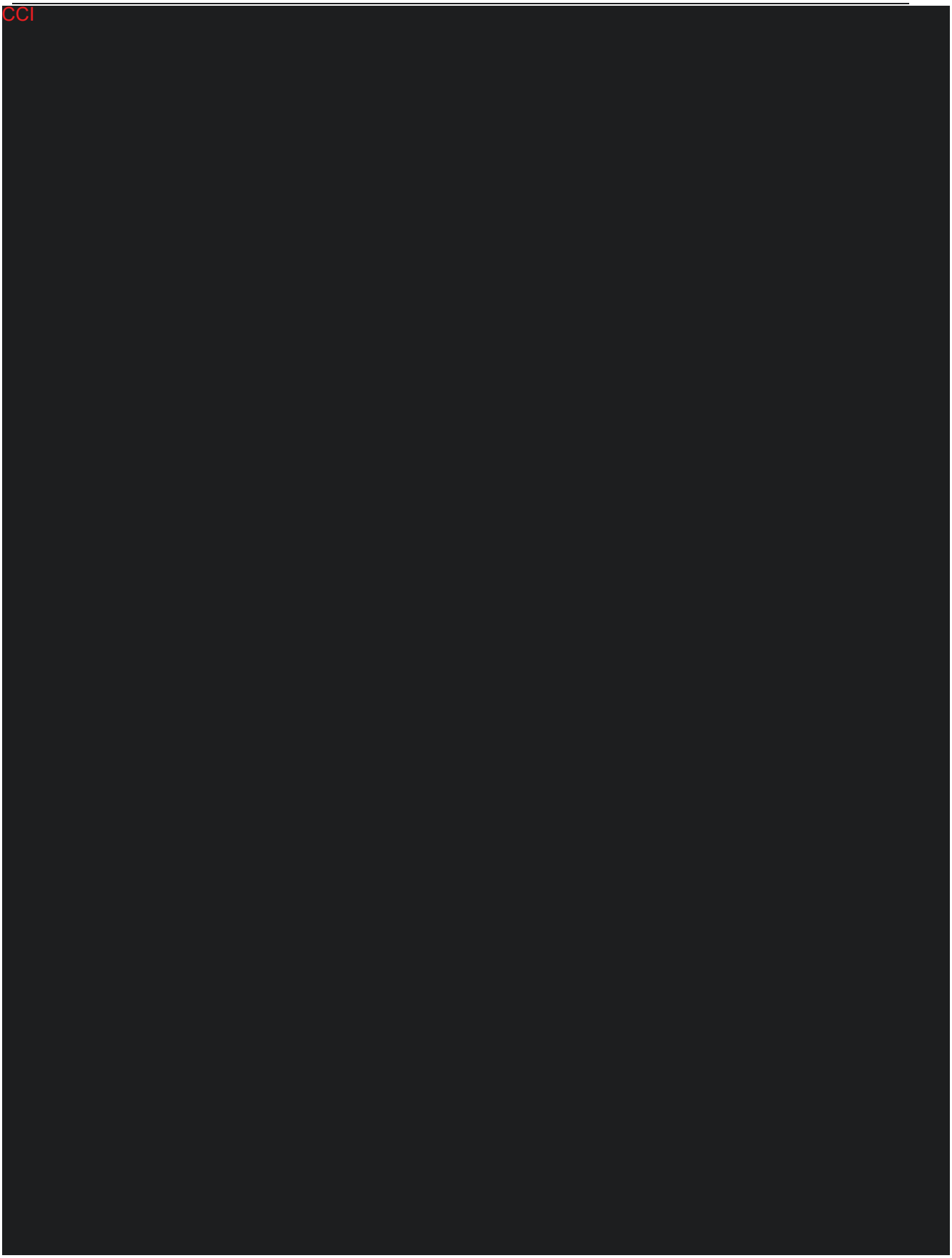
The following PK parameters (Table 15) will be calculated, when appropriate:

Table 15 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)
AUC_{0-t} (Safety only)	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0-\infty}$ (Safety only):	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at $t_{last,}$ as estimated using the linear regression from λ_z determination. $AUC_{0-\infty} = AUC_{0-t}+C_{last\ pred}/\ \lambda_z$
λ_z (Safety only):	Terminal first order (elimination) rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve
C_{max} (Safety only)	Maximum observed concentration
t_{max} (Safety only):	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)

- Blood samples of approximately 3.5 mL will be collected for measurement of serum concentrations of M7824, as specified in the Schedule of Activities (Section 1.3). 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 to calculate actual time elapsed since the prior dose administration.
- The quantification of M7824 in serum will be performed using a validated assay method. Concentrations will be used to evaluate the PK of M7824.
- Remaining samples collected for analyses of M7824 concentration may also be used to evaluate immunogenicity and safety or efficacy aspects related to concerns arising during or after the study.
- Details on processes for collection and shipment of these samples are in Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.
- The PK parameters will be summarized using descriptive statistics. Individual as well as mean concentration-time plots will be depicted.

CCI



CCI [redacted]

8.10 Immunogenicity Assessments

- Whole blood samples of approximately 5 mL will be collected for detection of antibodies against M7824 in serum, as specified in the Schedule of Activities (Section 1.3). Samples will be collected prior to any M7824 administration on the same study day.
- The detection of antibodies to M7824 will be performed using a validated assay method with tiered testing of screening, confirmatory and titration. Confirmed positive antibodies may be further characterized.

CCI [redacted]

- Details on processes for collection and shipment of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

Sample collection has been stopped as communicated in the Investigator letter dated as 02 November 2021.

CCI [redacted]

CCI

[redacted]

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.

Table 17 Population for Analysis

Analysis Population	Description
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's study intervention status in the study.
Safety (DLT)	Participants who were administered with at least 90% of the M7824 infusion during the DLT observation period of 3 weeks and did not discontinue treatment for other reasons than DLT. Analyses will consider participants as treated.
Full Analysis Set (FAS)	All participants, who were administered any dose of any study intervention. Analyses will include participants as treated (i.e. in case the chemotherapy regimen was switched the latter one is used in analysis).
Safety Analysis Set (SAF)	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.
Biomarker-Tumor Analysis Set	The Biomarker-Tumor population includes all participants in the FAS, who provided at least 1 predose tumor biopsy.
CT = chemotherapy; DLT = dose-limiting toxicity.	

9.4 Statistical Analyses

General Considerations

All analyses will be described in detail in the Integrated Analysis Plan (IAP).

There is no formal significance level for this trial and all analyses are considered descriptive.

In general, continuous variables will be summarized using number of participants (n); mean, standard deviation; median, 25th Percentile to 75th Percentile (Q1-Q3), minimum, and maximum. If there are less than 5 observations available only mean and the observed data will be given.

Categorical variables will be summarized using frequency counts and percentages.

The calculation of proportions will be based on the number of participants in the analysis set of interest, unless otherwise specified in the study IAP.

Only tumor assessments performed before the start of any further anticancer treatment will be considered in the assessment of confirmed objective response. Clinical deterioration will not be considered as documented PD.

Baseline

In general, the last non-missing measurement prior to the first study intervention will serve as the baseline measurement.

9.4.1 Efficacy Analyses

All analyses for secondary efficacy endpoints will be performed on the FAS, unless otherwise specified (see Table 18). The focus of the efficacy analyses is on Cohort A after expansion to N = 40 participants, but descriptive analyses per cohort or pooled analyses may be conducted as specified in the IAP.

