Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Multicenter, Double Blind, Randomized, Controlled Study of M7824 with Concurrent Chemoradiation Followed by M7824 versus Concurrent Chemoradiation Plus Placebo Followed by Durvalumab in Participants with Unresectable Stage III Non-small Cell Lung Cancer
Study Number:	MS200647_0005
Merck Compound:	M7824
Merck Registered Compound Name in Japan:	Not Applicable
Study Phase:	Phase II
Short Title:	M7824 with cCRT in Unresectable Stage III NSCLC
Coordinating Investigator:	PPD
Sponsor Name and Legal Registered Address:	For all countries, except the US and Japan: Merck KGaA Frankfurter Str. 250 64293 Darmstadt, Germany Affiliates of Merck KGaA, Darmstadt, Germany: In the US: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA, 01821, USA Local Sponsor for Sites in Japan: Merck Biopharma Co., Ltd. Japan an affiliate of Merck KGaA, Darmstadt, Germany Arco Tower, 1-8-1 Shimomeguro Meguro-ku, Tokyo 153-8926, Japan
Regulatory Agency Identifying Numbers:	EudraCT 2018-003265-34 CCI
Protocol Version:	22 June 2021/Version 4.0

Medical Monitor Name and Contact Information:	PPD Phone: PPD E-mail: PPD

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original protocol	07-Dec-2018
2.0	Global Amendment	05-Mar-2019
2.1	Local Amendment (China)	08-May-2019
2.2	Local Amendment (EU countries participating in VHP)	21-May-2019
3.0	Global Amendment	05-Jul-2019
3.1	Local Amendment (Korea)	05-Nov-2019
4.0	Global Amendment	22-Jun-2021

Protocol Version [4.0] (22-JUN-2021)

Overall Rationale for the Amendment

The two key rationales for this amendment are: to reduce the sample size from 350 participants to approximately 160 participants to provide an earlier result from the primary analysis to give insight into the potential benefit of M7824 in patients with unresectable Stage III NSCLC, and to update the risk classification and minimization measures.

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

Section # and Name	Description of Change	Brief Rationale
Title page	Removal of details of medical responsible and approval date.	Updated for consistency with Merck protocol standards.
Title page	Change of Medical Monitor details.	To reflect change in Medical Monitor.
1.1 Synopsis (Objective and endpoints) 3 Objectives and Endpoints	• PFS and objective response changed from independent central review to Investigator assessment. CCI [redacted]	• See change to efficacy endpoints below. • CCI [redacted] • CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 4.1 Overall design 4.1.1.5 Stratification 6.3.2 Blinding CCI	CCI	CCI
1. 1 Synopsis 3. Objectives and Endpoints 8.1 Efficacy Assessments and Procedures 9.4.1 Efficacy Analyses 9.4.1.1 Tumor Assessment by IRC (new section) Appendix 8 Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)	The main analysis of efficacy endpoints based on radiographic scan data will be based on Investigator assessment, and not IRC. Appendix 8, Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1), has been added for guidance.	The Investigator assessment is appropriate given the double-blind nature of the study with low susceptibility to bias in imaging assessment. Centralized imaging collection will continue to allow further analyses, as applicable.
1.3 Schedule of Activities (Table 1) 4.1 Overall Design	• Screening has been extended to up to 28 days for selected assessments. • Additionally, the screening period has been changed from a specific number of days to "up to" 21 or 28 days.	• To allow for screening assessments that have been found to require more time to perform prior to Day 1. • The addition of "up to" has been made to allow flexibility in duration of the screening period up to a maximum number of days.
1.3 Schedule of Activities (Table 1) 8.1 Efficacy Assessments and Procedures	CCI	For clarification.
1.3 Schedule of Activities (Table 1)	The Week 1 Day 1 confirmation of eligibility checklist prior to dosing has been removed.	In this randomized clinical study, the confirmation of eligibility is performed during screening, prior to randomization.
1.3 Schedule of Activities (Table 1)	A note stating that screening tests performed prior to informed consent are acceptable if within the screening period has been removed.	The screening window is extended from 21 to 28 days for most of screening assessments.
1.3 Schedule of Activities (Table 2) 6.1 Study Intervention(s) Administration	The row for M7824/placebo premedication in Table 2 has been removed and premedication for M7824/placebo has been made optional.	For consistency with current management guidelines for M7824.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (Table 1 and Table 3)	CCI [redacted] CCI [redacted]	CCI [redacted]
1.3 Schedule of Activities (Table 1, Table 3 and Table 4)	Note describing documentation of adverse events has been replaced with reference to Appendix 4.	To simplify the schedule of activities and reference the appendix describing safety recording and reporting.
1.3 Schedule of Activities (Table 3)	CCI [redacted]	For clarification.
1.3 Schedule of Activities (Table 3) CCI [redacted]	CCI [redacted]	CCI [redacted]
1.3 Schedule of Activities (Table 4) 8.1 Efficacy Assessments and Procedures	Removal of participant contact prior to interim analysis.	The interim analysis has been removed.
2.2 Background	A reference to the Investigator's Brochure has been added.	To provide a reference to the current status of the clinical evaluation of M7824.
2.3 Benefit/Risk Assessment	Update of details of identified and potential risks for M7824.	For consistency with current knowledge of M7824 and the latest version of the Investigator's Brochure.
3 Objectives and Endpoints	CCI [redacted]	CCI [redacted]
3 Objectives and Endpoints	A note has been added to Table 6 stating that analysis of CCI [redacted] endpoints will be contingent on the outcomes of primary and secondary endpoints.	To provide flexibility in analysis of CCI [redacted] endpoints.
4.3 Justification for Dose	Detail on dose justification has been removed, and a reference to the IB added.	To streamline the section and ensure readers are directed to current details.

Section # and Name	Description of Change	Brief Rationale
4.1. Overall Design 4.3 Justification for Dose 6.1 Study Intervention(s) Administration 6.3.2 Blinding 6.4 Study Intervention Compliance 6.6 Dose Selection and Modification 6.9.5 Bleeding Adverse Events 7.1.1 Permanent Discontinuation	Section 6.9.5: addition of information of M7824 dose modifications in case of bleeding events. Section 6.3.2 provides details of preparation of reduced doses in a double-blind manner.	To facilitate proper management of bleeding events and allow blinding to be maintained.
4.1.1.1 PFS as the Primary Endpoint	The ITT set has been updated to the FAS.	For consistency with Merck standards.
4.4 End of Study Definition	The definition of end of study has been updated to either the date of primary analysis or when all participants have completed maintenance therapy and safety follow-up, whichever occurs later.	For consistency with the changes in study design and objectives.
5 Study Population Appendix 2	Text on the participant's legal representative has been added.	To clarify that legal representatives can only provide informed consent where allowed by local laws and regulations.
5.2 Exclusion Criteria	Exclusion criterion 7 has been split into two separate criteria: one referring to uncontrolled intercurrent illnesses (criterion 7 a), and one referring to bleeding diathesis and recent major bleeding events (criterion 7 b). Additionally, clinically relevant bleeding events of hemoptysis Grade ≥ 2 within the last month were added to the new criterion 7 b.	The criterion was split at the request of a health authority. The addition of hemoptysis was for consistency with a similar M7824 study in which this request was made by the IDMC.
5.2 Exclusion Criteria	Addition of exclusion criterion 24: prior radiotherapy if delivered in adjuvant/neo-adjuvant regimen.	To further clarify need to exclude participants who underwent prior radiotherapy if delivered in adjuvant/neo-adjuvant regimen.
5.4 Screen Failures	Language on extension of screening window in cases of abnormal screening laboratory value or test that may correct has been removed.	The screening window is extended from 21 to 28 days for some screening assessments.
6.1 Study Intervention(s) Administration	Updates to details of provision of M7824, durvalumab, and chemotherapy.	To allow appropriate provision of study interventions across all sites.
6.1.1 Radiation	Daily use of image guidance has been changed from required to recommended.	Recommendation considered more appropriate in absence of method of reconciliation.
6.1.2 Chemotherapy	Option to deliver etoposide according to local practice added.	To allow delivery of chemotherapy by local practice.

Section # and Name	Description of Change	Brief Rationale
6.2.3 Durvalumab	Update of characteristics and guidance of use for durvalumab.	To provide most recent details on durvalumab.
6.3.2 Blinding	Deleted mention of interim analysis and stated that IDMC will receive unblinded data to perform their ongoing safety analyses.	To update after removal of interim analysis, and for clarity of blinding status of IDMC.
6.3.3 Emergency Unblinding	Language was added to state that if emergency unblinding is required, the participant can continue study treatment unless there are other circumstances that require participant discontinuation.	To clarify the status of participants after emergency unbinding.
6.5.2 Prohibited Medicines	Language on vaccines has been updated to specifically allow approved SARS-CoV-2 vaccines at any point.	To allow participants to be protected against COVID-19 disease.
6.8 Special Precautions 6.9 Management of Adverse Events of Interest	Sections have been simplified for clarity and to reduce repetition, and are now organized as follows: • 6.8 Special Precautions • 6.9 Management of Adverse Events of Interest • 6.10 Risk Management for Chemoradiation 6.11 Adverse Drug Reactions Requiring Treatment Discontinuation	Primarily to streamline and simplify these sections, reducing repetition and improving clarity. Additionally, risk classification was updated according to current profile of M7824, and details on management of bleeding events were added to allow appropriate management.
6.8 Special Precautions Appendix 5 (deleted)	General guidance previously in Section 6.9.2 (Adverse Drug Reactions Requiring Treatment Discontinuation) has been relocated to 6.8 to reduce repetition and ensure all information is easily accessible. No significant changes have been made to general guidance for management of ADRs. References to the current NCCN guidelines have been added.	
6.9.1 Infusion-related Reactions Including Immediate Hypersensitivity	Guidelines for management have been simplified, and risk reclassification from "important identified" to "identified" risk has been done.	
6.9.2 Immune-related Adverse Events	Risk reclassification has been done and the list of events has been updated accordingly	
6.9.5 Bleeding Adverse Events	Bleeding events are reclassified from "potential risk" to "important identified risk" for M7824. Details of dose reductions for management of bleeding events have been added.	

Section # and Name	Description of Change	Brief Rationale
6.9.6 Other Important Potential Risks	The risk name "Alterations in Wound Healing or Repair of Tissue Damage" has been changed to "Impaired Wound Healing".	
6.10 Risk Management for Chemoradiation	The following text was deleted: There will be no dose modifications for carboplatin and paclitaxel except carboplatin dose modifications for renal toxicity.	Text conflicted with other details in section.
6.10 Risk Management for Chemoradiation (carboplatin/paclitaxel)	The following text was added: If a Grade 2 anemia does not resolve to Grade ≤ 1 by the last day of the current cycle but is manageable and/or not clinically relevant, the Medical Monitor should be consulted to assess if it is clinically reasonable to administer the following infusion.	To provide flexibility for management of anemia when appropriate.
7.2 Participant Discontinuation/Withdrawal from the Study	Details on discontinuation have been updated.	For clarity.
8.1 Efficacy Assessments and Procedures	Language has been added stating that CT of the pelvis may be omitted if it is not part of the standard of care and CT of the abdomen includes the entirety of the liver and both adrenal glands, as well as all other known sites of disease.	For radiation protection reasons.
8.1 Efficacy Assessments and Procedures	Language has also been added stating that radiomic analysis of images for digital features potentially predictive of prognosis and/or future treatment benefit will only be performed retrospectively if deemed appropriate.	To clarify that radiomic analyses will only be performed if deemed appropriate.
8.1 Efficacy Assessments and Procedures	Text has been added starting high-resolution CT scans may be evaluated for radiation induced pulmonary fibrosis by an independent review committee.	To clarify status of analysis of high-resolution CT scan images.
8.1 Efficacy Assessments and Procedures	Language has been added stating diagnosis of disease progression based solely on nodal enlargement within 8 weeks of coronavirus vaccination should be made with extreme caution.	COVID-19 vaccination can mimic PD but resolves with time.
8.5 Pharmacokinetics	Language has been added stating that PK and ADA samples collected at the same time points may be used interchangeably if the dedicated sample has insufficient quantity.	To allow flexibility in case of issue with either sample collection. The participants will have consented to all collections and tests has been added.
CCI		

Section # and Name	Description of Change	Brief Rationale
	• The ITT set has been updated to the FAS. • Details of efficacy hypothesis and analyses have been updated in Sections 9.1, 9.2 and 9.4.1. • Three-tier approach to analysis of adverse events has been removed from Table 25. • The sequences of analyses (Section 9.4.4) has been updated.	• For consistency with Merck standards. • To reflect changes in reclassification of some secondary efficacy endpoints to exploratory endpoints. Changes to the trial sample size no longer support this analysis approach. • To reflect the removal of the interim analysis and the separate OS primary analysis.
Appendix 2 Study Governance	Addition of language on study and site closure	For clarification and consistency with current Merck best practice.
Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Addition of bleeding events as an AESI	For consistency with IB version 7.
Throughout protocol	Minor updates to formatting, phrasing, etc.	For clarity, to correct typos and formatting issues, and for consistency with Merck current practices.

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A Multicenter, Double Blind, Randomized, Controlled Study of M7824 with Concurrent Chemoradiation Followed by M7824 versus Concurrent Chemoradiation Plus Placebo Followed by Durvalumab in Participants with Unresectable Stage III Non-small Cell Lung Cancer

Short Title: M7824 with cCRT in Unresectable Stage III NSCLC

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Objectives and Endpoints:

Primary Objective	Primary Endpoint
To evaluate PFS in participants treated with cCRT plus M7824 followed by M7824 or cCRT plus placebo followed by durvalumab	PFS according to RECIST 1.1 assessed by Investigator
Secondary Objectives	**Secondary Endpoints**
To evaluate the safety in participants treated with cCRT plus M7824 followed by M7824 or cCRT plus placebo followed by durvalumab	Occurrence of TEAEs and treatment-related AEs
To evaluate OS in participants treated with cCRT plus M7824 followed by M7824 or cCRT plus placebo followed by durvalumab	OS
To evaluate objective tumor response in participants treated with cCRT plus M7824 followed by M7824 or cCRT plus placebo followed by durvalumab	Objective response according to RECIST 1.1 assessed by Investigator
To evaluate duration of response in participants treated with cCRT plus M7824 followed by M7824 or cCRT plus placebo followed by durvalumab	Duration of response assessed from CR or PR until PD, death, or last tumor assessment
To characterize PK profile of M7824 plus cCRT and after cCRT	PK profile of M7824 in terms of C_{eoi} and C_{trough} during treatment and Safety follow- up visit.
To characterize the immunogenicity of M7824 plus cCRT and after cCRT	Immunogenicity of M7824 as measured by ADA assays from Screening through last Safety Follow-up visit.

AE=adverse event, ADA=antidrug antibody, cCRT=concomitant chemoradiation therapy; C_{eoi}=concentration immediately at the end of infusion, CR=complete response, ctDNA=circulating tumor DNA, C_{trough}=concentration immediately before next dosing, OS=overall survival, PD=progressive disease, PFS=progression-free survival, PK=pharmacokinetics, PR=partial response, RECIST 1.1 =Response Evaluation Criteria in Solid Tumors Version 1.1, TEAE=treatment-emergent adverse event.

Overall Design: This is a global, multicenter, randomized, double-blind, controlled study in unresectable Stage III NSCLC. This study has 2 arms:

- cCRT plus M7824 followed by M7824 (Arm 1)
- cCRT plus placebo followed by durvalumab (Arm 2)

During the safety run-in, the first 42 participants (12 Japanese, and 30 non-Japanese) will be randomized in 1:1 ratio between Arm 1 and Arm 2. Japanese participants are defined by ethnicity only and not by country. Ethnicity will be the stratification factor during the safety run-in to ensure a 1:1 treatment arm allocation for both Japanese and non-Japanese participants during the safety run-in. CCI [redacted] at baseline will be determined retrospectively in these participants.

Approximately 118 additional participants will be randomized in 1:1 ratio between Arm 1 and Arm 2. The Independent data Monitoring Committee (IDMC) will periodically review the safety data during the safety run-in as well as expansion part of the study. During the safety run-in, IDMC will assess the safety of the combination of cCRT and M7824 in non-Japanese participants and may also decide upon continuous enrollment subsequent to the safety run-in based on prespecified rules in the IDMC charter. IDMC will make separate assessment for Japanese

participants and determine if additional Japanese participants can be enrolled in the expansion part of the study as part of the approximately 118 additional participants.

Chemotherapy regimen and PD-L1 expression in tumor cells (< 1% versus ≥ 1%) will be the stratification factors in the expansion part of the study.

Number of Participants: A sample size of approximately 160 randomized participants (consisting of 42 participants in the safety run-in as well as 118 in the expansion phase) is planned in order to observe 70 progression-free survival (PFS) events at the primary analysis.