Table 18 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary Confirmed objective response	Counts and percentages will be presented. Confirmed objective response (either partial or complete confirmed response according to RECIST 1.1) reported with rate and 95% Clopper-Pearson confidence interval.
PFS	PFS according to RECIST 1.1, is defined as the time from first administration of study intervention until date of the first documentation of PD or death due to any cause in the absence of documented PD, whichever occurs first. Participants with progression or death after more than 2 scheduled tumor assessment intervals after the last evaluable tumor assessment will be censored at the date of the last evaluable response assessment for PFS analyses. Kaplan-Meier estimates will be provided; Median PFS and the 95% confidence interval for the median will be calculated according to Brookmeyer & Crowley (1982).
OS	OS is defined as the time from first administration of study intervention to the date of death due to any cause. Participants last known to be alive will be censored at date of last contact. Kaplan-Meier estimates will be provided; Median OS and the 95% confidence interval for the median will be calculated according to Brookmeyer & Crowley (1982).

DoR	DoR is defined, for participants with a confirmed objective response, as the time from first documentation of objective response (CR or PR) to the date of first documentation of objective progression of disease (PD) or death due to any cause whichever occurs first. The censoring rules for DoR are as described above for PFS. Kaplan-Meier estimates will be provided for confirmed responders according to RECIST 1.1; Median DoR and the 95% confidence interval for the median will be calculated according to Brookmeyer & Crowley (1982).
CCI [redacted]	[redacted]
CR = complete response; DoR = duration of response; IAP = Integrated Analysis Plan; OS = overall survival; PD = progression of disease; PFS = progression-free survival; PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.	

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis population (see Table 19).

Table 19 Safety Analysis

Endpoint	Statistical Analysis Methods
Primary Occurrence of TEAEs and treatment-related AEs including AESIs according to MedDRA Occurrence of DLTs during the 3-week DLT observation period	The Safety Analysis will report adverse events, AESIs and laboratory tests outcomes. The safety endpoints will be tabulated using descriptive statistics. The incidence of TEAEs, regardless of attribution, will be summarized by preferred term and system organ class for each treatment cohort, and described in terms of intensity and relationship to treatment. Further details of safety analyses will be provided in the IAP. Participants will be analyzed according to the actual treatment they receive. Count and rate of DLT per cohort will be presented with 95% Clopper-Pearson confidence interval in the DLT analysis set.
Secondary	Not applicable
CCI [redacted]	[redacted]
AE = adverse event; AESIs = adverse events of special interest; DLT = dose-limiting toxicity; IAP = Integrated Analysis Plan; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.	

9.4.3 Other Analyses

PK, immunogenicity, and CCI [redacted] will be specified in the IAP finalized before database lock. Integrated analyses across studies, such as the population PK analysis and exposure-response analyses will be presented separately from the clinical study report (CSR).

9.4.4 Sequence of Analyses

There are 2 data cutoff time points in this study:

1. The SMC will clear safety based on DLTs observed in the 4 cohorts during the safety run-in part of the study when the last participant completes DLT observation period in the corresponding cohort. SMC meetings for the different combinations can be combined, whereas a delay for the decision regarding the expansion of Cohort A should be avoided.

2. If Cohort A is expanded to N = 40 participants an interim analysis will be conducted 6 months after the treatment start of the last participant in the expanded pilot cohort (Cohort A).

In case a new safety signal is observed, an additional analysis will be done at end of study and included in study report. In the other cases, no further analyses will be planned.

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CCI [redacted]

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11 Appendices

Appendix 1 Abbreviations

1L	First-line
2L	Second-line
ADR	Adverse drug reaction
AE	Adverse events
AESI	Adverse events of special interest
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
CNS	Central nervous system
CR	Complete response
CrCL	Creatinine clearance
CRF	Case report form
cSCC	Cutaneous squamous cell carcinoma
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI [redacted]	[redacted]
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EDC	Electronic Data Capture
EGFR	Epidermal growth factor receptor

FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
IAP	Integrated Analysis Plan
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICF	Informed consent form
IEC	Independent Ethics Committee
INR	International normalized ratio
irAE	Immune-related AE
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-related reaction
CCI	[redacted]
IWRS	Interactive Web Response System
KA	Keratoacanthoma
LFT	Liver function test
mAbs	Monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
PD	Progression of disease

PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PT	Prothrombin time
Q2W	Every two weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumors 1.1
RT	Radiation therapy
SAE	Serious adverse event
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
TGFβ	Transforming growth factor beta
CCI	[redacted]
TNF	Tumor necrosis factor
TO	Target occupancy
TSH	Thyroid-stimulating hormone
TTP	Thrombotic thrombocytopenic purpura
ULN	Upper limit of normal
W1D1	Week 1 Day 1
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 (an individual or judicial or other body authorized to consent on behalf of a prospective participant under applicable law to the participant'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 purpose.
- 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 Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH-GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the CSR.

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

Details of structures and associated procedures will be defined in a separate Integrated Project Management Plan.

Regulatory and Ethical Considerations

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

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

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g. unblinding) will follow the standard process established for Investigators.
- When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor (or designee) physician. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor (or designee) physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

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

Clinical Study Report

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

Publication

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

Dissemination of Clinical Study Data

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

Data Quality Assurance

- All participant study data will be recorded on printed or eCRFs or transmitted to the Sponsor or designee electronically (e.g. laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the eCRF Guidelines.
- The Investigator must maintain accurate documentation (source data) that supports the information in the CRF.
- 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.
- Monitoring details describing strategy (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan or contracts.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the CRFs will be provided to the Investigators at study completion.
- Study monitors will perform ongoing source data verification to confirm that data in the CRF 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 (i.e. the Sponsor's study number) and participant's study number.
  - Dates of entry into the study (i.e. signature date on the informed consent) and each visit to the site
  - Any medical examinations and clinical findings predefined in the protocol
  - All AEs
  - Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.
- All source data must be filed (e.g. CT or MRI scan images, ECG recordings, and laboratory results). Each document must have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- Data recorded on printed or eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The study monitors will use printouts of electronic files for source data verification. These printouts must be signed and dated by the Investigator and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH-GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in 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

Definitions:

Woman of Childbearing Potential (WOCBP)

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

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

A WOCBP is **not**:

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

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

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

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods That Have Low User Dependency

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

Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - Oral
  - Injectable
- Sexual abstinence: a highly effective method **only** if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence is evaluated in relation to the duration of the study.

Acceptable Methods

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide. Male condom and female condom cannot be used together (due to risk of failure with friction)
- Cervical cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)

Contraceptive use by men or women is consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

Highly effective methods have a failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

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

Acceptable methods are considered effective, but **not** highly effective (i.e. have a failure rate of ≥ 1% per year). Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are **not** acceptable methods of contraception.

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

Definitions

Adverse Event

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

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

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

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

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

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

The 5 general grades are:

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

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

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

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

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

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

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

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

Serious Adverse Events

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

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

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

Events that Do Not Meet the Definition of an SAE

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

Events Not to Be Considered as AEs/SAEs

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

AE/SAEs Observed in Association with Disease Progression

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

Adverse Events of Special Interest

Adverse events of special interest (AESI) can be serious or nonserious events.

Categories of AESIs related to M7824 include:

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

Other Adverse Events to be Reported Following a Specialized Procedure

Not applicable.

Recording and Follow-up of AE and/or SAE

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

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

Reporting Serious Adverse Events and Dose-Limiting Toxicities

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the

Sponsor or its designee using the electronic SAE report form in the Electronic Data Capture (EDC) system.

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

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

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

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

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

Dose-Limiting Toxicities

Each event meeting the criteria of a DLT, as specified in Section 6.9.1 must be recorded in the CRF within 24 HOURS after becoming aware of the event. Serious DLTs must be reported in an expedited manner as SAEs, as outlined above.