Study Intervention Groups and Duration: The study intervention consists of 60 Gy of radiation therapy concurrent with standard chemotherapy plus M7824 in Arm 1 or placebo in Arm 2, followed by up to 26 doses of M7824 (Arm 1) or durvalumab (Arm 2).

Involvement of Special Committee(s): Yes

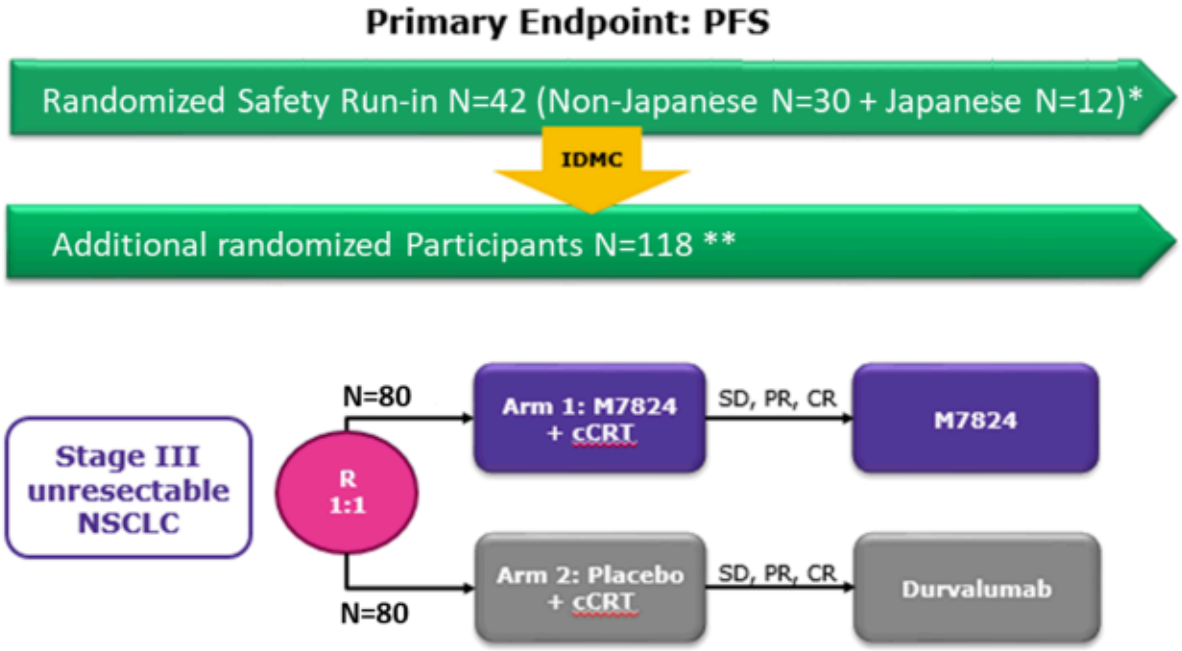
IDMC: The IDMC will periodically review the safety data during the safety run-in as well as expansion part of the study. Independent data Monitoring Committee roles and responsibilities are detailed in the IDMC charter.

Independent Review Committee (IRC): Assessment of radiographic scans will be performed by the Investigator in this study. Scans will be collected and held for any potential later independent read. If a clinically relevant PFS treatment effect according to Investigator assessment is observed at the primary analysis, an IRC may be established to independently assess the images and centrally exclude Investigator bias.

1.2 Schema

The overall study design is shown in Figure 1. Detailed schedule of study procedures/assessments is provided in Section 1.3.

Figure 1 Diagram of Study Design



CR=complete response, PFS=progression-free survival, PR=partial response, SD=stable disease

*: In the safety run-in, 42 participants (12 Japanese and 30 non-Japanese) will be randomized in 1:1 ratio with stratification based on ethnicity to ensure a 1:1 treatment arm allocation for both Japanese and non-Japanese participants during the safety run-in. Japanese participants are defined by ethnicity only and not by country.

**: In the expansion phase, approximately 118 additional participants will be randomized in a 1:1 ratio in Arm 1 and Arm 2. The stratification in the expansion part is based on chemotherapy regimen and PD-L1 expression in tumor cells (< 1% versus ≥ 1%).

1.3 Schedule of Activities

Table 1 Schedule of Activities for cCRT-based Treatment

cCRT-based Treatment	Screening		cCRT-based Treatment (± 3 days)							End-of-cCRT Visit (+5 days)	Notes
	Up to Day -28 to Random-ization	Up to Day -21 to Random-ization	V1	V6	V11	V16	V21	V26	V31		End of cCRT visit may coincide with Week 9 dosing visit. Overlapping assessments only need to be performed once and should follow Week 9 visit window (± 3 days). See Table 3 and Section 4.1 for additional details.
			W1	W2	W3	W4	W5	W6	W7		
			D1	D8	D15	D22	D29	D36	D43	D57	
Administrative Procedures											
Written informed consent	X										
Inclusion/ exclusion/ Enrollment (if eligible)		X									
Demographic data		X									
Medical history		X									Medical history includes substance usage (tobacco and nicotine).
Documentation concomitant medication and procedures		X	X	X	X	X	X	X	X	X	
Prior anticancer drug/radiotherapy/procedures		X									
Viral serology (HBV, 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.

cCRT-based Treatment	Screening		cCRT-based Treatment (± 3 days)							End-of-cCRT Visit (+5 days)	Notes
	Up to Day -28 to Random-ization	Up to Day -21 to Random-ization	V1	V6	V11	V16	V21	V26	V31		End of cCRT visit may coincide with Week 9 dosing visit. Overlapping assessments only need to be performed once and should follow Week 9 visit window (± 3 days). See Table 3 and Section 4.1 for additional details.
			W1	W2	W3	W4	W5	W6	W7		
			D1	D8	D15	D22	D29	D36	D43	D57	
Drug Administration During CRT-based Treatment (See Table 2)											
Tumor Evaluation / Staging											
Thorax Abdomen Pelvis CT (preferred)/MRI		X[a]								X[b]	a: ideally within 14 days prior to randomization. b: CT scans must be acquired prior to first dose of M7824 or durvalumab after cCRT (the +5 days end of cCRT visit window does not apply to the tumor assessment). See Section 8.1
Brain MRI (preferred)/CT		X[c]								X[d]	c: ideally within 14 days prior to randomization. d: Brain scans must be done prior to first dose of M7824 or durvalumab after cCRT. See Section 8.1
FDG-PET Scan	X										
Safety Assessments											
Documentation of AEs	X	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X	e: Performed at each visit according to Table 2. See Appendix 4 for safety recording and reporting.
Physical examination		X	X	X	X	X	X	X	X	X	Complete PE at Screening. Subsequent focused PEs to be performed as per local standard practice and as clinically indicated. Thorax exam at each visit and findings must be reported in the eCRF.
Skin Assessment		X								X	See Section 6.9.3 for participants experiencing a dermatologic-related AE.

cCRT-based Treatment	Screening		cCRT-based Treatment (± 3 days)							End-of-cCRT Visit (+5 days)	Notes
	Up to Day -28 to Random-ization	Up to Day -21 to Random-ization	V1	V6	V11	V16	V21	V26	V31		End of cCRT visit may coincide with Week 9 dosing visit. Overlapping assessments only need to be performed once and should follow Week 9 visit window (± 3 days). See Table 3 and Section 4.1 for additional details.
			W1	W2	W3	W4	W5	W6	W7		
			D1	D8	D15	D22	D29	D36	D43	D57	
Vital signs		X	X	X	X	X	X	X	X	X	Including weight and height (height at Screening only). Temperature, pulse rate, respiratory rate, blood pressure, and resting pulse oximetry must be done at each visit and must be reported in the eCRF. See Section 8.2.2 for additional details.
ECOG PS		X	X	X	X	X	X	X	X	X	
12-lead ECG		X									
Spirometry		X[f]								X[g]	VC_{max}, FEV_1, FVC, FEV_1/FVC ratio, must be reported f: Data should be entered to the vendor portal prior to randomization. g: Day 57 (± 7 days)
High resolution CT Scan		X									Perform only if participant meets all the inclusion criteria for the study
6-min walking test		X								X[h]	Distance and O_2 saturation must be reported h: Day 57 (± 7 days)
CCI											
Laboratory Assessments											
Hemostaseology		X	X[k]		X		X		X		k: W1D1 must be done if test at Screening is performed more than 2 weeks prior to W1D1.

cCRT-based Treatment	Screening		cCRT-based Treatment (± 3 days)							End-of-cCRT Visit (+5 days)	Notes
	Up to Day -28 to Random-ization	Up to Day -21 to Random-ization	V1	V6	V11	V16	V21	V26	V31		End of cCRT visit may coincide with Week 9 dosing visit. Overlapping assessments only need to be performed once and should follow Week 9 visit window (± 3 days). See Table 3 and Section 4.1 for additional details.
			W1	W2	W3	W4	W5	W6	W7		
			D1	D8	D15	D22	D29	D36	D43	D57	
Hematology		X	X	X	X	X	X	X	X	X	See Appendix 5 for individual tests in each laboratory panel. Samples must also be drawn within 3 days and results to be reviewed prior to dose administration. Lab test to be repeated in case of toxicity as clinically indicated. All Lab tests must be reported on eCRF.
Core serum chemistry			X[l]	X		X		X			See Appendix 5 for individual tests in each laboratory panel. l: Only needed if full chemistry is taken more than 7 days prior D1 or clinically indicated. Samples must also be drawn within 3 days and results to be reviewed prior to dose administration. Lab test to be repeated in case of toxicity as clinically indicated. All Lab tests must be reported on eCRF.
Full serum chemistry Panel A		X			X		X		X	X	See Appendix 5 for individual tests in each laboratory panel. Samples must also be drawn within 3 days and results to be reviewed prior to dose administration. Lab test to be repeated in case of toxicity as clinically indicated. All Lab tests must be reported on eCRF.
Full serum chemistry Panel B		X									See Appendix 5 for individual tests in each laboratory panel. Lab test to be repeated as clinically indicated. All Lab tests must be reported on eCRF.
Urinalysis		X	As clinically indicated								Full urinalysis (dipstick plus microscopic evaluation) at the Screening visit. If the urinalysis is abnormal, then a culture should be performed.

cCRT-based Treatment	Screening		cCRT-based Treatment (± 3 days)							End-of-cCRT Visit (+5 days)	Notes
	Up to Day -28 to Random-ization	Up to Day -21 to Random-ization	V1	V6	V11	V16	V21	V26	V31		End of cCRT visit may coincide with Week 9 dosing visit. Overlapping assessments only need to be performed once and should follow Week 9 visit window (± 3 days). See Table 3 and Section 4.1 for additional details.
			W1	W2	W3	W4	W5	W6	W7		
			D1	D8	D15	D22	D29	D36	D43	D57	
β-HCG pregnancy test (only applicable to WOCBP)		X	X				X				β-HCG must be determined from serum at Screening and from a urine or serum sample thereafter every 4 weeks. Results of the most recent pregnancy test are to be available prior to dosing of study intervention.
T_4 and TSH		X								X	
Serum KL-6, SP-A and SP-D		X^m			X^m		X^m		X^m	X^m	m: Tests required in Japanese participants enrolled in Japan.
Patient Reported Outcomes											
CCI [redacted]											

cCRT-based Treatment	Screening		cCRT-based Treatment (± 3 days)							End-of-cCRT Visit (+5 days)	Notes
	Up to Day -28 to Random-ization	Up to Day -21 to Random-ization	V1	V6	V11	V16	V21	V26	V31		End of cCRT visit may coincide with Week 9 dosing visit. Overlapping assessments only need to be performed once and should follow Week 9 visit window (± 3 days). See Table 3 and Section 4.1 for additional details.
			W1	W2	W3	W4	W5	W6	W7		
			D1	D8	D15	D22	D29	D36	D43	D57	
PK, ADA, Biomarker											
Blood sample for PK			X/X (pre/eoi)		X/X (pre/eoi)		X/- (pre/eoi)			X/- (pre/eoi)[o]	Samples for PK analysis to be taken before (pre) infusion (as close to the start of the infusion as possible, prior to M7824 or placebo administration on the same day), immediately after the end of M7824 or placebo 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. o: If End-of-cCRT and Day 57 treatment are on the same day, sample to be collected before dosing. If different day, sample to be collected at End-of-cCRT.
Blood sample for ADA		X			X/- (pre/eoi)		X/- (pre/eoi)			X/- (pre/eoi)[p]	Samples will be collected prior to M7824 or placebo administration. p: If End-of-cCRT and Day 57 treatment are on the same day, sample to be collected before dosing. If different day, sample to be collected at End-of-cCRT.
CCI											
CCI											

cCRT-based Treatment	Screening		cCRT-based Treatment (± 3 days)							End-of-cCRT Visit (+5 days)	Notes
	Up to Day -28 to Random-ization	Up to Day -21 to Random-ization	V1	V6	V11	V16	V21	V26	V31		End of cCRT visit may coincide with Week 9 dosing visit. Overlapping assessments only need to be performed once and should follow Week 9 visit window (± 3 days). See Table 3 and Section 4.1 for additional details.
			W1	W2	W3	W4	W5	W6	W7		
			D1	D8	D15	D22	D29	D36	D43	D57	
CCI											
CCI											

ADA=anti-drug antibody, AE=adverse events, βHCG=β-human chorionic gonadotropin, cCRT=concomitant chemoradiation therapy, CT=computed tomography, CCI, D=Day, CCI, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, CCI re, eoi=end of infusion, CCI
HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=Human immunodeficiency virus, MRI=magnetic resonance imaging, NSCLC-SAQ=non-small cell lung cancer Symptom Assessment Questionnaire, CCI, PK=pharmacokinetics, CCI, T_4=free thyroxine, CCI, TSH=thyroid-stimulating hormone, V=visit, W=Week, WOCBP=Woman of childbearing potential.

Table 2 Drug Administration Schedule During cCRT-based Treatment

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28	V29	V30	V31	V32	V33	V34	V35	Notes
cCRT-based Treatment	W1					W2					W3					W4					W5					W6					W7					V32, V33, V34, and V35 are optional in case participant has not completed cCRT. See Section 4.1 for additional details
	D1	D2	D3	D4	D5	D8	D9	D10	D11	D12	D15	D16	D17	D18	D19	D22	D23	D24	D25	D26	D29	D30	D31	D32	D33	D36	D37	D38	D39	D40	D43	D44	D45	D46	D47	
CCI [redacted]																																				
Cisplatin/Etoposide (allowed window for administration ±3 days unless dose delay is required due to AEs-see Section 6.10)																																				
Cisplatin 50 mg/m² day (dose for cisplatin/etoposide regimen)	X					X															X					X										
Etoposide 50 mg/m² day	X	X	X	X	X																X	X	X	X	X											
Hydration	X					X															X					X										In participants receiving cisplatin/etoposide ensure adequate hydration. All the medications used as hydration (drugs and fluids) must be reported in the eCRF.

cCRT-based Treatment	V1 / W1 / D1	V2 / D2	V3 / D3	V4 / D4	V5 / D5	V6 / W2 / D8	V7 / D9	V8 / D10	V9 / D11	V10 / D12	V11 / W3 / D15	V12 / D16	V13 / D17	V14 / D18	V15 / D19	V16 / W4 / D22	V17 / D23	V18 / D24	V19 / D25	V20 / D26	V21 / W5 / D29	V22 / D30	V23 / D31	V24 / D32	V25 / D33	V26 / W6 / D36	V27 / D37	V28 / D38	V29 / D39	V30 / D40	V31 / W7 / D43	V32 / D44	V33 / D45	V34 / D46	V35 / D47	Notes
																																				V32, V33, V34, and V35 are optional in case participant has not completed cCRT. See Section 4.1 for additional details
Paclitaxel/Carboplatin (allowed window for administration ±3 days unless dose delay is required due to AEs -see Section 6.10)																																				
Paclitaxel 45 mg/m²	X					X					X					X					X					X					X					
Carboplatin AUC 2	X					X					X					X					X					X					X					
Pemetrexed/Cisplatin (allowed window for administration ±3 days unless dose delay is required due to AEs-see Section 6.10)																																				
Cisplatin 75 mg/m² day (dose for cisplatin/pemetrexed regimen)	X															X															X					
Pemetrexed 500 mg/m²	X															X															X					
Folic acid 350-1000 µg	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Starting at Day -5 and continuing 21 days after the last dose of pemetrexed
Vitamin B_{12} 1000 µg	During the week before the first dose of pemetrexed and at the end of cCRT																																			
Premedication for all chemotherapy regimens	All participants should be premedicated with oral or injectable steroids according to the approved product label and/or standard practice. Additional 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. Drugs used in premedication must be reported in the eCRF.																																			

Table 3 Schedule of Assessments for Treatment after cCRT

Treatment after cCRT	Treatment after cCRT (± 3 days)								End-of-Treatment Visit	Notes
	V36	V37	V38	V39	V40	V41	V42	Until End-of-Treatment	On the Day of or Within 7 Days of Decision to End Treatment	End of cCRT visit may coincide with Week 9 dosing visit. Overlapping assessments only need to be performed once and should follow Week 9 visit window (± 3 days). See Section 4.1 for additional details.
	W9	W11	W13	W15	W17	W19	W21			
	D57	D71	D85	D99	D113	D127	D141			
Administrative Procedures										
Documentation concomitant medication and procedures	X	X	X	X	X	X	X	Once every 2 weeks	X	
Viral titer (HBV, HCV)	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.
M7824 and durvalumab Administration										
M7824 or durvalumab	X[a]	X	X	X	X	X	X	Once every 2 weeks[b]		a: If clinically indicated, the first dose of durvalumab or M7824 after the end of cCRT should be administered on Day 57 but not before 14 days from the previous dose of M7824 or placebo b: Once every 2 weeks for a maximum of 26 doses of study intervention after cCRT. Allowed window for administration (± 3 days)
Safety Assessments										
Documentation of AEs	X	X	X	X	X	X	X	Once every 2 weeks	X	See Appendix 4 for safety recording and reporting.

Treatment after cCRT	Treatment after cCRT (± 3 days)								End-of-Treatment Visit	Notes
	V36	V37	V38	V39	V40	V41	V42	Until End-of-Treatment	On the Day of or Within 7 Days of Decision to End Treatment	End of cCRT visit may coincide with Week 9 dosing visit. Overlapping assessments only need to be performed once and should follow Week 9 visit window (± 3 days). See Section 4.1 for additional details.
	W9	W11	W13	W15	W17	W19	W21			
	D57	D71	D85	D99	D113	D127	D141			
Physical examination	X	X	X	X	X	X	X	Once every 2 weeks	X	Complete PE at Screening. Subsequent focused PEs to be performed as per local standard practice and as clinically indicated Thorax exam at each visit and findings must be reported in the eCRF.
Skin Assessment				X			X	Once every 6 weeks	X	See Section 6.9.3 for participants experiencing a dermatologic-related AE.
Vital signs	X	X	X	X	X	X	X	Once every 2 weeks	X	Including weight and height (height at Screening only). Temperature, pulse rate, respiratory rate, blood pressure, and resting pulse oximetry must be done at each visit and must be reported in the eCRF.
ECOG PS	X	X	X	X	X	X	X	Once every 2 weeks	X	
Spirometry	Once every 12 weeks (± 7 days) until EoT								X[c]	VC_{max}, FEV_1, FVC, FEV_1/FVC ratio must be reported. c: Does not need to be performed at End-of-Treatment if performed within 7 days of EoT Visit.
6-min Walking Test	Once every 12 weeks (± 7 days) until EoT								X[c]	Distance and O_2 saturation must be reported. c: Does not need to be performed at End-of-Treatment if performed within 7 days of EoT Visit.
CCI										
High resolution CT scan	At Week 33 and Week 57 (± 7 days)									Can be performed within ± 7 days of the target visits and if possible, should coincide with CT scan.
Laboratory Assessments										
Hemostaseology	As clinically indicated									

Treatment after cCRT	Treatment after cCRT (± 3 days)								End-of-Treatment Visit	Notes
	V36	V37	V38	V39	V40	V41	V42	Until End-of-Treatment	On the Day of or Within 7 Days of Decision to End Treatment	End of cCRT visit may coincide with Week 9 dosing visit. Overlapping assessments only need to be performed once and should follow Week 9 visit window (± 3 days). See Section 4.1 for additional details.
	W9	W11	W13	W15	W17	W19	W21			
	D57	D71	D85	D99	D113	D127	D141			
Hematology	X	Once every 2 weeks							X	See Appendix 5 for individual tests in each laboratory panel. Samples must also be drawn within 3 days and results to be reviewed prior to dose administration.
Core serum chemistry	X[d]		X		X		X	Once every 2 weeks		Core serum chemistry are listed in Appendix 5 Samples must also be drawn within 3 days and results to be reviewed prior to dose administration. d: Core serum chemistry not needed if end of cCRT visit and D57 W9 treatment visits overlap. For such overlapping visits, only panel A chemistry must be done.
Full serum chemistry Panel A		X		X		X			X	See Appendix 5 for individual tests in each laboratory panel. Samples must also be drawn within 3 days and results to be reviewed prior to dose administration. After Week 19, repeat full serum chemistry panel A as clinically indicated.
Urinalysis	As clinically indicated									If the urinalysis is abnormal, then a culture should be performed.
β-HCG pregnancy test (only applicable to WOCBP)	Once every 4 weeks									β-HCG to be determined from a urine or serum sample once every 4 weeks. Results of the most recent pregnancy test should be available prior to dosing of study intervention.
T_4 and TSH				X			X	Once every 6 weeks		
Serum KL-6, SP-A and SP-D	Every 2 weeks for Japanese participants enrolled in Japan for the first 12 weeks after cCRT followed by every 4 weeks until EoT									

Treatment after cCRT	Treatment after cCRT (± 3 days)								End-of-Treatment Visit	Notes
	V36	V37	V38	V39	V40	V41	V42	Until End-of-Treatment	On the Day of or Within 7 Days of Decision to End Treatment	End of cCRT visit may coincide with Week 9 dosing visit. Overlapping assessments only need to be performed once and should follow Week 9 visit window (± 3 days). See Section 4.1 for additional details.
	W9	W11	W13	W15	W17	W19	W21			
	D57	D71	D85	D99	D113	D127	D141			
Patient Reported Outcomes										
CCI [redacted]										
Tumor Assessments										
Thorax Abdomen Pelvis CT (preferred)/MRI					X (± 7 days)			Every 8 weeks (± 7 days)		Confirmation of CR or PR should be performed preferably at the regularly scheduled 8 weekly assessment intervals, but no sooner than 4 weeks after the initial documentation. Confirmation of PD is also required and should be performed preferably and if clinically feasible, at the regularly scheduled 8 weekly assessment intervals, but no sooner than 4 weeks after the initial documentation. The schedule of CT scan (every 8 weeks ± 7 days) should be maintained regardless of dosing. A bone scan will be done as clinically indicated. See Section 8.1

Treatment after cCRT	Treatment after cCRT (± 3 days)								End-of-Treatment Visit	Notes
	V36	V37	V38	V39	V40	V41	V42	Until End-of-Treatment	On the Day of or Within 7 Days of Decision to End Treatment	End of cCRT visit may coincide with Week 9 dosing visit. Overlapping assessments only need to be performed once and should follow Week 9 visit window (± 3 days). See Section 4.1 for additional details.
	W9	W11	W13	W15	W17	W19	W21			
	D57	D71	D85	D99	D113	D127	D141			
Brain MRI (preferred)/CT	Once every 12 weeks (± 7 days)									The schedule of Brain MRI/CT scan (every 12 weeks ± 7 days) should be maintained regardless of dosing. See Section 8.1
PK, ADA, PD and Biomarker										
Blood sample for PK			X/- (pre/ eoi)			X/- (pre/ eoi)		Pre-infusion samples every 6 weeks up to Week 25. Pre- and postinfusion samples every 12 weeks until Week 49	X/- (pre/eoi)	Samples for PK analysis to be taken before (pre) infusion (as close to the start of the infusion as possible), immediately after the completion of infusion (eoi, as close to the completion as possible but no later than 30 min post end of infusion). The predose sample will still be drawn even if dosing is ultimately deferred at the study visit. The exact time of each draw must be recorded. A protocol deviation will be defined by a sample not being drawn.
Blood sample for ADA			X/- (pre/ eoi)			X/- (pre/ eoi)		Every 6 weeks up to Week 25 (included), then every 12 weeks until Week 49	X/- (pre/ eoi)	Samples will be collected prior to M7824 or durvalumab administration.

Treatment after cCRT	Treatment after cCRT (± 3 days)								End-of-Treatment Visit	Notes
	V36	V37	V38	V39	V40	V41	V42	Until End-of-Treatment	On the Day of or Within 7 Days of Decision to End Treatment	End of cCRT visit may coincide with Week 9 dosing visit. Overlapping assessments only need to be performed once and should follow Week 9 visit window (± 3 days). See Section 4.1 for additional details.
	W9	W11	W13	W15	W17	W19	W21			
	D57	D71	D85	D99	D113	D127	D141			
CCI										
CCI										
CCI										

ADA=anti-drug antibody, AE=adverse events, βHCG=β-human chorionic gonadotropin, cCRT=concomitant chemoradiation therapy, CT=computed tomography, CCI, D=Day, CCI, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, CCI, eoi=end of infusion, CCI, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=Human immunodeficiency virus, MRI=magnetic resonance imaging, NSCLC-SAQ=non-small cell lung cancer Symptom Assessment Questionnaire, CCI PK=pharmacokinetics, CCI, T_4=free thyroxine, CCI rden, TSH=thyroid-stimulating hormone, V=visit, W=Week, WOCBP=Woman of childbearing potential.

Table 4 Schedule of Assessments for Safety and Long-term Follow-up

Safety and Long-term Follow-up	Safety Follow-up Visit		Long-term Follow-up[a]	Notes
	28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment	Every 12 weeks (± 2 weeks) starting 24 weeks after Last Treatment	a: Long term follow-up will be conducted by phone or may be conducted during a clinic visit
Documentation concomitant therapy	X	X	X[b]	b: May be conducted via phone call in Long-term Follow-up phase.
Documentation of AEs	X	X[c]	X[c]	See Appendix 4 for safety recording and reporting. c: The 12-week Safety Follow-up and Long-term Follow-up may be conducted via telephone calls or patient chart reviews as necessary unless there is medical necessity requiring a clinical visit.
Physical examination	X		X[d]	Focused PEs to be performed as per local standard practice. d: Not mandatory, only perform if clinically indicated
Skin assessment	X			
Vital signs	X			Including weight. Temperature, pulse rate, respiratory rate, blood pressure, and resting pulse oximetry must be measured.
ECOG PS	X			
12-lead ECG	X			
Hematology	X			Details on blood tests under this category are listed in Appendix 5.
Full serum chemistry Panel A	X			See Appendix 5 for individual tests in each laboratory panel.
Urinalysis	X			
β-hCG pregnancy test	X			β-hCG must be determined from urine or serum.
T_4 and TSH	X			

Safety and Long-term Follow-up	Safety Follow-up Visit		Long-term Follow-up[a]	Notes
	28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment	Every 12 weeks (± 2 weeks) starting 24 weeks after Last Treatment	a: Long term follow-up will be conducted by phone or may be conducted during a clinic visit
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Subsequent anticancer therapy (any line)	X	X	X	
Survival follow-up			X	Participants will be contacted shortly before the data cut-off for the primary analysis to provide complete survival data.
Tumor evaluation/staging (CT Scan of Thorax, abdomen and pelvis /MRI/other established methods) during follow-up			For participants who did not experience PD: CT scan every 8 weeks up to 24 months and then every 8-12 weeks up to progression, start of new treatment or death. Brain MRI every 12 weeks up to 24 months and then according to local practice. For participants who experienced PD: imaging for tumor evaluation will be evaluated as part of PFS2 assessment using RECIST 1.1.	
Response and progression on subsequent treatment	X	X	X	

Safety and Long-term Follow-up	Safety Follow-up Visit		Long-term Follow-up[a]	Notes
	28 Days (± 5 days) after Last Treatment	12 Weeks (± 2 weeks) after Last Treatment	Every 12 weeks (± 2 weeks) starting 24 weeks after Last Treatment	a: Long term follow-up will be conducted by phone or may be conducted during a clinic visit

AE=adverse event, β-hCG=beta-human chorionic gonadotropin, CT=computed tomography, ECG=electrocardiogram, CCI [redacted] e, CCI [redacted], MRI=magnetic resonance imaging, NSCLC-SAQ=non-small cell lung cancer Symptom Assessment Questionnaire, OS=Overall survival, PD=Progressive disease, PE=physical examination, PFS=Progression-free survival, CCI [redacted], SAE=serious adverse event, T_4=free thyroxine, TSH=thyroid-stimulating hormone.

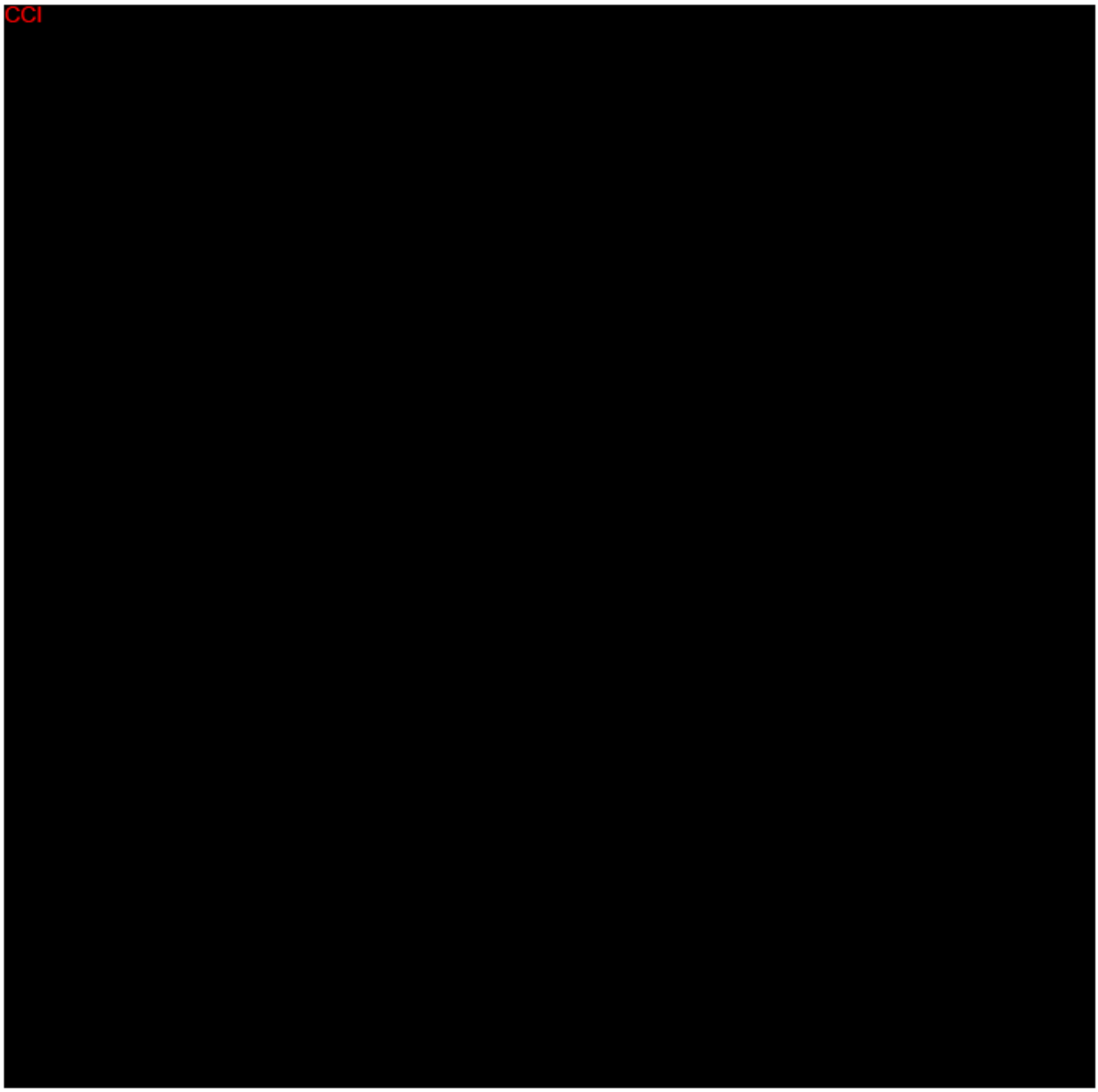
2 Introduction

M7824 (MSB0011359C, bintrafusp alfa) is an innovative first-in-class bifunctional fusion protein composed of the extracellular domain of TGF-β receptor II (TGF-βRII or TGF-β Trap) covalently linked via a flexible linker to the C-terminus of each heavy chain of an immunoglobulin (IgG1) antibody blocking programmed death-ligand 1 (anti-PD-L1). Bintrafusp alfa is the proposed international nonproprietary name for M7824.

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

[redacted]


CCI



2.2 Background

Approximately one third of patients with NSCLC have Stage III, locally advanced disease at diagnosis (Aupérin 2010). Although surgery is appropriate for some of these patients, most of the patients are considered to be inoperable.