Appendix 5 Clinical Laboratory Tests

Table A: Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	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[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	Lactose dehydrogenase		
Full Clinical Chemistry Panel B[b]		T-SPOT TB test or TST or QuantiFERON TB Gold Test (QFT-G) (if positive history of tuberculosis exposure)	Virology: HBV and HCV serology (repeat as per Schedule of Activities if participant with infection history)[c]	
Core Chemistry[a]	Liver Panel: alkaline phosphatase, ALT, AST, total and indirect/direct bilirubin	Serum Electrolytes: sodium, potassium	Renal Panel: BUN/total urea, creatinine	Glucose, amylase, lipase
Thyroid Panel	• T_4, TSH			
Routine Urinalysis[b]	• 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 woman of nonchildbearing potential **only**) • Serum or highly sensitive urine human chorionic gonadotropin (β-hCG) pregnancy test (as needed for woman of childbearing potential).			

ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = β human chorionic gonadotropin; BUN = blood urea nitrogen; 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; PCR = polymerase chain reaction; RBC = red blood cell; RDW = red cell distribution width; T_4 = free thyroxine; TB = tuberculosis; TSH = thyroid-stimulating hormone; WBC = white blood cell; TST = tuberculin skin test.

a Performed as indicated in the Schedule of Activities.

b Performed at Screening then as clinically indicated.

Laboratory Assessments	Parameters
c	Testing will include Hepatitis B core antibody, Hepatitis B surface antigen and Hepatitis C antibody. Hepatitis B surface antibody can be tested if locally required. If Hepatitis B surface antigen and Hepatitis B core antibody are positive or if Hepatitis B core antibody is positive alone, then quantitative testing of Hepatitis B DNA is required (PCR); if Hepatitis C antibody is positive, then quantitative testing of Hepatitis C RNA is required (PCR).

Appendix 6 The Recommendations for Immune-Related Adverse Events (irAE) Management

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

Table A1 Management of Skin irAEs in Patients Treated with ICPis

1.0 Skin Toxicities	
1.1 Rash/inflammatory dermatitis	
Definition: Erythema multiforme minor (a targetoid reaction in the skin and mucous membranes usually triggered by infections, such as herpes simplex viruses, but can be associated with an immune-related drug eruption and if progresses to erythema multiforme major, it and can be a harbinger of SCAR, such as SJS), lichenoid (resembling the flat-topped, polygonal, and sometimes scaly or hypertrophic lesions of lichen-planus), eczematous (inflammatory dermatitis characterized by pruritic, erythematous, scaly, or crusted papules or plaques on the skin), which is vulnerable to superinfection, psoriasiform (resembling the well-demarcated, erythematous, and scaly papules and plaques of psoriasis), morbilliform (a nonpustular, nonbullous measles-like exanthematous rash of the skin often referred to as "maculopapular" and without systemic symptoms or laboratory abnormalities, excluding occasional isolated peripheral eosinophilia), palmoplantar erythrodysesthesia (hand-foot syndrome; redness, numbness, burning, itching, and superficial desquamation of the palms and soles), neutrophilic dermatoses (e.g. Sweet syndrome, and others).	
Diagnostic work-up Pertinent history and physical examination Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease or unrelated primary skin disorder If needed, a biologic checkup, including a blood cell count and liver and kidney tests Directed serologic studies if an autoimmune condition is suspected, such as lupus or dermatomyositis: a screening antinuclear antibody test, SS-A/Anti-Ro, SS-B/Anti-La if predominantly photodistributed/photosensitivity, antihistone, double-stranded DNA, and other relevant serologies. Consider expanding serologic studies or diagnostic work-up if other autoimmune conditions are considered based on signs, symptoms, and 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	**Permanently discontinue ICPi** Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves

1.0 Skin Toxicities	
	Monitor closely for progression to severe cutaneous adverse reaction Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology
1.2 Bullous dermatoses	
Definition: Including bullous pemphigoid or other autoimmune bullous dermatoses, bullous drug reaction **Diagnostic work-up:** Physical examination Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease If needed, a biologic checkup, including a blood cell count, liver, and kidney tests; consider serum antibody tests to rule out bullous pemphigoid or, under the guidance of dermatology, sending patient serum for indirect immunofluorescent testing to rule out other autoimmune blistering diseases Referral to dermatology for blisters that are not explained by infectious or transient other causes (e.g. herpes simplex, herpes zoster, bullous impetigo, bullous insect bite, friction or pressure blister) Consider skin biopsy (both hematoxylin and eosin evaluation of lesional skin and direct immunofluorescence evaluation of perilesional skin)	
Grading	**Management**
G1: Asymptomatic, blisters covering < 10% BSA and no associated erythema	If blisters are < 10% BSA, asymptomatic, and noninflammatory (such as the case with friction blisters or pressure blisters), cessation of ICPi is not necessary, and only observation and/or local wound care is warranted. When symptomatic bullae or erosions, which are deroofed vesicles or bullae, are observed on the skin or mucosal surfaces, the cutaneous irAE is by definition considered at least G2 See G2 management recommendations
G2: Blistering that affects quality of life and requires intervention based on diagnosis not meeting criteria for Grade > 2 Blisters covering 10%-30% BSA	Hold ICPi therapy and consult with dermatology for work-up and to determine appropriateness of resuming Attention given to general local wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions, which are left over on the skin after the blister has popped or if the roof of the blister easily sloughs off Counsel patients to avoid skin irritants and overexposure to sun, wear protective clothing, use sunscreens Work-up for autoimmune bullous disease as above Initiate Class 1 high-potency topical corticosteroid (e.g. clobetasol, betamethasone or equivalent) and reassess every 3 days for progression or improvement Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg dosing and taper over at least 4 weeks Monitor patients with G2 irAEs closely for progression to involvement of greater BSA and/or mucous membrane involvement. Consider following patients closely using serial photography Primer on monitoring for complicated cutaneous adverse drug reactions:

1.0 Skin Toxicities	
	Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements
	Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema", which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (e.g. pemphigus) and SJS/TEN
G3: Skin sloughing covering > 30% BSA with associated pain and limiting self-care ADL	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab, as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.
G4: Blisters covering > 30% BSA with associated fluid or electrolyte abnormalities	Permanently discontinue ICPi Admit patient immediately and place under supervision of a dermatologist Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg with tapering over at least 4 weeks when the toxicity resolves If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc
1.3 SCARs, including SJS, TEN, acute generalized exanthematous pustulosis, and DRESS/DIHS	
Definition: Severe changes in either structure or functions of skin, the appendages or the mucous membranes due to a drug	
Diagnostic work-up	
Total body skin examination with attention to examining all mucous membranes as well as complete review of systems Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease	

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

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

Table A2 Management of GI irAEs in Patients Treated with ICPis

2.0 GI Toxicities

2.1 Colitis	
Definition: A disorder characterized by inflammation of the colon Diagnostic work-up	
G2 Work-up of blood (CBC, comprehensive metabolic panel, TSH, ESR, CRP), stool (culture, Clostridium difficile, parasite, CMV or other viral etiology, ova and parasite) should be performed Consider testing for lactoferrin (for patient stratification to determine who needs more urgent endoscopy) and calprotectin (to follow-up on disease activity) Screening laboratories (HIV, hepatitis A and B, and blood quantiFERON for TB) to prepare patients to start infliximab should be routinely done in patients at high risk for those infections and appropriately selected patients based on infectious disease expert's evaluation Imaging (e.g. CT scan of abdomen and pelvis and GI endoscopy with biopsy) should be considered as there is evidence showing that the presence of ulceration in the colon can predict a corticosteroid refractory course, which may require early infliximab Consider repeating endoscopy for patients who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring can be considered when clinically indicated and when planning to resume therapy	
G3-4 All the work-up listed for G2 (blood, stool, imaging, and scope with biopsy) should be completed immediately Consider repeating endoscopy for patients who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring should only be considered when clinically indicated and when planning to resume ICPi	
Grading (based on CTCAE for diarrhea, as most often used clinically)	Management
All patients	Counsel all patients to be aware of and inform their health care provider immediately if they experience: Abdominal pain, nausea, cramping, blood or mucus in stool or changes in bowel habits, fever, abdominal distention, obstipation, constipation For G2 or higher, consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less; concurrent immunosuppressant maintenance therapy should be considered only if clinically indicated in individual cases
G1: Increase of fewer than 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Continue ICPi; alternatively, ICPi may be held temporarily and resumed if toxicity does not exceed G1 Monitor for dehydration and recommend dietary changes Facilitate expedited phone contact with patient/caregiver May obtain gastroenterology consult for prolonged G1 cases
G2: Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared with baseline	Should hold ICPi temporarily until patient's symptoms recover to G1; can consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less Concurrent immunosuppressant maintenance therapy (10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases May also include supportive care with medications such as Imodium if infection has been ruled out Should consult with gastroenterology for G2 or higher