Until the approval of durvalumab, the standard of care for unresectable Stage III NSCLC patients with a good performance status has been platinum-based doublet chemotherapy concurrent with radiotherapy (chemoradiotherapy, cCRT) followed by observation until evidence of disease progression (PD) (Yoon 2017). However, the median PFS (mPFS) among patients who have received cCRT was poor (approximately 8 to 10 months), and only 15% of patients were alive at 5 years (Aupérin 2010, Ahn 2016).

Durvalumab (IMFINZI®) is a PD-L1 blocking antibody and has been approved by FDA in February 2018 in patients with disease control after concurrent platinum-based chemotherapy and radiation therapy. PACIFIC study demonstrated that, in patients with disease control after cCRT, durvalumab increased mPFS by 11.2 months compared to placebo control (Antonia 2017) and mOS has not been reached compared to 28.7 months in the placebo control arm (Antonia 2018) Moreover, as summarized in Table 5, durvalumab showed improvement in all secondary endpoints as published so far.

Table 5 Activity of Durvalumab in PACIFIC Study

Study Intervention	mPFS (month)[a]	12m PFS (%)[a]	18m PFS (%)[a]	Median Time to Death or Distant Metastasis (months)[a]	Frequency of New Lesion (%)[a]	ORR (%)[a]	PD (%)[a]	12m DoR (%)[a]	18m DoR (%)[a]	mOS (month)[b]
Durvalumab	16.8	55.9	44.2	23.2	20.4	28.4	16.5	72.8	72.8	NR
Placebo	5.6	35.3	27.0	14.6	32.1	16.0	27.7	56.1	46.8	28.7

ORR=objective response rate, mPFS= median progression-free survival, PD= progression disease, DoR=duration of response, mOS= median overall survival, NR= not reached.
Source: [a] Antonia, 2017; [b] Antonia 2018.

M7824 is a bifunctional fusion protein that combines an anti-PD-L1 antibody and the extracellular domain of TG-Fβ receptor II (TGF-βRII) as a TGF-β neutralizing 'trap', into a single molecule. Complete information on the chemistry, pharmacology, efficacy, and safety of M7824 is in the M7824 Investigator's Brochure (M7824 IB).

The novel design of M7824, which neutralizes TGF-β and simultaneously inhibits the anti-PD-L1 pathway in the tumor microenvironment, may be more effective than agents targeting PD-L1 and TGF-β separately. CCI [redacted]

The evaluation of the clinical profile of M7824 is ongoing; refer to the current IB for further details. M7824 has demonstrated a manageable safety profile to date (See Section 4.3) and promising clinical activity in participants with 2L NSCLC across PD-L1 expression levels in tumor cells (see Section 2.1).

The mechanism of action of M7824, together with its encouraging Phase I clinical activity in NSCLC, along with clinical benefit demonstrated by durvalumab following cCRT in PACIFIC study support the study of M7824 concomitant with cCRT followed by M7824 in unresectable Stage III NSCLC.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of M7824 or durvalumab or any other study intervention administered in this study may be found in Section 2.1 and the Investigator's Brochure, Participant Information Leaflet, Package Insert, Development Safety Update Report or Summary of Product Characteristics.

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

The benefit and risk assessment to conduct this study in Stage III unresectable NSCLC is based on a strong scientific rationale observed during preclinical studies with M7824. In addition, in 2L NSCLC patients, M7824 showed promising clinical activity and a manageable safety profile consistent with overall safety of anti-PD-(L)1 and TGF-β agents. Acceptable safety profiles have also been observed in ongoing clinical studies with other checkpoint inhibitors in combination with CRT (Peters 2018).

PD-L1 expression is observed to be upregulated in the tumor microenvironment after radiation therapy and chemotherapeutic agents in multiple human cancer cell lines (Lin 2017, Samanta 2018, Grabosch, 2015) and murine tumor models (Deng 2014, Dovedi 2014). Notably, such upregulation of PD-L1 expression by irradiation can be further enhanced by TGF-β blockade (Vanpouille-Box 2015), supporting the hypothesis that combining M7824 with radiotherapy will likely provide beneficial effect in participants regardless of the initial PD-L1 status of the tumor.

Important identified risks for M7824 are immune-related adverse events (immune-related pneumonitis, immune-related hepatitis, immune-related colitis, immune-related nephritis and renal dysfunction, immune-related endocrinopathies [thyroid disorders, adrenal insufficiency, Type 1 Diabetes mellitus, pituitary disorders], immune-related rash and other irAEs [myositis, myocarditis, encephalitis]), TGF-β inhibition mediated skin reactions, anemia, and bleeding adverse events (refer to IB for full safety details).

Infusion-related reactions are an identified risk of M7824. In pooled data from 765 participants who received bintrafusp alfa monotherapy at 1200 mg q2w, infusion-related reactions were reported in 6.3% of participants. The majority of IRRs were Grade 1 or 2, including 2.9% who experienced IRRs during the first infusion. Permanent discontinuation and interruptions due to IRRs occurred in low frequency.

Important potential risks are further immune-related adverse events (Guillain-Barré syndrome, uveitis, pancreatitis, myasthenia gravis/myasthenic syndrome), impaired wound healing, and embryofetal toxicity.

Infusion-related reactions are important identified risks for durvalumab. The immune-related AEs immune mediated colitis or diarrhea, hepatitis, pneumonitis, hypophysitis or hypopituitarism, nephritis, hyperthyroidism, hypothyroidism, Type I diabetes, adrenal insufficiency, rash or dermatitis, and myocarditis are important identified risks for durvalumab.

The rationale for combining cCRT with M7824 at 1200 mg flat dose from the Phase I studies is based on no projected risk of PK interactions due to different clearance mechanisms for chemotherapy (cisplatin/etoposide, cisplatin/pemetrexed or carboplatin/paclitaxel) versus M7824. Although radiotherapy is expected to increase expression of PD-L1 and/or TGF-β in the tumors (see Section 2.1), contribution of target-mediated clearance mechanisms to the clearance of M7824 is not projected at 1200 mg once every two weeks (q2w) dose regimen. In addition, based on the mechanisms of action of M7824 or CRT, there is no projection of exaggerated immune response (e.g., cytokine release) in M7824/CRT combination. To date, cytokine data analysis in participants of the Phase I study, showed a transient mild effect of M7824 (at 1200 mg q2w dose) on inflammatory cytokines in blood. Therefore, no adjustment in the dose of cisplatin/etoposide, cisplatin/pemetrexed, carboplatin/paclitaxel or M7824 is considered necessary for this study.

In conclusion, the dual mode of action of bi-functional M7824 in tumor microenvironment, together with its encouraging nonclinical data with chemotherapy and radiation, and Phase I clinical activity in advanced NSCLC, support the investigation of M7824 with cCRT in unresectable Stage III NSCLC. Increased clinical benefit in terms of improved PFS, OS along with an improved QoL is anticipated with administration of M7824 with cCRT followed by M7824 treatment in this patient population. The overall benefit/risk assessment appears favorable to conduct this global study. Additionally, the safety of M7824 plus cCRT will be monitored by the IDMC periodically during the safety run-in and the continuation of the study is based on their assessment of the risk-benefit relationship on an ongoing basis.

3 Objectives and Endpoints

Table 6 Study Objectives and Endpoints

Primary Objective	Primary Endpoint
To evaluate PFS in participants treated with cCRT plus M7824 followed by M7824 or cCRT plus placebo followed by durvalumab	PFS according to RECIST 1.1 assessed by Investigator
Secondary Objectives	**Secondary Endpoints**
To evaluate the safety in participants treated with cCRT plus M7824 followed by M7824 or cCRT plus placebo followed by durvalumab	Occurrence of TEAEs and treatment-related AEs
To evaluate OS in participants treated with cCRT plus M7824 followed by M7824 or cCRT plus placebo followed by durvalumab	OS

To evaluate objective tumor response in participants treated with cCRT plus M7824 followed by M7824 or cCRT plus placebo followed by durvalumab	Objective response according to RECIST 1.1 assessed by Investigator
To evaluate duration of response in participants treated with cCRT plus M7824 followed by M7824 or cCRT plus placebo followed by durvalumab	Duration of response assessed from CR or PR until PD, death, or last tumor assessment
To characterize PK profile of M7824 plus cCRT and after cCRT	PK profile of M7824 in terms of C_{eoi} and C_{trough} during treatment and Safety follow- up visit.
To characterize the immunogenicity of M7824 plus cCRT and after cCRT	Immunogenicity of M7824 as measured by ADA assays from Screening through last Safety Follow-up visit.

CCI

[redacted]

AE=adverse event, CCI [redacted], ADA=antidrug antibody, cCRT=concomitant chemoradiation therapy; C_{eoi}=concentration immediately at the end of infusion, CR=complete response, CCI [redacted]

CCI , C_{trough}=concentration immediately before next dosing; CCI
CCI
, HRCT=high resolution CT, IHC=immunohistochemistry, NSCLC-SAQ=Non–Small Cell Lung Cancer Symptom Assessment Questionnaire, OS=overall survival, PD=progressive disease, CCI PFS=progression-free survival, CCI , CCI , PK=pharmacokinetics, PR=partial response, CCI , RECIST 1.1 =Response Evaluation Criteria in Solid Tumors Version 1.1, TEAE=treatment-emergent adverse event, CCI .
Note: analysis of CCI endpoints will be contingent on the outcomes of primary and secondary endpoints.

4 Study Design

4.1 Overall Design

This is a global, multicenter, randomized, double-blind, controlled Phase II study in unresectable Stage III NSCLC. This study has 2 arms:

- cCRT plus M7824 followed by M7824 (Arm 1)
- cCRT plus placebo followed by durvalumab (Arm 2)

A sample size of approximately 160 randomized participants (consisting of 42 participants in the safety run-in as well as approximately 118 in the expansion phase) is planned in order to observe 70 PFS events at the primary analysis.

During the safety run-in, the first 42 participants (12 Japanese and 30 non-Japanese) will be randomized in 1:1 ratio between Arm 1 and Arm 2. Japanese is defined by ethnicity and not by country. Ethnicity will be the stratification factor during the safety run-in to ensure a 1:1 treatment arm allocation for both Japanese and non-Japanese participants. The safety of M7824 in combination with cCRT will be evaluated in these 2 subgroups (12 Japanese and 30 non-Japanese) by IDMC separately and in parallel. PD-L1 expression in tumor cells at baseline will be determined retrospectively in these participants.

Independent Data Monitoring Committee (IDMC) will periodically review the safety data during the safety run-in as well as expansion part of the study. During the safety run-in, IDMC will assess the safety of the combination of cCRT and M7824 in non-Japanese participants and may also decide upon continuous enrollment subsequent to the safety run-in based on prespecified rules in the IDMC charter. IDMC will make separate assessment for Japanese participants and determine if additional Japanese participants can be enrolled in the expansion part of the study as part of the approximately 118 additional participants.

Participants enrolled in the safety run-in will continue to receive study intervention as per schedule during the safety evaluation by IDMC.

Safety evaluation will include but is not limited to the assessment of the numbers of adverse events leading to permanent discontinuation of study intervention in Arm 1 and Arm 2, judged by the Investigator and IDMC members as related or not related to the study drugs.

An approximately 118 additional participants will be randomized in 1:1 ratio between Arm 1 and Arm 2 after the safety of M7824 with CRT is cleared by IDMC. Chemotherapy regimen and PD-L1 expression in tumor cells (< 1% versus ≥ 1%) will be stratification factors in the expansion part of the study. PD-L1 expression will be determined prospectively by the Ventana PD-L1 (SP263) investigational use only (IUO) assay in central laboratories.

The chemotherapy regimens allowed are the following:

- cisplatin/etoposide for participants with squamous or nonsquamous Stage III NSCLC
- carboplatin/paclitaxel for participants with squamous or nonsquamous Stage III NSCLC
- cisplatin/pemetrexed for participants with nonsquamous Stage III NSCLC

Chemotherapy regimen will be decided by the Investigator prior to randomization. Intensity-modulated radiation therapy (IMRT) will be used in this study as further described in Section 4.1.1.2.

The dosing schedule of study interventions is as described in Table 2.

Participants who experience toxicities from the selected chemotherapy regimen (i.e., anaphylactic reaction to paclitaxel), will be allowed to switch to the other chemotherapy regimens if clinically indicated.

This study includes:

- Screening period of up to 28 days prior to randomization. Most of the evaluations should be performed within 21 days prior to randomization (see Table 1 for details).
- cCRT-based treatment is considered from the first dose of radiation to the last dose of radiation or chemotherapy, whichever occurs last. cCRT can be extended up to 5 business days in case of technical and logistic issues. The 5 business day period can be extended if participants require withholding of the study intervention due to toxicities. In such cases, treatment should be administered as described in Section 6.10. Discussion with Medical Monitor should occur on case by case basis.
  - Study intervention should be discontinued if there is confirmed PD during or at the end of cCRT unless participant meets the criteria for treatment beyond progression (see Section 4.1.1).
- End of cCRT visit must be performed at Day 57 (+ 5 days) except for participants who did not complete cCRT. In this case, the End of cCRT visit must occur within 2 weeks from last dose of M7824 or placebo and participant will:
  - enter follow-up or
  - continue M7824 in Arm 1 or start durvalumab in Arm 2.
- Study intervention after cCRT until unacceptable toxicity, confirmed PD assessed by Investigator (unless participant meets the criteria for study intervention beyond progression), or for up to 26 doses of M7824 or durvalumab, whichever occurs first (see Section 1.3).

- The first dose of M7824 or durvalumab after cCRT must be administered 14 days from the previous administration of M7824 or placebo and not before tumor assessment and end of cCRT visit.
- In case cCRT is terminated early due to toxicity and if clinically indicated, participants in Arm 1 are allowed to continue M7824 and participants in Arm 2 are allowed to start durvalumab. Study intervention should begin 14 days from the last dose of M7824 or placebo and not before tumor assessment and end of cCRT visit has been performed.
- Study intervention should be discontinued if there is confirmed PD unless participant meets the criteria for treatment beyond progression (See Section 4.1.1)

- Participants who experience AEs are allowed to skip up to 3 consecutive doses of M7824, placebo, or durvalumab at any time during the entire study. In case participants recover from AEs within the allowed time (up to 3 doses of study M7824, placebo, or durvalumab) and are able to resume study intervention, they will not be withdrawn from treatment. Treatment may be resumed in participants who have experienced an AE with a prolonged dose hold (> 3 consecutive doses) and in the opinion of the Investigator will benefit from restarting treatment. Such cases must be discussed with the Medical Monitor prior to resuming treatment. See Section 6.9.5 for specific guidance on bleeding adverse events, for which dose reductions may be appropriate.
- Participants with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) will not be eligible to continue to receive study intervention unless clinically indicated and after discussion with the Medical Monitor and the Sponsor Medical Responsible.
- Participants who have a dose interruption for a reason different than toxicity at any time during the study may resume and receive up to 26 total doses of M7824 or durvalumab
- Long-term follow-up
  - Participants who experience PD and do not continue study intervention will enter follow-up.
  - Participants who discontinue study intervention due to reason other than PD will enter follow-up.
  - Participants who achieve and maintain disease control (CR, PR, or SD) through to the end of the 12-month study intervention after cCRT will enter follow-up.
  - Participants who start subsequent treatment should be monitored for response to that treatment according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Tumor scans should be performed following local clinical practice for monitoring disease status on subsequent lines of therapy. The study team encourages and requests scans to be performed every 8 to 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 in the eCRF. Best overall response according to RECIST 1.1 to the subsequent treatment after progressive disease should also be reported. A participant's progression may involve the following: objective radiological or death due to advancing disease. This should be

documented every 8 to 12 weeks until initiation of the next subsequent treatment, withdrawal of consent, or death.

4.1.1 Study Intervention Beyond Progression

Study intervention beyond initial progression

Participants will receive M7824 or durvalumab until unacceptable toxicity, confirmed PD assessed by Investigator, or for up to 26 doses of M7824 or durvalumab, whichever occurs first (see Section 1.3). M7824 or durvalumab may continue past the initial determination of disease progression according to RECIST 1.1 as long as the following criteria are met:

- Investigator-assessed clinical benefit, without any rapid disease progression
- No new unacceptable treatment or disease-related toxicity
- Tolerance of study interventions
- Stable ECOG PS
- Study intervention beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system metastases).

A radiographic assessment should be performed preferably within 8 weeks (but no sooner than 4 weeks) of original PD, at the next scheduled visit, to determine whether there has been a decrease in the tumor burden, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with M7824 or durvalumab.

Study intervention beyond confirmed progression

After confirmed PD, if per Investigator's assessment the participant continues to achieve clinical benefit by continuing study intervention, the participant should remain on the study and continue to receive study intervention and monitoring according to the Schedule of Activities. 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 as per the protocol schedule. 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. In case of continuation of study intervention beyond PD, study intervention will be discontinued once any other criteria for withdrawal are met (see Section 7.1).

Continuation of study intervention after local treatment of disease progression:

If disease progression is due to brain metastasis or bone metastasis, participants may continue study interventions after the local treatment of the brain or bone lesions (if clinically indicated) and discussion with the Medical Monitor 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
- If clinically indicated, 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)
- If clinically indicated, bone lesions have been treated with palliative radiotherapy at least 2 weeks prior to continuation of study interventions
- Benefit-risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator.

4.1.1.1 PFS as the Primary Endpoint

This is the first study evaluating the safety and efficacy of cCRT plus M7824 followed by treatment with M7824. The primary endpoint is PFS, which can be considered as a primary endpoint for demonstration of efficacy per the FDA and European Medicines Agency (EMA) guidance for NSCLC.

Progression-free survival will be evaluated in the full analysis set in the study. The sequence of analysis is in Section 9.4.4.

4.1.1.2 Chemotherapy Regimens and Radiotherapy

Platinum-based doublet chemotherapy given concurrently with radiation is the backbone of the treatment for patients with unresectable Stage III NSCLC (Aupérin 2010).

Studies suggesting superior efficacy of one chemotherapy regimen compared to the others remain contradictory and there is no consensus for the most favorable and optimal doublet.

Cisplatin/etoposide and carboplatin/paclitaxel are the most commonly used platinum-based doublet chemotherapy regimens across several countries (Steuer 2017). In a large retrospective analysis, there were no significant differences in efficacy, whether comparing ORR, PFS, or OS. However, cisplatin-etoposide was associated with higher rates of adverse events, specifically Grade 3 nausea and/or vomiting and hematologic toxicities (Steuer 2017, Wang 2012).

Several clinical studies have shown that pemetrexed with cisplatin can be administered concurrently with thoracic radiation therapy without increasing the expected toxicity of this combined treatment (Brade 2011, Govindan 2008, Choy 2015). Although the PROCLAIM study did not show improved OS in patients treated with cisplatin/pemetrexed followed by consolidation with pemetrexed, compared to cisplatin/etoposide followed by consolidation with platinum-based chemotherapy, the incidence of possible treatment-related Grade 3 to 4 events, was significantly

lower in patients treated with cisplatin/pemetrexed followed by pemetrexed in consolidation (Senan 2016).

All three regimens are allowed in this study and individual study intervention selection should be made by the Investigator for a given participant based on specific factors such as age, performance status and comorbidities. The evaluation and risk managements are described in Section 6.10.

For over 30 years the accepted dose of radiotherapy for unresectable Stage III NSCLC has been 60-66 Gy and a recent randomized clinical study demonstrated that a higher dose of 74 Gy is not associated with increased clinical benefit compared to the standard dosing of 60 Gy and is more toxic (Bradley 2015). In this study the total dose of radiation allowed is 60 Gy.

IMRT uses complex modulated radiation beams that sculpt the radiation dose to precisely conform to complex geometric targets, which creates sharper radiation dose gradients between tumor and normal tissue. For these reasons, IMRT can improve radiation coverage of tumors and enhance the therapeutic ratio by sparing critical adjacent structures (Wu 2004; Chun 2017). In a secondary analysis of large prospective study (RTOG 0617), despite similar efficacy, IMRT was associated with a significant reduction of Grade 3 pneumonitis compared to 3D-CRT (three-dimensional conformal external beam radiation therapy). Moreover, IMRT was shown to reduce radiation doses delivered to the heart and preserved quality of life (Chun 2017; Movsas 2016). In this study the radiation treatment will be delivered by IMRT.

4.1.1.3 Durvalumab as Comparator

Durvalumab (IMFINZI®) is a PD-L1 blocking antibody and has been approved by FDA and PMDA in early 2018 for the treatment of patients with unresectable stage III NSCLC with disease control after chemotherapy and radiation therapy regardless of PD-L1 expression.

Recently, EMA granted approval for durvalumab for the treatment of locally advanced, unresectable NSCLC in adults whose tumors express PD-L1 on ≥ 1% of tumor cells and whose disease has not progressed following platinum-based chemoradiation therapy.

All comers Stage III NSCLC patients were enrolled in PACIFIC study and collection of tumor tissue at Baseline or PD-L1 expression status were not required for inclusion in the study.

CCI

CCI [redacted]

4.1.1.4 Double Blind Design

This study will use a double-blind design to fully assess the safety and efficacy of M7824 with cCRT followed by M7824 (Arm 1) compared to cCRT plus placebo followed by durvalumab (Arm 2). Chemotherapy regimen will be decided by the Investigator prior randomization and therefore the chemotherapy will not be blinded. See Section 6.1.2 for details.

4.1.1.5 Stratification

Participants enrolled in the safety run-in will be stratified for ethnicity (Japanese and non-Japanese) to ensure a 1:1 treatment arm allocation for both Japanese and non-Japanese participants. Japanese participants are defined by ethnicity only and not by country.

Chemotherapy regimen and PD-L1 expression in tumor cells (< 1% versus ≥ 1%) will be the stratification factors for the approximately 118 additional participants. Chemotherapy regimen will be either cisplatin/etoposide, cisplatin/pemetrexed or carboplatin/paclitaxel, and decided by the Investigator prior to randomization. PD-L1 expression will be determined prospectively by the Ventana PD-L1 (SP263) IUO assay in central laboratories.

4.2 Scientific Rationale for Study Design

See Section 2.1.

4.3 Justification for Dose

The RP2D for M7824 is 1200 mg administered as an IV infusion q2w including chemoradiation combination study. The selection of RP2D is based on the available clinical data from Phase I Study CCI [redacted] and Study CCI [redacted], including safety/tolerability, pharmacokinetics (PK), and CCI [redacted] such as CCI [redacted] target occupancy [TO] in PBMCs and CCI [redacted] trapping in blood, as well as efficacy in 2L NSCLC cohorts from Study EMR200647-001. The selection of RP2D is also supported by population PK (popPK) and exposure-response modeling and simulation and evaluation of potential overlapping toxicities and PK interactions in M7824/chemoradiation study. Refer to the IB for further details.

<u>M7824 in combination with cCRT</u>

Based on different clearance mechanisms for chemotherapy (cisplatin/etoposide, cisplatin/pemetrexed or carboplatin/paclitaxel) versus M7824, and the observed safety profile of M7824 monotherapy, PK interactions or overlapping toxicities of M7824 and chemotherapy are considered unlikely, except for anemia. Although radiotherapy is expected to increase expression of CCI [redacted] in the tumors (see Section 2.1), contribution of target-mediated clearance mechanisms to the clearance of M7824 is not expected at 1200 mg q2w dose regimen. In addition, based on mechanisms of action of M7824 or CRT, there are no expectations of exaggerated immune response (e.g., cytokine release) in M7824/CRT combination. To date, cytokine data

analysis in participants of the Phase I study, showed a transient mild effect of M7824 (at 1200 mg q2w dose) on inflammatory cytokines in blood. Therefore, no adjustment in the dose of cisplatin/etoposide, cisplatin/pemetrexed, carboplatin/paclitaxel or M7824 is considered necessary for this study, with the exception of dose reductions for bleeding events (see below). Initial safety run-in, as well as the risk management for chemotherapy (including dose modifications), radiotherapy, and M7824 is in place to address potential risks of overlapping toxicities between M7824 and cCRT. However, in the cases of bleeding events, a dose modification might be required. A 600 mg Q2W M7824 dose is recommended for the dose reduction in a participant with a bleeding event, since this dose is expected to reduce the risk of bleeding (based on a recent exposure-safety analysis for bleeding AEs conducted with preliminary data from Phase I and Phase II studies), while maintaining pharmacologically relevant exposures associated with PD-L-1 inhibition. For further details on dose modifications for management of bleeding see Section 6.9.5 and Section 6.3.2.

In summary, efficacy, safety/tolerability, PK and CCI data from the Phase I studies, the evaluation of potential overlapping toxicities and PK interactions of the M7824/cCRT combination and planned mitigation measures in the study (including dose interruptions and reductions), as well as preliminary popPK and exposure-response modeling of the data support evaluation of M7824 at 1200 mg q2w with cCRT in the proposed global study in advanced cancer patients with unresectable Stage III NSCLC.

4.4 End of Study Definition

The end of the study is defined as either the date of primary analysis or when all participants have completed maintenance therapy and safety follow-up (see Section 1.3), whichever occurs later. The analysis on the primary endpoint PFS is performed when 70 PFS events per Investigator are reached and after a minimum follow-up of 15 months after randomization of the last participant.

After stipulated End of Study, survival follow-up may continue until last participant has died or at discretion of the Sponsor.

The Sponsor may terminate the study at any time once access to M7824 or durvalumab for participants still benefitting is provisioned via a roll over study, expanded access, marketed product or another mechanism of access as appropriate. See also Appendix 2 for study and site closure.

A participant has completed the study if he/she has completed all study parts, including the last visit or the last scheduled procedure shown in Table 4.

5 Study Population

The criteria in Section 5.1 (Inclusion Criteria) and 5.2 (Exclusion Criteria) are designed to enroll only participants, who are appropriate for the study; thereby, ensuring the study fulfills its

objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this study.

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

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

5.1 Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

2. Participants must have measurable or non-measurable but evaluable disease assessed by the Investigator. Participants must have histologically documented NSCLC who present with Stage III locally advanced, unresectable disease (International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology [IASLC Staging Manual in Thoracic Oncology], v8).

3. Availability of tumor material (< 6 months old) adequate for biomarker analysis is mandatory for all participants and central laboratory confirmation is required. For participants enrolled in the safety run-in, PD-L1 expression will be tested retrospectively by a central laboratory. For participants enrolled in the expansion part of the study, PD-L1 expression must be tested by the central laboratory and results available before randomization. Only results from the central laboratory testing will be used for randomization and if PD-L1 status is non-evaluable, the participant is not eligible for this study. Tumor samples obtained by endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies, and surgical specimens that are < 6 months old and adequate for biomarker analysis are acceptable. Biopsies obtained by fine needle aspiration are not acceptable.

4. Participants with tumor harboring an EGFR sensitizing (activating) mutation, ALK translocation, ROS-1 rearrangement are eligible. These tests are not required for enrollment in the study.

5. Participants with ongoing post-obstructive pneumonia due to the tumor are eligible.

6. If a pleural effusion is present, the following criteria must be met to exclude malignant involvement (incurable T4 disease):

a. When pleural fluid is visible on both the CT scan and on a chest x-ray, a thoracentesis is required to confirm that the pleural fluid is cytologically negative.

b. Participants with exudative pleural effusions are excluded, regardless of cytology.

c. Participants with effusions that are minimal, i.e., are too small to safely tap are eligible.

7. Participants must be at least 3 weeks from prior thoracotomy (if performed).

8. Participants must have adequate pulmonary function defined as a forced expiratory volume in 1 second (FEV_1) $\geq$ 1.2 liters or $\geq$ 50% of predicted normal volume measured within 3 weeks prior to randomization. If participants do not meet the above criteria, treatment with inhaled steroids and bronchodilators can be initiated if clinically indicated and eligibility can be reassessed after 1-2 weeks.

9. ECOG performance status of 0 to 1 at Screening and on the day of first dose.

10. Life expectancy $\geq$ 12 weeks.

11. 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 $\geq$ 9 g/dL.

b. Adequate hepatic function defined by a total bilirubin level $\leq$ 1.5 × upper limit of normal (ULN), an aspartate aminotransferase (AST) level $\leq$ 3.0 × ULN, an alanine aminotransferase (ALT) level $\leq$ 3.0 × ULN and alkaline phosphatase $\leq$ 2.5 ULN.

c. Adequate renal function defined by creatinine $\leq$ 1.5 × ULN or calculated creatinine clearance (CrCl) $\geq$ 50 mL/min for participant with Cr > 1.5 × ULN (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 × ULN unless the participant is receiving anticoagulant therapy and activated partial thromboplastin time (aPTT) $\leq$ 1.5 × ULN unless the participant is receiving anticoagulant therapy.

Sex

12. 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 6 months after the last dose of study intervention

- Refrain from donating sperm.

PLUS, either:

- Abstain from intercourse with a WOCBP.

OR

- Use a male condom: When having sexual intercourse with a 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.

  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) for at least 4 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 SoA.

- 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

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Mixed small cell with non-small cell lung cancer histology.
2. Greater than minimal, exudative, or cytologically positive pleural effusions.
3. Recent major surgery within 4 weeks prior to entry into the study (excluding the placement of vascular access) that would prevent administration of study drug.
4. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).
5. History of organ transplant that requires therapeutic immunosuppression.
6. Significant acute or chronic infections including, among others:
   a. Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (testing at Screening is not required). If an Investigator has a strong suspicion of HIV infection without known history for a participant in Screening, however participant refuses testing, discuss with Medical Monitor to assess eligibility. (Note: HIV testing is not mandated for study inclusion; however, if it is performed at any point in Screening or while on study, a site must consent the participant for HIV testing as per local standard guidance.)
   b. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (HBV surface antigen positive and HBV core antibody positive with reflex to positive HBV DNA, or HBV core antibody positive alone with reflex to positive HBV DNA, or positive HCV antibody with reflex to positive HCV RNA) at Baseline. Discuss with the Medical Monitor if history of HBV or HCV infection is known. If medically indicated, participants infected with HBV must be treated and on a stable dose of antivirals (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 or hematologic abnormalities (must meet criteria above) and with planned monitoring and management according to appropriate labeling guidance. HBV and/or HCV viral titers must be monitored according to SoA 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).

7. a. Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses, active uveitis or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the patient to give written informed consent.

7. b. Participants with history of bleeding diathesis or recent major bleeding events considered by the Investigator as high risk for investigational drug treatment such as participants with clinically relevant bleeding events of hemoptysis Grade ≥ 2 within the last month are also excluded.

8. Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before randomization.

9. Known clinical history of tuberculosis, lung sarcoidosis and Interstitial Lung Diseases.

10. History of another primary malignancy within 3 years prior to starting study drug, except for adequately treated basal or squamous cell carcinoma of the skin, adequately treated carcinoma in situ, e.g., cancer of the cervix in situ, superficial bladder cancer. History of other localized malignancies treated with curative intent needs to be discussed with the Medical Monitor.

11. Uncontrolled neuropathy Grade 2 or greater regardless of cause.

12. Significant hearing loss and participants unwilling to accept potential for further hearing loss (Investigator should consider treating the participant with carboplatin/paclitaxel).

Prior/Concomitant Therapy

13. Any prior systemic cytotoxic chemotherapy for their NSCLC or any antibody or drug targeting T-cell coregulatory proteins (immune checkpoints) such as anti-PD-(L)1, or anti-CTLA-4 antibody.

14. Current or prior use of immunosuppressive medication within 28 days before the first dose of study drug, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. Systemic steroid administration required to manage

toxicities arising from radiation therapy delivered as part of the cCRT for locally advanced NSCLC is allowed.

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

16. Receipt of live attenuated vaccination within 30 days of receiving study drug.

17. Use of a prohibited concomitant drug, as defined in Section 6.5.2 within 4 weeks randomization.

18. Known severe hypersensitivity (Grade ≥ 3 National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0) to study interventions or any components in their formulations, or uncontrolled asthma (i.e., 3 or more features of partially controlled asthma).

Prior/Concurrent Clinical Study Experience

19. Participation in another clinical study with an investigational product within the last 4 weeks.
20. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study.

Diagnostic Assessments

21. ≥ 10% weight loss within the past month.
22. Female patients who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control.

Other Exclusions

23. Any condition that, in the opinion of the Investigator, would interfere with evaluation of the study drug or interpretation of participant safety or study results.
24. Prior radiotherapy if delivered in adjuvant/neo-adjuvant regimen.

5.3 Lifestyle Considerations

Not Applicable.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

Rescreened participants will be assigned a new participant number. In situations when a participant has been screen-failed, the site should contact the Medical Monitor to discuss whether the participant may be rescreened.

6 Study Intervention(s)

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

6.1 Study Intervention(s) Administration

Preferred sequence of study intervention during cCRT is M7824 or placebo administered first followed by 2-hour in-house safety monitoring for the first 2 doses prior to chemotherapy when administered on the same visit.

When the radiotherapy is delivered at a separate location, logistic considerations may result in radiotherapy being delivered prior to the administration of M7824 or placebo. If radiotherapy is administered first, M7824 or placebo must be followed with 2-hour in-house safety monitoring before administration of chemotherapy. RT should be delivered after chemotherapy when administered on the same visit.