2.0 GI Toxicities

	Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent When symptoms improve to G1 or less, taper corticosteroids over at least 4-6 weeks before resuming treatment, although resuming treatment while on low-dose corticosteroid may also be an option after an evaluation of the risks and benefits EGD/colonoscopy, endoscopy evaluation should be highly recommended for cases Grade ≥ 2 to stratify patients for early treatment with infliximab based on the endoscopic findings and to determine the safety of resuming PD-1, PD-L1 therapy Stool inflammatory markers can be considered (lactoferrin and calprotectin) in cases of G2 or higher to differentiate functional versus inflammatory diarrhea, and use calprotectin to monitor treatment response if provider prefers Repeat colonoscopy is optional for cases of G2 or higher for disease activity monitoring to achieve complete remission, especially if there is a plan to resume ICPi
G3: Increase of 7 or more stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL	Should consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less. Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent) Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance If symptoms persist ≥ 3-5 days or recur after improvement, consider administering IV corticosteroid or noncorticosteroid (e.g. infliximab) Consider colonoscopy in cases where patients have been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (i.e. CMV colitis) and for those who are anti-TNF or corticosteroid refractory
G4: Life-threatening consequences; urgent intervention indicated	Permanently discontinue treatment Should admit patient when clinically indicated; patients managed as outpatients should be very closely monitored Administer 1-2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks Consider early infliximab 5-10 mg/kg if symptoms refractory to corticosteroid within 2-3 days. Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections
Additional considerations The use of vedolizumab may be considered in patients refractory to infliximab and/or contraindicated to TNF-α blocker. The decision should be made on an individual basis from gastroenterology and oncology evaluation. This is based on case series showing promising results. 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 1 to 2 times weekly Manage with supportive care for symptom control
G2: Asymptomatic (AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN)	Hold ICPi temporarily and resume if recover to G1 or less on prednisone ≤ 10 mg/d For Grade 2 hepatic toxicity with symptoms, may administer corticosteroid 0.5-1 mg/kg/d prednisone or equivalent if the abnormal elevation persists with significant clinical symptoms in 3-5 days Increase frequency of monitoring to every 3 days Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of idiosyncratic liver failure (Note: No clear evidence shows the liver toxicity from infliximab from other studies) In follow-up, may resume ICPi treatment followed by taper only when symptoms improve to G1 or less and corticosteroid ≤ 10 mg/d; taper over at least 1 month Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs
G3: Symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis (AST or ALT 5-20 x ULN and/or total bilirubin 3-10 x 3 ULN)	Permanently discontinue ICPi Immediately start corticosteroid 1-2 mg/kg methylprednisolone or equivalent If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using azathioprine should test for thiopurine methyltransferase deficiency) 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

2.0 GI Toxicities

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

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

4.0 Endocrine Toxicity	
4.2 Adrenal – primary adrenal insufficiency	
Definition: Adrenal gland failure leading to low morning cortisol, high morning ACTH, as well as hyponatremia and hyperkalemia with orthostasis and volume depletion due to loss of aldosterone	
Diagnostic work-up for patients in whom adrenal insufficiency is suspected: Evaluate ACTH (AM), cortisol level (AM) Basic metabolic panel (Na, K, CO_2, glucose) Consider ACTH stimulation test for indeterminate results If primary adrenal insufficiency (high ACTH, low cortisol) is found biochemically: Evaluate for precipitating cause of crisis such as infection Perform an adrenal CT for metastasis/hemorrhage	
Grading	**Management**
G1: Asymptomatic or mild symptoms	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Replacement therapy with prednisone (5-10 mg daily) or hydrocortisone (10-20 mg orally every morning, 5-10 mg orally in early afternoon) May require fludrocortisone (0.1 mg/d) for mineralocorticoid replacement in primary adrenal insufficiency Titrate dose up or down as symptoms dictate
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Initiate outpatient treatment at 2 to 3 times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg in the morning, and 10-20 mg in the afternoon) to manage acute symptoms. Taper stress-dose corticosteroids down to maintenance doses over 5-10 days Maintenance therapy as in G1.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormone Endocrine consultation See in clinic or, for after hours, make an emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation (hydrocortisone 100 mg or dexamethasone 4 mg) (if the diagnosis is not clear and stimulation testing will be needed) Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge Maintenance therapy as in G1
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).	

4.0 Endocrine Toxicity	
Emergent therapy for someone with suspected adrenal insufficiency is best done with dexamethasone as a stimulation test can still be performed. If the diagnosis is already confirmed, can use hydrocortisone 100 mg. All patients need education on stress dosing and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS. Endocrine consultation prior to surgery or any procedure for stress-dose planning.	
4.3 Pituitary – hypophysitis	
Definition: Inflammation of the pituitary with varying effects on hormone function. Most commonly presenting with central adrenal insufficiency. May also have central hypothyroidism, diabetes insipidus, and hypogonadism. Diagnostic work-up Diagnosis: Low ACTH with a low cortisol. Low or normal TSH with a low FT4. Hypernatremia and volume depletion with diabetes insipidus. Low testosterone or estradiol with low LH and FSH. Testing: Evaluate ACTH, cortisol (AM), TSH, FT4, electrolytes Consider evaluating LH, FSH, and testosterone levels in males or estrogen in premenopausal females with fatigue, loss of libido, and mood changes Consider MRI of the brain with or without contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities 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.	

4.0 Endocrine Toxicity	
Grading	**Management**
G1: Asymptomatic or mild symptoms; fasting glucose value > ULN (160 mg/dL); fasting glucose value > ULN (8.9 mmol/L); no evidence of ketosis or laboratory evidence of T1DM	Can continue ICPi with close clinical follow-up and laboratory evaluation May initiate oral therapy for those with new-onset T2DM Screen for T1DM if appropriate, for example, acute onset with prior normal values or clinical concern for ketosis
G2: Moderate symptoms, able to perform ADL, fasting glucose value > 160-250 mg/dL; fasting glucose value> 8.9-13.9 mmol/L, ketosis or evidence of T1DM at any glucose level	May hold ICPi until glucose control is obtained Titrate oral therapy or add insulin for worsening control in T2DM Should administer insulin for T1DM (or as default therapy if there is confusion about type) Urgent endocrine consultation for any patient with T1DM; in the absence of endocrinology, internal medicine may suffice Consider admission for T1DM if early outpatient evaluation is not available or signs of ketoacidosis are present
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL G3: > 250-500 mg/dL (> 13.9-27.8 mmol/L) G4: > 500 mg/dL (> 27.8 mmol/L)	Hold ICPi until glucose control is obtained on therapy with reduction of toxicity to G1 or less Urgent endocrine consultation for all patients Initiate insulin therapy for all patients Admit for inpatient management: Concerns for developing DKA, Symptomatic patients regardless of diabetes type, New-onset T1DM unable to see endocrinology
Additional considerations Insulin therapy can be used as the default in any case with hyperglycemia Long-acting therapy alone is not usually sufficient for T1DM, where half of daily requirements are usually given in divided doses as prandial coverage and half as long-acting. Insulin doses will be lower in T1DM because of preserved sensitivity (total daily requirement can be estimated at 0.3-0.4 units/kg/d). In T2DM, sliding-scale coverage with meals over a few days provides data to estimate a patient's daily requirements and can be used to more rapidly titrate basal needs. All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate. Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; CT=computed tomography; DKA=diabetic ketoacidosis; DM=diabetes mellitus; EMS=emergency medical services; FSH=follicle-stimulating hormone; FT4=free thyroxine; G=Grade; ICPi=immune checkpoint inhibitor; irAE=immune-related adverse event; LH=luteinizing hormone; MRI=magnetic resonance imaging; PTU=propylthiouracil; 2L, second-line; SSKI,=potassium iodide; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus; TRAb=thyroid-stimulating hormone receptor antibody; TSH=thyroid-stimulating hormone; TSI=thyroid-stimulating immunoglobulin; ULN=upper limit of normal.	