After the first 2 infusions of M7824 or placebo, participants should be monitored for 1 hour before administration of chemotherapy on the same day. If no IRRs are observed during cCRT the mandated post infusion observation time is no longer required for the treatment after the end of cCRT. M7824, placebo and durvalumab will be administered in a blinded manner (see Section 6.3.2). For information regarding M7824, placebo, and durvalumab refer to Table 7.

Refer to each chemotherapy agent SmPC or package insert for more information. Depending on the local regulations, chemotherapy agent(s) may be either sourced from a local hospital pharmacy or supplied by the Sponsor (or designed service provider) and will be packaged, labeled, and distributed for this clinical study according to local requirements.

Table 7 Administration of M7824, Placebo, or Durvalumab

Study Intervention Name:	M7824 (MSB0011359C)	M7824 (MSB0011359C) Placebo	Durvalumab
Dose Formulation:	Sterile concentrate solution for infusion	Sterile concentrate solution for infusion. The composition of the placebo is identical to the composition of M7824 drug product, except for the presence of M7824	Clear to opalescent, colorless to slight yellow solution
Unit Dose Strength(s)/ Dosage Level(s):	10 mg/mL in single-use glass vials	placebo solution in a single-use glass vials	• 500 mg/10 mL (50 mg/mL) in a single-dose vial • 120 mg/2.4 mL (50 mg/mL) in a single-dose vial
Route of Administration:	Intravenous infusion	Intravenous infusion	Intravenous infusion
Dosing Instructions:	1200 mg over 1 hour (- 10 minutes/+20 minutes; i.e., over 50 to 80 minutes) q2w. See Section 6.8 for special precautions and Section 6.9 for management of AESI	Over 1 hour (-10 minutes/+20 minutes; i.e., over 50 to 80 minutes) q2w.	10 mg/Kg over 1 hour (- 10 minutes/+20 minutes; i.e., over 50 to 80 minutes) q2w.
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Commercial product, provided centrally by the Sponsor, site pharmacy, or by the designated third party supplier
Packaging and Labeling	Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.	Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.	Commercial product: Refer to durvalumab SmPC or Package Insert for more information. Investigational Medicinal Product: Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

Premedication for M7824 or placebo is optional. In order to mitigate infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] IV or oral equivalent dose) approximately 30 to 60 minutes prior to M7824 or placebo should be administered at the discretion of the Investigator. Steroids as premedication for M7824, placebo, or durvalumab are not permitted (steroids as premedication are allowed prior to chemotherapy, see Section 6.5.2).

There are no dose reductions for M7824, placebo, or durvalumab, with the exception of dose reductions as a result of bleeding events (see Section 6.9.5). Dosing modifications (i.e., changes

in infusion rate) and dose delays are described in Section 6.6 to as part of precautions and risk management.

Dose reductions and modifications for chemotherapy and radiotherapy are allowed (see Section 6.6).

6.1.1 Radiation

Full details of protocol requirements for radiotherapy can be found in the Radiotherapy Guidelines for this study provided to the sites. Prior to initiating RT, the radiation treatment plan should be submitted by the Investigator to the radiation oncology vendor for review. A brief summary of requirements follows.

Patients will be treated with photons to a prescription dose of 60 Gy in 30 fractions (2 Gy/fraction). Treatment should be delivered 5 days a week (Day 1-5, each week) during cCRT as per protocol. The radiation treatment plan must be submitted to the radiotherapy vendor as soon as it is approved by the site. Ideally, the plan will be submitted before the start of treatment but no later than 7 days following the initiation of treatment. All study interventions must be administered on Week 1, Day 1. It is preferred that radiation is administered after chemotherapy on the same day of the scheduled visit. (see Section 1.3 for additional details). Radiotherapy simulation must consist of creation of some form of immobilization device (e.g., alpha-cradle, vacuum bad, etc.), and acquisition of a planning CT. IV contrast should be used, unless there is a diagnostic CT with contrast that can be co-registered to the simulation CT, or there is a medical contraindication to contrast. If available, the PET/CT should be co-registered as well. Additionally, some form of both (1) motion assessment (e.g., 4D-CT, fluoroscopy) and (2) motion management (e.g., abdominal compression, gating, etc.) is required.

Delineation of targets and organs at risk will follow standard ICRU 62 guidelines with more specific details in the Radiotherapy Guidelines. Final target volumes will be representative of the motion management strategy selected. The use of IMRT and megavoltage photons for radiotherapy treatment planning is required. Compliance criteria for target coverage and organ at risk dose will be defined in the Radiotherapy Guidelines.

Daily use of image-guidance for treatment delivery is recommended to minimize the requirements for PTV expansions, which may include, but is not limited to on-board portal imaging, cone-beam CT, or orthogonal kV/MV imaging.

6.1.2 Chemotherapy

Investigators can select the chemotherapy regimen from the following 3 standard options according to NCCN guidelines:

Cisplatin (50 mg/m^2)/Etoposide (50 mg/m^2)

Cisplatin/ Etoposide may be sourced from the local pharmacy where allowed.

Cisplatin is administered at a dose of 50 mg/m^2 intravenously over 60 minutes or according to local standards on Days 1, 8, 29, 36 during cCRT. Cisplatin should not be employed in participants with renal or hearing impairment. Cautions must be observed in the case of nausea, vomiting, and dehydration.

Etoposide is administered at a dose of 50 mg/m^2 intravenously over a minimum of 30 minutes up to 60 minutes, or according to local standards, daily on Days 1-5, 29-33 during cCRT.

Standard premedication consisting of an H2 blocker, antiemetics, dexamethasone (oral or intravenous) should be administered according to local guidelines. Adequate hydration pre- and post-treatment in participants receiving cisplatin/etoposide must be ensured according to the local practice and reported in the eCRF.

Carboplatin (AUC 2)/Paclitaxel (45 mg/m^2)

Carboplatin/ Paclitaxel may be sourced from the local pharmacy where allowed.

Carboplatin is administered intravenously based on AUC 2 over 30 minutes or according to local standards on Day 1, Day 8, Day 15, Day 22, Day 29, Day 36, and Day 43 during cCRT. Carboplatin will be given with standard antiemetics after the paclitaxel is administered.

Paclitaxel is administered intravenously at a dose of 45 mg/m^2 over 60 minutes on Day 1, Day 8, Day 15, Day 22, Day 29, Day 36, and Day 43 during cCRT. Standard premedication consisting of diphenhydramine 25-50 mg, an H2 blocker, and dexamethasone (oral or IV is acceptable) should be administered at least 30 minutes prior to paclitaxel or according to local standards, and reported in the eCRF.

Cisplatin (75 mg/m^2)/Pemetrexed (500 mg/m^2)

Cisplatin/ Pemetrexed may be sourced from the local pharmacy where allowed.

Cisplatin is administered at a dose of 75 mg/m^2 intravenously over 60 minutes or according to local standards on Days 1, 22, and 43 during cCRT. Cisplatin should not be employed in participants with renal or hearing impairment. Cautions must be observed in the case of nausea, vomiting, and dehydration.

Pemetrexed is administered after cisplatin at a dose of 500 mg/m^2 intravenously over 10 minutes or according to local standards on Days 1, 22, and 43 during cCRT.

Participants treated with this chemotherapy regimen will also receive mandatory supplementation with folic acid and vitamin B12. Folic acid administered at dose 350-1000 µg oral administration daily for at least 5 days must be taken during the 7-day period preceding the first dose of pemetrexed and continuing throughout study intervention and for 21 days after the last dose of pemetrexed.

Vitamin B12 will be administered at 1000 µg intramuscular injection once during the week preceding the first dose of pemetrexed, and at the end of cCRT.

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

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

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

6.2.1 M7824

M7824 drug product should be stored in a refrigerator CCI [redacted] until use. M7824 must not be frozen and should be stored in the original packaging.

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

6.2.2 Placebo

Placebo should be stored in a refrigerator (CCI [redacted]) until use. The composition of the placebo is identical to the composition of M7824 drug product (a sterile, clear concentrate for solution for infusion), except for the presence of M7824. Placebo must not be frozen and should be stored in the original packaging.

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

6.2.3 Durvalumab

Durvalumab is a clear to opalescent, colorless to slight yellow concentrate for solution for infusion provided in a single dose vial. Durvalumab drug product should be stored in a refrigerator (CCI [redacted]). If not used immediately after dilution, chemical and physical in-use stability of durvalumab has been demonstrated for no more than 24 hours at CCI [redacted] or 4 hours at room temperature up to 25°C from the time of vial puncture to the start of administration. Durvalumab must not be frozen and should be stored in the original package in order to protect from light.

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

6.2.4 Chemotherapy agents

Chemotherapy agents must be stored according to the Pharmacy Manual.

Additional instructions for the preparation, handling, storage, and disposal of chemotherapy agent(s) will be provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Participants will be randomly assigned to study intervention in a 1:1 ratio to minimize the bias due to confounding factors. The randomization will be stratified by ethnicity during the safety run-in. Investigator selected chemotherapy regimen and PD-L1 expression in tumor cells (< 1% versus ≥ 1%) will be stratification factors in the expansion phase. Once a participant meets the eligibility criteria, and is enrolled, the participant will be randomly assigned to a unique randomization number that is associated with the study intervention assignment per the randomization schedule.

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

After confirmation of participant's eligibility and at the last practical moment prior to study intervention administration, participants will be centrally allocated to either Arm 1 or Arm 2 in a 1:1 ratio using an Interactive Web Response System (IWRS) and per a computer-generated randomization list.

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

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

6.3.2 Blinding

Blinding Method

This is a double-blind study, thus the participants and all of the Investigator or Sponsor and CRO staff who are involved in the treatment or clinical evaluation of the participants will be blinded to study intervention allocation. As the IMP packaging and labeling is not blinded, an unblinded study site pharmacist is needed to prepare M7824 or placebo or durvalumab for a participant as specified by the randomization scheme (only the unblinded pharmacist will know the randomization/treatment allocation details).

To ensure the blinding of the study, unblinded pharmacists will be given specific instructions in the Pharmacy Manual for study intervention preparation and handover to a blinded study staff member who will administer the study intervention. Unblinded pharmacists will note if the double-blind conditions have been compromised or the blind broken.

To ensure proper study intervention administration, Investigator or study stuff must communicate to the unblinded pharmacist when participant has completed cCRT and will receive M7824 or durvalumab. Sponsor will undertake measures to preserve the blind of the study by masking the identity of the study intervention(s) namely M7824, placebo, and durvalumab. Details to be provided in the Pharmacy Manual.

The IDMC will be provided with unblinded data to perform ongoing safety analyses.

The Sponsor study team is unblinded at the time of the PFS primary analysis (data cut-off when 70 PFS events reached and a minimum follow-up of 15 months after randomization of the last participant has been reached), while the Investigator and participants remain blinded until End of Study.

Unblinding Clinical Studies for Sample Analysis of Special Data

The bioanalytical monitors and analytical laboratory for measurement of M7824 concentrations will be unblinded since obtaining the result reveals the study intervention arm for the participant.

M7824 concentration information that may unblind the study will not be reported to study sites or blinded personnel until the study has been unblinded.

It is planned that the bioanalyst may have access to the randomization list to facilitate analysis of the PK/antidrug antibody (ADA) samples (i.e., to avoid the unnecessary analysis of placebo samples). However, the bioanalyst will not share the randomization details to prevent the study team from being unblinded prematurely.

Pharmacist Unblinding

An unblinded pharmacist is required to prepare and handle study intervention(s) to maintain study blind.

If the Investigator decides a reduction in blinded treatment is needed to manage toxicity per Section 6.9.5 (M7824/placebo in cCRT treatment period, M7824/durvalumab in maintenance treatment period), he/she should record it on the eCRF. The unblinded pharmacist will:

- In the cCRT treatment period: Prepare a reduced dose of M7824 or placebo.
- In the maintenance treatment period: Prepare a reduced dose of M7824 for participants receiving M7824, OR prepare the usual dose of durvalumab.
- The actual dose should be recorded via IWRS by the unblinded pharmacist.

Regardless of the dose, the infusion bag volume should be 250 mL.

6.3.3 Emergency Unblinding

In an emergency, the Investigator is solely responsible for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in this decision. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to the unblinding, unless this could delay emergency treatment. The Sponsor must be notified within 24 hours after unblinding. The Investigator must provide the Sponsor the reason for unblinding without revealing the study intervention, except to the designated drug safety representative via the Emergency Unblinding Notification Form. The date of and reason for unblinding must be recorded in the source documents and CRF. Contact information for unblinding in an emergency is given on the participant emergency card provided to each participant, as noted in Appendix 2. If a dose reduction is warranted, refer to Section 6.3.2. If emergency unblinding is required, the participant can continue study treatment unless there are other circumstances that require participant discontinuation.

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

6.4 Study Intervention Compliance

In this study, participants will receive study intervention at the investigational site. Well-trained medical staff will monitor and perform the study intervention administration. The information of each study intervention administration including the date, time, and dose for chemotherapy and RT and if patient completed infusion for M7824, durvalumab, and placebo and 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. Dose reductions for blinded treatment due to bleeding events (see Section 6.9.5) should be recorded in the eCRF, the actual dose should be recorded by IWRS to maintain blinding (see Section 6.3.2). Any reason for noncompliance should be documented.

Non-compliance would be defined as a participant missing > 1 infusion of study intervention for non-medical reasons.

6.5 Concomitant Therapy

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

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

6.5.1 Permitted Medicines

The only permitted medications are the following:

- Any medications (other than those excluded by the exclusion criteria or the prohibited medicines) that are considered necessary for the participants' welfare and will not interfere with the study drug may be given at the Investigator's discretion
- Other drugs to be used for prophylaxis, treatment of hypersensitivity reactions, and treatment of fever or flu-like symptoms are described in Section 6.5.1 as part of precautions
- Secondary prophylaxis with G-CSF is allowed if clinically indicated per Investigator assessment. Investigators should be aware that G-CSF use in patients with NSCLC treated with CRT is associated with increased incidence of severe thrombocytopenia and anemia, but not associated with an increased risk of esophagitis or pneumonitis and not detrimental for PFS and OS as reported on the CONVERT Phase III study (Gomes, ELCC and Annals Oncology, 2017)
- Erythropoietin is allowed if clinically indicated
- Steroids are allowed as premedication for chemotherapy. 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 (National Comprehensive Cancer Network [NCCN] Clinical Practice Guidelines in Oncology [NCCN Guidelines®] Antiemesis, 2019)

The Investigator will record all concomitant medications taken by the participant during the study, from the date of signature of informed consent, in the appropriate section of the eCRF. Any additional concomitant therapy that becomes necessary during the study and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug. 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.

6.5.2 Prohibited Medicines

- Cytoreductive therapy
- Use of any investigational drug within 4 weeks before randomization
- Immunotherapy, immunosuppressive drugs, chemotherapy or systemic corticosteroids except:
  - When required for treatment of allergic reactions or for the treatment of irAEs or infusion related reactions/hypersensitivity
  - Systemic corticosteroids for management of patients with allergy to Radiographic Contrast Media
  - Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent

    Note: The use of systemic corticosteroids for participants randomized to receive chemotherapy is per Investigator's discretion and is to be based on local and institutional guidelines. A corticosteroid-sparing approach for antiemetic prophylaxis should be preferred and evaluated on a case by case and chemotherapy regimen basis (NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines®] - Antiemesis, 2019)
- Vaccine administration within 4 weeks before randomization. Vaccination with live vaccines while on study is prohibited. Administration of inactivated vaccines (for example, inactivated influenza vaccines) is allowed. Approved SARS-CoV-2 vaccines are allowed at any time, including before and during screening.
- Primary prophylaxis with G-CSF

Any traditional Chinese medication or herbal supplement with approval for use as anticancer treatment (regardless of the type of cancer) will not be permitted. Traditional Chinese medication for indications other than anticancer treatment, such as supportive care, may be administered at the discretion of the Investigator (Appendix 7).

If the administration of a nonpermitted concomitant drug becomes necessary during the study, the participant will be withdrawn from study treatment (the Sponsor may be contacted to discuss whether the study intervention must be discontinued). The participant should complete the End-of-Treatment visit and be followed for survival.

6.5.2.1 Medicines to Use with Caution

Caution should be used when administering cisplatin concomitant with the following:

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

Caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4

- 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 (e.g., rifampin)

* Not approved in Japan

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.

For additional details, refer to each chemotherapy agent label.

6.5.3 Permitted/Prohibited Procedures

Permitted Procedures

Supportive care and procedures are permitted during cCRT (e.g., feeding tube) if clinically indicated. Palliative radiotherapy may be allowed in participants who experience PD while on study after discussion with the Medical Monitor.