Table A5 Management of Musculoskeletal irAEs in Patients Treated with ICPis

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

5.0 Musculoskeletal Toxicities	
	Biologic: consider anticytokine therapy such as TNF-α or IL-6 receptor inhibitors. (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis.) Test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment Referral to rheumatology.
Additional considerations Early recognition is critical to avoid erosive joint damage. Corticosteroids can be used as part of initial therapy in inflammatory arthritis, but due to likely prolonged treatment requirements, physicians should consider starting corticosteroid-sparing agents earlier than one would with other irAEs Oligoarthritis can be treated early on with intra-articular corticosteroids; consider early referral. Consider PCP prophylaxis for patients treated with high-dose of corticosteroids for 12 weeks, as per local guidelines.	
5.2 Myositis	
Definition: A disorder characterized by muscle inflammation with weakness and elevated muscle enzymes (CK). Muscle pain can be present in severe cases. Can be life-threatening if respiratory muscles or myocardium are involved Diagnostic work-up Complete rheumatologic and neurologic history regarding differential diagnosis; rheumatologic and neurologic examination, including muscle strength; and examination of the skin for findings suggestive of dermatomyositis. Muscle weakness is more typical of myositis than pain. Consider 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

5.0 Musculoskeletal Toxicities	
	May require permanent discontinuation of ICPi in most patients with G2 symptoms and objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy)
G3-4: Severe weakness with or without pain, limiting self-care ADL	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

5.0 Musculoskeletal Toxicities	
	Should initiate prednisone 20 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a corticosteroid-sparing agent such as methotrexate or IL-6 inhibition with tocilizumab (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis or GI metastases). Consider admission for pain control
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate. Abbreviations: ADL=activities of daily living; ALT=alanine aminotransferase; ANA=antinuclear antibodies; AST=aspartate aminotransferase; CCP=citrullinated protein antibody; CK=creatine kinase; CRP=C-reactive protein; DMARD=disease-modifying antirheumatic drug; EMG=electromyography; ESR=erythrocyte sedimentation rate; G=Grade; HLA=human leukocyte antigen; ICPi=immune checkpoint inhibitor; IL=interleukin; irAE=immune-related adverse event; IV=intravenous; IVIG=intravenous immunoglobulin; LDH= lactate dehydrogenase; MRI=magnetic resonance imaging, NSAID=nonsteroidal anti-inflammatory drug; PCP=Pneumocystis pneumonia; RF=rheumatoid factor; TB=tuberculosis; TNF=tumor necrosis factor.	

Table A6 Management of Renal irAEs in Patients Treated with ICPis

6.0 Renal Toxicities	
Nephritis and renal dysfunction: diagnosis and monitoring For any suspected immune-mediated adverse reactions, exclude other causes Monitor patients for elevated serum creatinine prior to every dose Routine urinalysis is not necessary, other than to rule out UTIs, etc; nephrology may consider further If no potential alternative cause of AKI identified, then one should forego biopsy and proceed directly with immunosuppressive therapy Swift treatment of autoimmune component important	
6.1 Nephritis	
Definition: Inflammation of the kidney affecting the structure	
Grading (updated from original ASCO guidelines according to CTCAE V5.0)	**Management**
G1: Creatinine level increase > ULN - 1.5 x ULN	Consider temporarily holding ICPi, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status) and baseline renal function. A change that is still < 1.5 ULN could be meaningful
G2: **> 1.5 - 3.0 x baseline; > 1.5 - 3.0 x ULN**	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: **> 3.0 x baseline; > 3.0 - 6.0 x ULN**	Permanently discontinue ICPi
G4: Life-threatening consequences; dialysis indicated, **> 6.0 x ULN**	**Permanently discontinue ICPi** Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc) Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent)
Additional considerations Monitor creatinine weekly Reflex kidney biopsy should be discouraged until corticosteroid treatment has been attempted	
6.2 Symptomatic nephritis: follow-up	
Grading	**Management**
G1	Improved to baseline, resume routine creatinine monitoring
G2	If improved to G1, taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring If elevations persist > 7 days or worsen and no other cause found, treat as G3
G3	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist 3-5 days or worsen, consider additional immunosuppression (e.g. mycophenolate)

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 (e.g. mycophenolate)
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate. Abbreviations: AKI=acute kidney injury; G=Grade; ICPi=immune checkpoint inhibitor; irAE=immune-related adverse event; IV=intravenous; ULN=upper limit of normal; UTI=urinary tract infection.	

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

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

7.0 Nervous System Toxicities	
7.2 Guillain-Barré syndrome	
Definition: Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. Often starts with sensory symptoms/neuropathic pain localized to lower back and thighs. May involve extremities (typically ascending weakness but not always), facial, respiratory, and bulbar and oculomotor nerves. May have dysregulation of autonomic nerves.	
Diagnostic work-up Neurologic consultation MRI of spine with or without contrast (rule out compressive lesion and evaluate for nerve root enhancement/thickening) Lumbar puncture: CSF typically has elevated protein and often elevated WBCs; even though this is not typically seen in classic Guillain-Barré syndrome, cytology should be sent with any CSF sample from a patient with cancer. Serum antibody tests for Guillain-Barré syndrome variants (GQ1b for Miller Fisher variant a/w ataxia and ophthalmoplegia) Electrodiagnostic studies to evaluate polyneuropathy Pulmonary function testing (NIF/VC) Frequent neurochecks	
Grading	**Management**
All grades	Warrant work-up and intervention given potential for progressive Guillain-Barré syndrome to lead to respiratory compromise Note: There is no G1 toxicity
G1: Mild, none	NA
G2: Moderate, some interference with ADL, symptoms concerning to patient	Discontinue ICPi
G3-4: Severe, limiting self-care and aids warranted, weakness, limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms	**Permanently discontinue ICPi** Admission to inpatient unit with capability of rapid transfer to ICU-level monitoring Start IVIG (0.4 g/kg/d for 5 days for a total dose of 2 g/kg) or plasmapheresis. Corticosteroids are usually not recommended for idiopathic Guillain-Barré syndrome; however, in ICPi-related forms, a trial is reasonable (methylprednisolone 2-4 mg/kg/d), followed by slow corticosteroid taper Pulse corticosteroid dosing (methylprednisolone 1 g/d for 5 days) may also be considered for G3-4 along with IVIG or plasmapheresis Frequent neurochecks and pulmonary function monitoring Monitor for concurrent autonomic dysfunction Nonopioid management of neuropathic pain Treatment of constipation/ileus
Additional considerations Slow prednisone taper after corticosteroid pulse plus IVIG or plasmapheresis May require repeat IVIG courses	
7.3 Peripheral neuropathy	
Definition: Can present as asymmetric or symmetric sensory, motor, or sensory motor deficit. Focal mononeuropathies, including cranial neuropathies (e.g. facial neuropathies/Bell palsy) may be present. Numbness and paresthesias may be painful or painless. Hypo- or areflexia or sensory ataxia may be present.	
Diagnostic work-up G1 Screen for reversible neuropathy causes: diabetic screen, B12, folate, TSH, HIV, consider serum protein electrophoresis, and other vasculitic and autoimmune screen Neurologic consultation Consider MRI of spine with or without contrast G2: in addition to above	