Prohibited Procedures

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

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

6.5.4 Other Interventions

The following nondrug therapies must not be administered during the study (or within 21 days before randomization):

- Herbal remedies with immune-stimulating properties (for example, mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin)

6.6 Dose Selection and Modification

Dose modification of M7824/placebo due to bleeding events is described in Section 6.9.5, preparation and recording of reduced doses are described in Section 6.3.2. There are no dose reductions for durvalumab. Dose reductions and modifications for chemotherapy and radiotherapy are allowed (see Section 6.10).

6.7 Study Intervention after the End of the Study

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

6.8 Special Precautions

Any treatment-emergent AE (TEAE) that is assessed as related to study treatment may require permanent or transient discontinuation of study treatment.

Single laboratory values out of the normal range that do not have any clinical correlate do not necessarily need treatment interruption. Questions or concerns with regard to management and/or follow-up of TEAEs should be discussed with the Medical Monitor.

Immune-related AEs, IRRs, anemia, TGF-β inhibition mediated skin reactions, and bleeding AEs 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 suspected irAEs, general guidance and management are provided in Section 6.9.2. Immune-related AEs are AESIs for M7824 and durvalumab.
- IRR and hypersensitivity reaction management guidance is presented in Section 6.9.1. Infusion-related reaction AEs are AESIs for M7824 and durvalumab.
- Anemia management guidance is presented in Section 6.9.4.
- TGF-β inhibition mediated skin reactions management guidance is provided in Section 6.9.3. Skin reactions are study specific AESIs for radiation in combination with M7824.
  - Additionally, skin reactions are study specific AESIs for radiation in combination with M7824. Radiation dermatitis is a significant acute and chronic adverse effect of RT. Acute reactions can have severe sequelae that impact quality of life and cancer treatment, thus prompt symptom management is advised per local standard practice. Chronic skin changes are a unique subset of adverse reactions to RT that may develop months to years following treatment and are often permanent, progressive, and potentially irreversible, as in radiation-induced fibrosis, with substantial impact on quality of life. See Table 18 for study intervention modification according to the grade of severity and see Section 6.10 for management guidelines.
- For guidance and management of bleeding AEs, see Section 6.9.5.

General guidance:

- In all cases, if ≥ 2 doses of M7824 or durvalumab are missed due to AE, the Medical Monitor should be consulted.
- In all cases, if ≥ 2 doses of chemotherapy are missed due to AE, the Medical Monitor should be consulted.
- Generally, inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks is an indication for permanent treatment discontinuation (except for use of steroids as hormone substitution).
- Persistent endocrinopathies controlled with hormone replacement therapy generally do not require permanent treatment discontinuation. However, other persistent Grade 2 treatment-related AEs that either do not resolve or improve to Grade 1 within 12 weeks after last dose of study intervention are an indication for permanent treatment discontinuation.

In general, the following applies for TEAEs related to M7824 that are not covered by the recommendations for irAE management in the current NCCN guideline available at http://www.nccn.org:

Grade 4 treatment-related TEAEs

1. Any Grade 4 treatment-related TEAEs require permanent treatment discontinuation, except:

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

Refer to the current NCCN guideline available at http://www.nccn.org for guidance on specific Grade 4 irAEs, as most require permanent treatment discontinuation.

For management of Grade 4 AEs related to radiotherapy and chemotherapy see Section 6.10.

Grade 3 treatment-related TEAE

1. Participants with any recurrent Grade 3 treatment-related AEs that recur should be permanently discontinued. Exceptions may be considered for the following after discussion with Medical Monitor:
    a. Transient Grade 3 flu-like symptoms or fever that is controlled with medical management
    b. Transient Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1 or baseline
    c. Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumors
    d. Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis
    e. Grade 3 hemoglobin decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor use
    f. Increases in Eastern Cooperative Oncology Group performance status (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).
    g. Keratoacanthoma (KA) and cutaneous squamous cell carcinoma (cSCC)
    h. Grade 3 non-tumor bleeding requiring intervention or hospitalization if alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic event, etc.).
2. Participants with persistent Grade 3 AEs (excluding endocrinopathies controlled with hormone replacement therapy) that either do not resolve or improve to Grade 1 within 12 weeks after last dose of treatment must be permanently discontinued.

See the current NCCN guideline available at http://www.nccn.org for guidance on specific Grade 3 irAEs as many require permanent treatment discontinuation, including pneumonitis and nephritis.

For management of Grade 3 AEs related to radiotherapy and chemotherapy see Section 6.10.

Grade 2 treatment-related TEAE

1. If a Grade 2 treatment-related TEAE resolves to Grade $\leq$ 1 by the day before the next infusion, study intervention may be continued.

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

Note that treatment recommendations regarding continuation, hold, or discontinuation by grade are different depending on the specific toxicity (see the current NCCN guideline available at http://www.nccn.org). Toxicity grading is assigned based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

For management of Grade 2 AEs related to radiotherapy and chemotherapy see Section 6.10.

6.9 Management of Adverse Events of Interest

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

For this study, AESIs include only the following:

- Infusion-related reactions including immediate hypersensitivity.
- Immune-related adverse events.
- TGF-β inhibition mediated skin reactions.
- Anemia.
- Bleeding AEs.
- Pneumonitis.
  Pneumonitis is an AESI for both chemoradiation and immunotherapy, and an important identified risk for durvalumab. See Section 6.9.2 for immune-related AE management and see Section 6.10 for grading and management of pneumonitis associated with cCRT.

6.9.1 Infusion-related Reactions Including Immediate Hypersensitivity

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

Infusion-Related Reactions

Infusion-related reactions are signs or symptoms experienced by participants during study intervention administration or within 1 day thereafter. An assessment for possible IRR should be triggered based on the clinical picture and temporal relationship to drug administration.

Possible IRRs are defined based on the following 2 lists of Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) and temporal relationship criteria. Events are divided into reactions versus signs and symptoms:

- Reactions include the PTs infusion-related reaction, drug-hypersensitivity, hypersensitivity, type-1-hypersensitivity, and anaphylactic reaction. These PTs should be considered when onset is during the infusion or within 1 day thereafter (irrespective of resolution).
- Signs and symptoms of infusion-related reactions include the PTs pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain, and urticaria. These PTs should be considered, if the onset occurs during or within 1 day after an infusion and resolves within 2 days.

Management of Infusion-Related Reactions

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

If an Investigator deems it 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.

Management of symptoms should follow the guidelines shown in Table 8.

Table 8 Treatment Modification Guidance for Symptoms of Infusion-Related Reactions Including Immediate Hypersensitivity

NCI-CTCAE v5.0 Grade	Treatment 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 responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop the infusion of the study intervention 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 mandated premedication for the next scheduled visit. If not improving, consider administration of glucocorticoids and stop the infusion for that day. If the participant has a second IRR Grade ≥ 2 on the slower infusion rate despite premedication, the infusion should be stopped and the Investigator may consider withdrawal of this participant from the study.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the infusion of study intervention- 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 study intervention 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.	

Immediate Hypersensitivity Reaction

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 can be found at https://www.resus.org.uk/pages/reaction.pdf.

Flu-Like Symptoms

Treatment is based on clinical assessment and at the discretion of the Investigator. 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 IV infusion.

6.9.2 Immune-related Adverse Events

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

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, and 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 list of irAEs which are important identified risks for durvalumab includes immune mediated colitis or diarrhea, hepatitis, pneumonitis, hypophysitis or hypopituitarism, nephritis, hyperthyroidism, hypothyroidism, Type I diabetes, adrenal insufficiency, rash or dermatitis, myocarditis (refer to Imfinzi® current Risk Management Plan [RMP]).

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

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

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 manifested 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.

6.9.4 Anemia

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

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

General guidance for anemia management and evaluation:

1. Participants must enter the study with Hgb values ≥ 9 g/dL; routine blood test parameters are required per the SoA (see Section 1.3).

2. All relevant hematologic testing for anemias should be done prior to a blood transfusion, if clinically feasible.

3. 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 anemia is provided in Table 9.

If participant recovers to Grade 1 anemia with a blood transfusion, suspend the next dosing until stable control of anemia is confirmed, and the underlying cause of anemia is resolved. As guidance, the Investigator should wait for at least 1 week post-transfusion to confirm stabilization. If anemia is stabilized and the dosing criteria (Hgb Grade 1 or baseline) are met 1 week after the transfusion, the Investigator can proceed to the next dosing.

Table 9 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 Vit B12 values c. Coagulation factors (PT, PTT, INR) d. Fecal occult blood testing e. Urinalysis f. Hormone panel: TSH, Erythropoietin g. Peripheral blood smear for cell morphological assessment	
Further Recommendation Based on Suspected Etiology (in Addition to 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; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RDW = red blood cell distribution width; TIBC = total iron binding capacity; and TSH = thyroid-stimulating hormone.

6.9.5 Bleeding Adverse Events

Bleeding AEs are AESIs and considered an important identified risk for M7824.

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.

For Grade 2 non-tumor bleeding, see Section 6.8 for general management of Grade 2 treatment-related TEAEs.

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 $\leq$ 1. Upon resumption of the study intervention dose should be reduced to 600 mg Q2W or corresponding volume of matching placebo if Grade 3 or severe bleeding event is observed regardless of causality with the study intervention. Preparation and recording of reduced M7824/placebo doses are described in Section 6.3.2. There are no dose reductions for durvalumab.

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

In case of rapid decrease of hemoglobin (Hgb), such as a decrease greater than 3.0 g/dL across a 2-week period, withhold the subsequent cycles of study intervention until Hgb is stabilized and do a thorough assessment of bleeding (for example, upper and lower GI endoscopy, enhancement CT etc.); if Grade 1 or greater bleeding is observed or suspected, withhold the M7824/placebo until the bleeding is resolved/controlled and resume the dose of M7824 reduced to 600 mg Q2W or corresponding volume of matching placebo. Preparation and recording of reduced M7824/placebo doses are described in Section 6.3.2. There are no dose reductions for durvalumab. Once Hgb decrease is recovered to $\leq$ Grade 1 or baseline and stably controlled, the Investigator is encouraged to communicate with Medical Monitor to re-escalate the dose. The dose of M7824/placebo may be re-escalated to full dose (M7824 1200 mg or corresponding volume for placebo) once Hgb is stabilized without further need for blood transfusion in the subsequent cycles. The timing of re-escalation may need a case-by-case decision. See Section 6.9.4 regarding stabilization of anemia.

Tumor Bleeding

Participants treated with M7824 were reported in lower frequencies, with Grade $\geq$ 3 hemorrhages including tumor bleeding. For Grade $\geq$ 2 tumor bleeding, study treatment must be held until the event recovers to Grade $\leq$ 1. Upon resumption of the study intervention dose should be reduced to 600 mg Q2W or corresponding volume of matching placebo if Grade 3 or severe bleeding event is observed regardless of causality with the study intervention. Treatment should be permanently discontinued if the Investigator considers the participant to be at risk for additional severe bleeding.

6.9.6 Other Important Potential Risks

6.9.6.1 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 TGF-β in wound healing. Management should be discussed with the Medical Monitor for participants requiring surgery on study. It is recommended to hold study intervention for approximately 4 weeks post major surgery for observation. Postoperative wound healing will be closely monitored.

6.9.6.2 Embryofetal Toxicity

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

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

6.10 Risk Management for Chemoradiation

Toxicities of cCRT may arise to different degrees at different timepoints in various subpopulations and scenarios. First, with regards to chemotherapy, the presence of important variables such as age, performance status, and preexisting comorbidities plays a large role in how well the participants can tolerate cCRT. Some participants may also benefit from chemotherapy alterations in doses, intervals or even specific compounds and regimens. Second, from the RT perspective, because advanced radiotherapy techniques have developed, and image-guided RT has now become the standard of care, fewer RT-related toxicities are expected (Verma 2017). Risk management of chemoradiation side effects mainly includes early detection, study intervention modification and prompt toxicity management. Based on NCCN guidelines for the treatment of Stage III NSCLC, RT interruptions and dose reductions for manageable acute toxicities should be avoided by employing supportive care.

Management and workup must be done in accordance with labeling instructions and local institutional guidelines and in discussion with the Medical Monitor. In case of clear correlation of AEs and cCRT, treatment with either M7824 or durvalumab should be considered and discussed with the Medical Monitor.

Carboplatin/Paclitaxel

See Table 10 and Table 11 for guidelines for withholding study intervention for hematologic and main nonhematologic toxicities, respectively. Dose modifications (dose delays and dose

reductions) for toxicities not listed below should be made in accordance with labeling instructions and local institutional guidelines. Discontinuation of chemotherapy due to AEs should also be done in accordance with the chemotherapy label and local institutional practice and discussed with the Sponsor.

When study intervention is withheld for hematologic toxicities, repeat CBC weekly (or more frequently if clinically indicated) and resume chemotherapy based on Table 10. Doses of carboplatin/paclitaxel that are missed will not be made up and will be documented. If study intervention must be withheld for greater than two consecutive weeks, consider withholding carboplatin/paclitaxel permanently for the duration of concurrent radiotherapy.

A change of > 10% in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose.

If a Grade 2 anemia does not resolve to Grade $\leq$ 1 by the last day of the current cycle but is manageable and/or not clinically relevant, the Medical Monitor should be consulted to assess if it is clinically reasonable to administer the following infusion.

Hypersensitivity reactions: Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment. Angioedema, and generalized urticaria have occurred in 2% to 4% of patients receiving paclitaxel in clinical studies. All participants receiving paclitaxel should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists at least 30 minutes prior paclitaxel administration. Participants who experience severe hypersensitivity reactions to paclitaxel should not be re-challenged with the drug.

Table 10 Grading and Guidelines for Dose Modifications of Carboplatin/Paclitaxel Related Hematologic Adverse Events

Carboplatin/Paclitaxel Related Hematologic Adverse Events (CTCAE v5.0)	Paclitaxel	Carboplatin
Neutropenia		
G1 (1500-1999/mm^3)	No change	No change
G2 (1000-1499/mm^3)	No change	No change
G3 (500-999/mm^3)	Withhold therapy	Withhold therapy
G4 (< 500/mm^3)	Withhold therapy	Withhold therapy
Neutropenic fever ANC < 1000/mm^3 with a single temperature of > 38.3°C (101°F) or sustained temperature of ≥ 38°C (100.4°F) for more than one hour	Withhold therapy	Withhold therapy
Thrombocytopenia		
G1 (< LLN-75,000/mm^3)	No change	No change
G2 (50,000-74,999/mm^3)	Withhold therapy	Withhold therapy
G3 (25,000-49,999/mm^3)	Withhold therapy	Withhold therapy
G4 (< 25,000/mm^3)	Withhold therapy	Withhold therapy
ANC = absolute neutrophil count Reference: Bradley 2015 Other hematologic toxicities: There will be no dose modifications/reductions for changes in leucopenia and lymphopenia. If study intervention is withheld for greater than two consecutive weeks, permanent discontinuation should be considered. Benefit of resuming treatment after withholding > 2 weeks must be evaluated on a case by case basis and discussed with the Medical Monitor		

Table 11 Dose Modifications of Carboplatin/Paclitaxel Related Main Nonhematologic Adverse Events

Carboplatin/Paclitaxel Related Main Nonhematologic Adverse Events (CTCAE v5.0)[a, b]	Paclitaxel	Carboplatin
Paronychia G2	No change	No change
Neuropathy		
≤ G1	No change	No change
G2	Hold therapy until resolve to ≤ G1. Restart at full dose	No change
G3	Discontinue therapy	No change
Other nonhematologic toxicities		
G3	Hold therapy until resolve to ≤ G2	Hold therapy until resolve to ≤ G2

[a] Maintain dose for the ≤ G2 nonhematologic toxicities not listed in this Table. Follow the guidelines listed in this Table for neuropathy.

[b] RT should continue to be delivered for ≤ Grade 3 nonhematologic toxicities in or outside the radiation treatment field. RT should be withheld for all Grade 4 nonhematologic toxicity in or outside the treatment field and resumed only when toxicity is ≤ Grade 2. If study intervention is withheld for greater than two consecutive weeks, permanent discontinuation should be considered. Benefit of resuming treatment after withholding > 2 weeks must be evaluated on a case by case basis and discussed with the Medical Monitor.

Cisplatin/Etoposide

See Table 12 for predosing considerations for cisplatin. Adequate hydration must be ensured before and after cisplatin infusion to reduce the risk of nephrotoxicity.

Table 12 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 IV 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.
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 1500 cells/mm^3. Dose modifications for subsequent administrations will be based on the neutrophil and platelet nadir from the preceding cycle (see Table 13). According to NCI-CTCAE v5.0 febrile neutropenia (FN) is defined as ANC < 1000/mm3 and a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than one hour. FN treatment should be done per local practice and reported in eCRF. FN Prophylaxis: According to NCCN guidelines for the use of myeloid growth factors (v1.2018)[d], primary prophylaxis with G-CSF in order to reduce the risk of FN is not recommended. Secondary prophylaxis with G-CSFs should be considered and the risk benefit associated with their use must be carefully evaluated. Investigators must be aware that the use of G-CSF during chemoradiation is associated with 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 must be performed prior to each cisplatin dosing and during the study intervention.