7.0 Nervous System Toxicities	
MRI spine advised/MRI of brain if cranial nerve Consider EMG/NCS Consider neurology consultation G3-4: go to Guillain-Barré syndrome algorithm	
Grading	**Management**
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate	Low threshold to hold ICPi and monitor symptoms for a week If to continue, monitor very closely for any symptom progression
G2: Moderate, some interference with ADL, symptoms concerning to patient (i.e. pain but no weakness or gait limitation)	Hold ICPi and resume once return to G1 Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild) Neurontin, pregabalin, or duloxetine for pain
G3-4: Severe, limiting self-care and aids warranted, weakness limiting walking or respiratory problems (i.e. leg weakness, foot drop, rapidly ascending sensory changes) Severe may be Guillain-Barré syndrome and should be managed as such	Permanently discontinue ICPi Admit patient Neurologic consultation Initiate IV methylprednisolone 2-4 mg/kg and proceed as per Guillain-Barré syndrome management
7.4 Autonomic neuropathy	
Definition: Nerves that control involuntary bodily functions are damaged. This may affect blood pressure, temperature control, digestion, bladder function, and sexual function. A case of severe enteric neuropathy with ICPi has been reported. Can present with GI difficulties such as new severe constipation, nausea, urinary problems, sexual difficulties, sweating abnormalities, sluggish pupil reaction, and orthostatic hypertension.	
Diagnostic work-up An evaluation by neurologist or relevant specialist, depending on organ system, with testing that may include Screening for other causes of autonomic dysfunction: diabetic screen, adrenal insufficiency, HIV, paraproteinemia, amyloidosis, botulism; consider chronic diseases such as Parkinson and other autoimmune screening AM orthostatic vitals Consider electrodiagnostic studies to evaluate for concurrent polyneuropathy Consider paraneoplastic Lambert-Eaton myasthenic syndrome, antineutrophil cytoplasmic antibodies, and ganglionic AChR antibody testing	
Grading	**Management**
G1: Mild, no interference with function and symptoms not concerning to patient	Low threshold to hold ICPi and monitor symptoms for a week; if to continue, monitor very closely for any symptom progression
G2: Moderate, some interference with ADL, symptoms concerning to patient	Hold ICPi and resume once return to G1 Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild) Neurologic consultation
G3-4: Severe, limiting self-care and aids warranted	Permanently discontinue ICPi Admit patient Initiate methylprednisolone 1 g daily for 3 days followed by oral corticosteroid taper Neurologic consultation
7.5 Aseptic meningitis	
Definition: may present with headache, photophobia, and neck stiffness; often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis). Diagnostic work-up MRI of brain with or without contrast + pituitary protocol AM cortisol, ACTH to rule out adrenal insufficiency Consider lumbar puncture: measure opening pressure; check cell count and protein glucose; and perform Gram stain, culture, PCR for HSV, and other viral PCRs depending on suspicion, cytology May see elevated WBC count with normal glucose, normal culture, and Gram stain; may see reactive lymphocytes or histiocytes on cytology	

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 (i.e. pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	**For G1-3:** Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits **For G4: permanently discontinue ICPi.** **In case of any aseptic meningitis events (G1-4),** consider empirical antiviral (IV acyclovir) and antibacterial therapy until CSF results Once bacterial and viral infection are negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg or IV methylprednisolone 1 mg/kg if moderate/severe symptoms
7.6 Encephalitis	
Definition: As for aseptic meningitis, need to exclude infectious causes, especially viral (i.e. HSV). Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality Diagnostic work-up	
Diagnostic work-up Neurologic consultation MRI of brain with or without contrast may reveal T2/fluid-attenuated inversion recovery changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal Lumbar puncture: check cell count and protein glucose and perform Gram stain, culture, PCR for HSV and other viral PCRs depending on suspicion, cytology, oligoclonal bands, autoimmune encephalopathy, and paraneoplastic panels. May see elevated WBC count with lymphocytic predominance and/or elevated protein EEG to evaluate for subclinical seizures Blood: metabolic, CBC, ESR, CRP, ANCA (if suspect vasculitic process), thyroid panel including TPO and thyroglobulin Rule out concurrent anemia/thrombocytopenia, which can present with severe headaches and confusion	
Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (i.e. pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	**For G1, 2, and 3:** Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits **For G4: Permanently discontinue ICPi** As above for aseptic meningitis, **in case of any encephalitis events,** suggest concurrent IV acyclovir until PCR results obtained and negative Trial of methylprednisolone 1-2 mg/kg If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids methylprednisolone 1 g IV daily for 3-5 days plus IVIG 2 g/kg over 5 days If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab or plasmapheresis in consultation with neurology. **In case of management with rituximab, ICPi treatment should be discontinued.**
7.7 Transverse myelitis	
Definition: Acute or subacute weakness or sensory changes bilateral, often with increased deep tendon reflexes	
Diagnostic work-up Neurologic consultation MRI of spine (with thin axial cuts through the region of suspected abnormality) and MRI of brain Lumbar puncture: cell count, protein, glucose, oligoclonal bands, viral PCRs, cytology, onconeural antibodies Blood: B12, HIV, RPR, ANA, Ro/La, TSH, aquaporin-4 IgG	

7.0 Nervous System Toxicities	
Evaluation for urinary retention, constipation	
Grading	**Management**
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (i.e. pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Permanently discontinue ICPi Methylprednisolone 2 mg/kg Strongly consider higher doses of 1 g/d for 3-5 days Strongly consider IVIG
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate. Abbreviations: AChR=acetylcholine receptor; ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ANA=antinuclear antibody; ANCA=antineutrophil cytoplasmic antibodies; CBC=complete blood count; CNS=central nervous system; CPK=creatine phosphokinase; CRP=C-reactive protein; CSF=cerebrospinal fluid; ECG=electrocardiogram; EEG=electroencephalogram; EMG=electromyography; ESR=erythrocyte sedimentation rate; G=Grade; GI=gastrointestinal; HIV=human immunodeficiency virus; HSV=herpes simplex virus; ICPi=immune checkpoint inhibitor; ICU=intensive care unit; IgG=immunoglobulin G; IV=intravenous; IVIG=intravenous immunoglobulin; irAE=immune-related adverse event; MGFA=Myasthenia Gravis Foundation of America; MRI=magnetic resonance imaging; NA,=not applicable; NCS=nerve conduction study; NIF=negative inspiratory force; PCR=polymerase chain reaction; RPR=rapid plasma reagin, TPO=thyroid peroxidase; TSH=thyroid-stimulating hormone; TTE=transthoracic echocardiogram; VC=vital capacity; WBC=white blood cell count.	

Table A8 Management of Hematologic irAEs in Patients Treated with ICPis

8.0 Hematologic Toxicities	
8.1 Autoimmune hemolytic anemia	
Definition: A condition in which RBCs are destroyed and removed from the blood stream before their normal lifespan is over. Symptoms include weakness, paleness, jaundice, dark-colored urine, fever, inability to do physical activity, and heart murmur.	
Diagnostic work-up History and physical examination (with special consideration of history of new drugs and insect, spider, or snake bites) Blood chemistry, CBC with evidence of anemia, macrocytosis, evidence of hemolysis on peripheral smear; LDH, haptoglobin, bilirubin, reticulocyte count, free Hgb DIC panel, which could include PTNIR infectious causes Autoimmune serology Paroxysmal nocturnal hemoglobinuria screening Direct and indirect bilirubin; LDH; direct agglutinin test; and if no obvious cause, bone marrow analysis, cytogenetic analysis to evaluate for myelodysplastic syndromes Evaluation for viral/bacterial (mycoplasma, etc) causes of hemolysis studies Protein electrophoresis, cryoglobulin analysis Work-up for bone marrow failure syndrome if refractory, including B12, folate, copper, parvovirus, FE, thyroid, infection Glucose-6-phosphate dehydrogenase Evaluation of common drug causes (ribavirin, rifampin, dapsone, interferon, cephalosporins, penicillin, NSAIDs, quinine/quinidine, fludarabine, ciprofloxacin, lorazepam, diclofenac, etc) Assessment of methemoglobinemia	
Grading	**Management**
G1: Hgb < LLN to 10.0 g/dL; < LLN to 6.2 mmol/L; < LLN to 100 g/L	Continue ICPi with close clinical follow-up and laboratory evaluation
G2: Hgb < 10.0 to 8.0 g/dL; < 6.2to4.9mmol/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

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

8.0 Hematologic Toxicities	
	In case of management with rituximab, ICPi treatment will be discontinued.
8.3 Hemolytic uremic syndrome	
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia. Signs and symptoms of hemolytic uremic syndrome can include: Bloody diarrhea Decreased urination or blood in the urine Abdominal pain, vomiting, and occasionally fever Pallor Small, unexplained bruises or bleeding from the nose and mouth Fatigue and irritability Confusion or seizures High blood pressure Swelling of the face, hands, feet, or entire body	
Diagnostic work-up History and physical examination (special consideration for new history of high-risk drugs, hypertension, or cardiac causes) CBC with indices Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis. Serum creatinine ADAMTS13 (to rule out TTP) Homocysteine/methylmalonic acid Complement testing C3, C4, CH50 (complement inhibitory antibodies for suspected familial) Evaluate reticulocyte count and mean corpuscular volume Evaluation of infectious cause, including screening for EBV, CMV, HHV6 Evaluation for nutritional causes of macrocytosis (B12 and folate) Pancreatic enzymes Evaluation for diarrheal causes, shiga toxin, Escherichia coli 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 (e.g. renal insufficiency, petechiae) G4: Life-threatening consequences (e.g. CNS thrombosis/ embolism or renal failure)	**For G1 and G2: Continue ICPi with close clinical follow up and laboratory evaluation** **Supportive care.** **For G3 and G4: Permanently discontinue ICPi.** **Begin therapy with eculizumab 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	

8.0 Hematologic Toxicities	
Flow cytometry to evaluate loss of GPI-anchored proteins Type and screen patient for transfusions and notify blood bank that all transfusions need to be irradiated and filtered	
Grading	**Management**
G1: Nonsevere, < 0.5 polymorphonuclear cells x 10^9/L hypocellular marrow, with marrow cellularity < 25%, peripheral platelet count. 20,000, reticulocyte count < 20,000	Hold ICPi and provide growth factor support and close clinical follow-up, and laboratory evaluation Supportive transfusions as per local guidelines
G2: Severe, hypocellular marrow < 25% and two of the following: ANC < 500, peripheral platelet < 20,000, and reticulocyte < 20,000	Hold ICPi and provide growth factor support and close clinical laboratory evaluations daily Administer ATG + cyclosporine; HLA typing and evaluation for bone marrow transplantation if patient is candidate; all blood products should be irradiated and filtered Supportive care with granulocyte-colonystimulating factor may be added in addition
G3-4: Very severe, ANC > 200, platelet count > 20,000, reticulocyte count > 20,000, plus hypocellular marrow > 25%	**For G3: Hold ICPi and monitor weekly for improvement; if not resolved, discontinue treatment until AE has reverted to G1.** **For G4: permanently discontinue ICPi** Hematology consult, growth factor support Horse ATG plus cyclosporine If no response, repeat immunosuppression with rabbit ATG plus cyclosporine, cyclophosphamide For refractory patients, consider eltrombopag plus supportive care
8.5 Lymphopenia	
Definition: An abnormally low level of lymphocytes in PB; for adults, counts of < 1,500/mm^3	
Diagnostic work-up History and physical examination (special attention for lymphocyte-depleting therapy such as fludarabine, ATG, corticosteroids, cytotoxic chemotherapy, radiation exposure, etc, as well as history of autoimmune disease, family history of autoimmune disease) Evaluation of nutritional state as cause Spleen size CBC with differential, peripheral smear and reticulocyte counts CXR for evaluation of presence of thymoma Bacterial cultures and evaluation for infection (fungal, viral, bacterial specifically CMV/HIV)	
Grading	**Management**
G1-2: 500-1,000 PB lymphocyte count G3: 250-499 PB lymphocyte count G4: < 250 PB lymphocyte count	**Continue ICPi for G1-2** **For G3, single laboratory values out of normal range without any clinical correlates hold treatment until resolution to Grade 1.** **For G4, for single laboratory values out of normal range without any clinical correlates, permanent treatment discontinuation is not required. Treatment should be held until the etiology is determined. Permanent treatment discontinuation will only be required, if lymphopenia is considered of immune-related in nature, no clear alternative explanation exists for the event, and Grade 4 lymphopenia does not resolve within 14 days. If the**

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

8.0 Hematologic Toxicities	
	If previous treatment with corticosteroids and/or IVIG unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more-potent immunosuppression (From American Society of Hematology guideline on immune thrombocytopenia; consult for further details)
8.7 Acquired hemophilia	
Definition: Disorder caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors	
Diagnostic work-up Full blood count to assess platelet number, fibrinogen, PT, PTT, INR; the typical finding in patients with acquired hemophilia A is a prolonged activated PTT with a normal PT MRI, CT, and ultrasonography may be indicated to localize, quantify, and serially monitor the location and response of bleeding Medication review to assess for alternative causes Determination of Bethesda unit level of inhibitor	
Grading	**Management**
G1: Mild, 5%-40% of normal factor activity in blood, 0.05-0.4 IU/mL of whole blood	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits Administer 0.5-1 mg/kg/d prednisone Transfusion support as required Treatment of bleeding disorders with hematology consult
G2: Moderate, 1%-5% of normal factor activity in blood, 0.01-0.05 IU/mL of whole blood	Hematology consult Administration of factor replacement (choice based on Bethesda unit of titer) Administer 1 mg/kg/d prednisone 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 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.	

8.0 Hematologic Toxicities
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

9.0 Cardiovascular Toxicities	
9.1 Myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis	
Definition: Signs and symptoms may include chest pain, arrhythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion, fatigue	
Diagnostic work-up At Baseline ECG Consider troponin, especially in patient treated with combination immune therapies Upon signs/symptoms (consider cardiology consult) ECG Troponin BNP Echocardiogram CXR Additional testing to be guided by cardiology and may include Stress test Cardiac catheterization Cardiac MRI	
Grading	**Management**
G1: Abnormal cardiac biomarker testing, including abnormal ECG G2: Abnormal screening tests with mild symptoms G3: Moderately abnormal testing or symptoms with mild activity G4: Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions	All grades warrant work-up and intervention given potential for cardiac compromise Consider the following: 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
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.	
9.2 Venous thromboembolism	
Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream. Clinical signs and symptoms are variable and may include pain, swelling, increased skin vein visibility, erythema, and cyanosis accompanied by unexplained fever for DVT and dyspnea, pleuritic pain, cough, wheezing, or hemoptysis for PE	
Diagnostic work-up Evaluation of signs and symptoms of PE or DVT may include Clinical prediction rule to stratify patients with suspected venous thromboembolism Venous ultrasound for suspected DVT CTPA for suspected PE Can also consider D-dimer for low-risk patients based on risk stratification by clinical prediction rule for DVT/PE when CT or Doppler are not available or appropriate Ventilation/perfusion scan is also an option when CTPA is not appropriate Consider other testing, including ECG, CXR, BNP and troponin levels, and arterial blood gas	

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

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

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- [redacted]

Appendix 8 Protocol Amendment History

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

Protocol Version [3.0] (12 November 2019)

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

Overall Rationale for the Amendment

The key changes of the protocol are:

- To introduce use of paclitaxel for participants enrolled in Cohort B
- To clarify the exceptions to the DLT definitions
- To clarify that either BUN or total urea should be collected (Appendix 5)

Other changes are to adjust the protocol language to the current standards and to maintain the protocol consistency and integrity.

Section # and Name	Description of Change	Brief Rationale
Throughout protocol	Paclitaxel use added to Cohort B	To allow the use of paclitaxel as alternative to nab-paclitaxel and to explore the safety of M7824 in combination with carboplatin and paclitaxel
6.9.1 Definition of Dose Limiting Toxicities	Clarified the duration for Grade 3 events not considered DLTs	Corrected the non-DLT annotation to avoid a potential overlap between DLTs and non-DLTs
7.3 Lost to Follow-up	Clarified the criteria for when a participant is unreachable	To update wording to be consistent with current Sponsor protocol template
Appendix 5 Clinical Laboratory Tests	Clarified that either BUN or total urea should be collected	For clarity and consistency

Protocol Version [2.0] (02 July 2019)

Overall Rationale for the Amendment

The key changes of the protocol were:

- To clarify eligibility criteria of the study population
- To modify nonserious adverse event of special interest (AESI) reporting
- To update the safety profile of M7824 according to the current Investigator's Brochure.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 9.2 Sample Size Determination	Updated the information about number of subjects enrolled from “up to” to “approximately”	To reflect the possibility to replace participants who are not DLT evaluable during the safety evaluation of each cohort
1.1 Synopsis 4.1 Overall Design	Deleted the information that Safety Follow-up Visit at 12 weeks should occur prior to starting a subsequent treatment	For clarity and consistency
1.3 Schedule of Activities and throughout the document as applicable	Included smoking information as part of medical history	To clarify that smoking/nicotine history is collected on the eCRF
	Clarified that CT chest scan is a required method for tumor assessment	To add clarity on tumor evaluation requirements in case a participant cannot receive iodinated contrast
	Specify the acceptable window for CT scan	To allow an acceptable window of ± 7 days for CT scan
	Clarified the protocol deviation for PK blood sample when the time of collection is not recorded	To add clarity on protocol deviation definition regarding PK sampling
	Included the acceptable window for M7824 administration in the Induction and Maintenance Periods	For clarity and consistency
	Included the use of steroids for antiemesis according to NCCN guidelines	To provide clarity for use of steroids as part of chemotherapy premedication and to align with latest NCCN recommendation
2.1 Introduction and throughout the document as applicable	Bintrafusp alfa was included as the proposed international nonproprietary name for M7824	For consistency across the development program
4.3 Justification for Dose	Reduced the section content and referred to the information provided in the Investigator’s Brochure	To summarize the key information while providing source for detailed information, if needed

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria 5.2 Exclusion Criteria and throughout the document as applicable	Modified the wording "ALK translocation" to "ALK positive"	To reflect NCCN guidelines requirements for ALK evaluation
	Revised the inclusion criterion #2c	To add clarity on the previous chemotherapy regimen
	Revised the exclusion criterion #5	To increase clarity about MRI being done prior to study intervention in case of radiotherapy treatment for brain metastasis
	Revised the exclusion criterion #6	To clarify which compounds are considered study intervention
	Revised the exclusion criterion #9	To allow participants with prior radiation pneumonitis
	Revised the inclusion criterion #2c and the exclusion criterion #17	The wash-out period was revised to align with the development program
	Clarified the exclusion criterion #11	To exclude participants with history of bleeding diatheses or recent major bleeding events
	Added the exclusion criterion #18: Diagnostic Assessments 18. Unable to tolerate computed tomography (CT) or MRI in the opinion of the Investigator and/or allergy to contrast material.	For safety and consistency of language across the development program
6.1.1 Administration of M7824	Clarified the acceptable window for M7824 administration	To add clarity on the dosing instructions
6.1.2 Administration of Chemotherapy and throughout the document as applicable	Clarified administration of chemotherapy	To clarify that chemotherapy should be administered according to the guidelines provided or to the local standard practice
6.8.1 Adverse Events of Special Interest (including 6.8.1.1, 6.8.1.2, and 6.8.1.3), 6.9.3.2, 8.3.2, 8.3.5, 8.4, and Appendix 4	Modified nonserious AESI reporting	To discontinue expedited reporting of nonserious AESI
6.8.2 Additional Potential Risks	Included low grade mucosal bleeding events as additional potential risks	To be aligned with newly identified potential risk as per current Investigator's Brochure (version 5)
6.9.3.3 Potential TGFβ-mediated Skin Adverse Events	Updated the management of potential TGFβ-mediated skin adverse events	To provide guidelines on the management of potential TGFβ-mediated skin adverse events
6.9.3.5 Bleeding Events	Added text to describe management of bleeding events	To provide guidelines for the management of bleeding events and indications for when participants should have study intervention held or discontinued

Section # and Name	Description of Change	Brief Rationale
6.9.4 Risk Management for Chemotherapy	Removed alopecia as an excluding event for dose modification	Updated according to alopecia classification on CTCAE v5
6.9.4 Risk Management for Chemotherapy	Added clarification to M7824 administration if chemotherapy is delayed	To increase clarity on what is expected in relation to M7824 administration if chemotherapy is delayed
7.1.2 Rechallenge	Clarified information about rechallenge	To clarity that reinitiation/rechallenge is allowed for M7824 alone and for M7824 and chemotherapy
8.1 Efficacy Assessments and Procedures	Clarified language for CT scan of pelvis	To clarify the requirements for tumor evaluation
8.5 Pharmacokinetics	Deleted the information below: Unresolved missing data may be imputed when the analysis integrity is affected. The conservative principle will be used for data imputation	Handling of missing data and imputation will be described in the IAP as indicated in Section 9.4.3
Appendix 5	Appendix 5 (Liver Safety: Suggested Actions and Follow-up Assessments) was deleted	For consistency across the development program
Appendix 5 (previous Appendix 6)	Clarified the acceptable tests for tuberculosis and virology	To clarity which tests are acceptable
Appendix 6 and throughout the document as applicable (previous Appendix 7)	Revised the recommendations for immune related adverse events (irAE) management	The contents were revised to include NCCN irAE management guidelines and FDA recommendations. Critical instructions include the requirement that treatment must be permanently discontinued for certain Grade 4 irAE toxicities.
Throughout	Minor editorial and document formatting revisions	Minor text revisions are made for clarity, readability, consistency of language across the development program, and compliance with current Sponsor guidelines

Appendix 9 Sponsor Signature Page

Study Title:	A Phase Ib/II, Open-Label Study of M7824 in Combination with Chemotherapy in Participants with Stage IV Non-small Cell Lung Cancer
Regulatory Agency Identifying Numbers:	IND: 124757 EudraCT: 2018-004040-28
Clinical Study Protocol Version:	22 December 2021/Version 5.0

PPD

Signature Date of Signature

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

Appendix 10 Coordinating Investigator Signature Page

Study Title:	A Phase Ib/II, Open-Label Study of M7824 in Combination with Chemotherapy in Participants with Stage IV Non-small Cell Lung Cancer
Regulatory Agency Identifying Numbers:	IND: 124757 EudraCT: 2018-004040-28
Clinical Study Protocol Version:	22 December 2021/Version 5.0
Site Number:	

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

PPD

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

CCI

Appendix 11 Principal Investigator Signature Page

Study Title:	A Phase Ib/II, Open-Label Study of M7824 in Combination with Chemotherapy in Participants with Stage IV Non-small Cell Lung Cancer
Regulatory Agency Identifying Numbers:	IND: 124757 EudraCT: 2018-004040-28
Clinical Study Protocol Version:	22 December 2021/Version 5.0
Site Number:	

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

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

_____ _____

Signature Date of Signature

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