ANC= Absolute neutrophil count, CSF = colony stimulating factor, ESMO = European Society for Medical Oncology, FN = febrile neutropenia, G-CSF = granulocyte-colony stimulating factor, IV = intravenous, MASCC = Multinational Association of Supportive Care in Cancer, NCCN = National Comprehensive Cancer Network, NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, SmPC = summary of product characteristics.

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

[b] NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines®] - Antiemesis, version 1.2019

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

[d] NCCN guidelines Myeloid growth factors version 1.2018

See Table 13 and Table 14 for dose modifications of cisplatin/etoposide in case of hematologic and nonhematologic adverse events, respectively. For toxicities ≥ Grade 3, treatment should be delayed until resolution to less than or equal to the patient's baseline value before resuming study intervention at a dose reduction. Dose modifications (dose delays and dose reductions) for toxicities not listed above should be made in accordance with labeling instructions and local institutional guidelines. Discontinuation of chemotherapy due to AEs should also be done in accordance with the chemotherapy label and local institutional practice and discussed with the Sponsor.

When study intervention is withheld for hematologic toxicities, repeat CBC weekly (or more frequently if clinically indicated) and resume chemotherapy based on Table 13. Treatment should be resumed if on the day of the administration platelet count is $\geq 100\times10^9$/L and neutrophil count is 1.5×10^9/L, per approved product label or standard practice. Doses of cisplatin/etoposide that are missed will not be made up and will be documented.

Table 13 Dose Reductions for Cisplatin/Etoposide-related Hematologic Adverse Events

Cisplatin/Etoposide-related Hematologic Adverse Events		Cisplatin	Etoposide
Neutrophils	Platelets		
> 0.5 x10^9/L	> 50 x10^9/L	100% of previous dose	100% of previous dose
< 0.5 x10^9/L	≥ 50 x10^9/L	75% of previous dose	75% of previous dose
< 1.0 x10^9/L with fever ≥ 38.5°C	≥ 50 x10^9/L	75% of previous dose	75% of previous dose
Any count	< 50 x10^9/L	50% of previous dose	75% of previous dose
Any count	≤ 25 x10^9/L < 50 x10^9/L with bleeding	50% of previous dose	50% of previous dose

Table 14 Dose Reductions for Cisplatin/Etoposide-related Nonhematologic Adverse Events

Cisplatin/Etoposide-related Nonhematologic Adverse Events (CTCAE v5.0)	Cisplatin	Etoposide
Hepatic/Transaminase elevation, G3-G4	75% of previous dose	75% of previous dose
Mucositis, G3-G4	100% of previous dose	75% of previous dose
Esophagitis, G3-G4	See Table 18	See Table 18
Neurotoxicity/Ototoxicity, G2	50% of previous dose	100% of previous dose
Neurotoxicity/Ototoxicity, G3	Discontinue	75% of previous dose
Neurotoxicity/Ototoxicity, G4	Discontinue	Discontinue
Other G1-G2	100% of previous dose	100% of previous dose
Other G3-G4	75% of previous dose	75% of previous dose

Cisplatin/Pemetrexed

See Table 15 to Table 17 for dose modification of cisplatin/pemetrexed in case of hematologic and nonhematologic adverse events. Dose modifications (dose delays and dose reductions) for toxicities not listed above should be made in accordance with labeling instructions and local

institutional guidelines. Discontinuation of chemotherapy due to AEs should also be done in accordance with the chemotherapy label and local institutional practice and discussed with the Sponsor. When study intervention is withheld for hematologic toxicities, repeat CBC weekly (or more frequently if clinically indicated) and resume chemotherapy based on Table 15. Doses of cisplatin/pemetrexed that are missed will not be made up and will be documented.

Table 15 Dose Modifications for Pemetrexed and Cisplatin Based on Hematologic Toxicities

Day	ANC ($x 10^9$/L)		Platelet ($x 10^9$/L)	Dose for Both Pemetrexed and Cisplatin (mg/m^2)
On Day 1 of the subsequent cycle	≥ 1.5	and	≥ 100	100% of previous dose
On Day 1 of the subsequent cycle	< 1.5	or	< 100	delay 1 week
After 1-week delay	≥ 1.5	and	≥ 100	100% of previous dose
After 1-week delay	< 1.5	or	< 100	notify principal systemic therapy Investigator or his/her designee to determine if further chemotherapy is possible
Any time	≥ 0.5	and	≥ 50	100% of previous dose
Any time	< 0.5	and	≥ 50	75% of previous dose
Any time	Any	and	< 50	75% of previous dose
Any time	ANC < 1.0 with fever defined as Fever is defined as temperature ≥ 38.5°C on 1 reading.			75% of previous dose
Any time	Platelets < 50 with bleeding regardless of ANC			50% of previous dose

Reference: Senan 2016
ANC = absolute neutrophil count

Table 16 Dose Modifications for Pemetrexed and Cisplatin Based on Nonhematologic Toxicities

Day	Events	Dose of Pemetrexed (mg/m^2)	Dose for Cisplatin (mg/m^2)
On Day 1 of the subsequent cycle	CrCl ≥ 45 mL/min	100% of previous dose	100% of previous dose
On Day 1 of the subsequent cycle	CrCl < 45 mL/min	delay 1 week	delay 1 week
If after 1-week delay	CrCl ≥ 45 mL/min	100% of previous dose	100% of previous dose and increase pre- and post-cisplatin hydration
If after 1-week delay	CrCl < 45 mL/min	notify principal systemic therapy Investigator or his/her designee to determine if further chemotherapy is possible	notify principal systemic therapy Investigator or his/her designee to determine if further chemotherapy is possible
Any	CTCAE Grade 3 or 4 nausea and/or vomiting	100% of previous dose and should be managed with appropriate changes in antiemetic regimen	100% of previous dose
Any	CTCAE Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose
Any	CTCAE Grade 3 esophagitis[a]	hold at the physician's discretion	hold at the physician's discretion
Any	CTCAE Grade 4 esophagitis[b]	hold pemetrexed	hold cisplatin
Any	CTCAE Grade 3 or 4 diarrhea or any grade requiring hospitalization	75% of previous dose	75% of previous dose
Any	Other CTCAE Grade 3 or 4	75% of previous dose	75% of previous dose

Reference: Senan 2016

CrCl = creatinine clearance; CTCAE = Common Terminology Criteria for Adverse Events.

[a] Grade 3 esophagitis will occur in a significant number of patients toward the end of radiation therapy. For participants who experience this event earlier in the course of their treatment than anticipated, the advice would be to hold chemotherapy and assess at weekly intervals. If symptoms do not progress at the time of assessment,chemotherapy can be resumed at 75% of previous dose for both drugs. If study intervention is withheld for greater than two consecutive weeks, permanent discontinuation should be considered. Benefit of resuming treatment after withholding > 2 weeks must be evaluated on a case by case basis and discussed with the Medical Monitor

[b] Grade 4 esophagitis results in holding chemotherapy until toxicity resolves to ≤ Grade 2, and then chemotherapy may be resumed at 75% of previous dose for both drugs. If study intervention is withheld for greater than two consecutive weeks, permanent discontinuation should be considered. Benefit of resuming treatment after withholding > 2 weeks must be evaluated on a case by case basis and discussed with the Medical Monitor

Table 17 Dose Modifications for Cisplatin Based on Neurotoxicity

Neurotoxicity CTCAE (v5.0)	Dose for Pemetrexed (mg/m^2)	Dose for Cisplatin (mg/m^2)
Grade 0 or 1	100% of previous dose	100% of previous dose
Grade 2	100% of previous dose	50% of previous dose
Grade 3 or 4[a]	discontinue pemetrexed	discontinue cisplatin

Reference: PROCLAIM protocol
CTCAE = Common Terminology Criteria for Adverse Events.
[a] At the discretion of the attending physician, participants experiencing Grade 3 neurologic toxicity as a transient ischemic attack that has completely resolved may not require dose reduction or discontinuation.

Thoracic Radiation Therapy

IMRT is reported to be associated with fewer observed toxicities and will be used in this study (see Section 4.2).

The expected acute onset side effects of radiation therapy are reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, pneumonitis and esophagitis (Verma 2017). Prompt recognition of signs/symptoms & its early management accordingly to local standard practice will be beneficial.

The late onset side effects can be but not limited to radiation-induced myocarditis or transverse myelitis, although rarely occur at doses lower than 50 Gy. Radiographic evidence of radiation changes in organs compactly situated in the thoracic cavity. Lung with subsequent lung fibrosis can occur in lung tissue irradiated at $\geq$ 20 Gy usually within the first 6 months after initiation of treatment. It is essential to spare as much normal lung as possible to avoid symptomatic lung injury.

See Table 18 for study intervention modifications for nonhematologic toxicities in RT field.

Table 18 Treatment Modifications for Nonhematologic Adverse Events in RT-Field

In field	CTCAE v5.0	RT	Chemotherapy
Esophagus/pharynx (on day of chemotherapy)	Grade 2	No change	No change
Esophagus/pharynx (on day of chemotherapy)	Grade 3	No change or hold ≤ 5 days	Hold study intervention until ≤ G2
Esophagus/pharynx (on day of chemotherapy)	Grade 4	Hold study intervention until ≤ G2	Hold study intervention until ≤ G2
Pulmonary	Grade 3	Hold study intervention until ≤ G2	Hold study intervention until ≤ G2
Pulmonary	Grade 4	Discontinue	Hold study intervention until ≤ G2
Skin	Grade 3	No change	No change
Skin	Grade 4	Hold study intervention until ≤ G2	Hold study intervention until ≤ G2
Reference: ROTG 06 17 protocol. If study intervention is withheld for greater than two consecutive weeks, permanent discontinuation should be considered. Benefit of resuming treatment after withholding > 2 weeks must be evaluated on a case by case basis and discussed with the Medical Monitor			

When study intervention is withheld, participants should be monitored weekly (or more frequently if clinically indicated). Chemotherapy and RT should be resumed based on Table 18.

Detailed description, staging and management of acute esophageal toxicity, pneumonitis, lung fibrosis and cardiotoxicity is provided below.

Acute esophageal toxicities

Acute esophageal toxicities (AET) include esophagitis, odynophagia, and dysphagia. Esophageal complaints are common with combined modality therapy. AET does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided early symptom management, oral intake is sufficient to maintain hydration and nutritional status. Participants should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Acute esophagitis may persist for 4 to 6 weeks and the severity should be closely monitored until resolution and discussed as deemed necessary.

Refer to Table 19 for the diagnosis and grading of esophagitis.

Table 19 Diagnosis and Grading of Esophagitis

Scale	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE v5.0	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
CTCAE=Common Terminology Criteria for Adverse Events, TPN = total parenteral nutrition.					

Study intervention should be interrupted for Grade 3 or greater dysphagia or odynophagia. AET, which typically can occur within 2 weeks of the initiation of study intervention and manifests as dysphagia, odynophagia, reflux symptoms, etc. should be pharmacologically managed with the following approach and should be initiated at the first signs or symptoms of esophageal toxicity. For the pharmacologic management consider the following:

- Ketoconazole 200 mg PO* q day OR Fluconazole 100 mg PO q day until the completion of radiation

  * No oral formulation is approved in Japan

Mixture of: 2% viscous lidocaine: 60 cc; Mylanta (not available in Japan): 30 cc; Sucralfate (1 gm/cc): 10 cc. Take 15-30 cc PO q3-4 hrs as needed. (Contraindications: patients on Dilantin [product name in Japan: Aleviatun], Cipro [product name in Japan: Ciproxan], Digoxin). For more detailed information on drug-drug interactions with sucralfate, refer to Sulochana 2016.

- Ranitidine 150 mg PO BID (or other H2 blocker or a proton pump inhibitor such as omeprazole) until the completion of radiation
- Grade 4 esophagitis: hold RT and chemotherapy until Grade 2 or less. (See also Table 18)

Pneumonitis

Acute and late onset pneumonitis are important side effects seen with cCRT. Radiation pneumonitis occurs as a result of the sensitivity of normal lung parenchyma to RT and it is typically thought to be treatment limiting and life threatening. The risk of developing radiation pneumonitis is directly related to the volume of irradiated lung, the amount of radiation given, and the use of concurrent chemotherapy. In a recent review including over 6000 patients from several clinical studies with CRT using either cisplatin/etoposide or carboplatin/paclitaxel, the rate of Grade 3 to 4 pneumonitis was reported to be similar between the two regimens (12% vs 9%; P=0.12, respectively) (Steuer 2017). In the PROCLAIM study, the incidence of Grade 2 pneumonitis was significantly higher in patients treated with cisplatin/pemetrexed followed by pemetrexed. Grade 3 to 4 events were observed in less than 3% of patients treated with cisplatin/pemetrexed followed by pemetrexed or cisplatin/etoposide followed by two cycles of consolidation platinum-based doublet chemotherapy (Senan 2016). Additional risk factors include comorbid lung disease, poor baseline pulmonary function testing, and performance status. Symptoms of radiation pneumonitis, including low-grade fever, congestion, dry cough, pleuritic chest pain, and a sensation of chest

fullness, usually develop 1 to 3 months after completion of radiation therapy. See Table 20 for diagnosis and grading.

Table 20 Diagnosis and Grading for Pneumonitis

Scale	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE v5.0	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
ADL=Activities of Daily Living, CTCAE=Common Toxicity Criteria for Adverse Events					

Pneumonitis has also been reported in patients treated with anti-PD-(L)1 inhibitors, therefore, pneumonitis occurring during cCRT must be managed as irAE according to Section 6.9.2 as it would be difficult to identify the main driver of this toxicity. Therefore, pneumonitis is study specific AESI due to combination with M7824.

Increased lung toxicity in Japanese patients with NSCLC treated with immunotherapy has been reported compared to non-Japanese patients (Vansteenkiste 2017). The safety of cCRT plus M7824 in Japanese participants will be first investigated in 12 Japanese participants in the safety run-in part of the study. As an additional safety measure, serum markers including KL-6, SP-A and SP-D will be measured in Japanese participants enrolled in Japan for potential early detection of pneumonitis. Increases in these markers are not necessarily indicators of pneumonitis or interstitial lung disease (ILD). Therefore, if clinically indicated, further investigation such as repeated blood tests and/or chest CT scan should be performed for confirmatory diagnosis. Treatment decisions should be discussed with Medical Monitor and based on confirmatory diagnosis.

Pulmonary Fibrosis

Pulmonary fibrosis is usually observed as a late complication of CRT. In summary:

- Many cases are asymptomatic at onset and early fibrotic alteration in lung tissue with minimal changes can be difficult to distinguish from inflammatory changes in the lung.
- Symptomatic cases often involve high chronic inflammation characterized by high levels of circulating platelet-derived and basic fibroblast growth factor expressed after initial acute inflammation. This leads to fibroblast proliferation and migration, the release of TGF-β (major profibrotic molecule), along with collagen deposition in any histologic space of the irradiated lung, including vascular and alveolar compartments; this can lead to ventilation-perfusion mismatch and result in worsening of pulmonary function (or even functional status) as a primary symptom.
- Other symptoms may be similar to acute-radiation pneumonitis, including nonproductive cough and dyspnea, although these symptoms are generally more chronic in nature. Owing to

the pathophysiologic time course, symptoms are not seen until several months after RT and may continue to progress for years after therapy. Radiographic evidence of radiation-induced changes and subsequent fibrosis of the lung may occur within lung volumes receiving ≥ 20 Gy.

Radiation can mainly cause 2 types of lung damage. Radiation pneumonitis typically occurs 2-6 months after completion of RT and is frequently followed by radiation fibrosis that usually becomes evident between 6 and 12 months (Vujaskovic 2000, Morgan 1995). Depending on the study assessments, the incidence of radiation fibrosis has been found to be variable, ranging from 1 to 40% (Kong 2005, Mehta 2005, Niezink 2016). Integrated radiological and clinical data are used for the diagnosis and the severity of lung damage. It is essential to spare as much normal lung as possible in order to avoid acute and long-term symptomatic lung injury. See Table 21 for diagnosis and grading. CCI

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Table 21 Diagnosis and Grading for Pulmonary Fibrosis

Scale	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE v5.0	Mild hypoxemia; radiologic pulmonary fibrosis	Moderate hypoxemia; evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25–50%	Severe hypoxemia; evidence of right-sided heart failure; radiographic pulmonary fibrosis > 50–75%	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis > 75% with severe honeycombing	Death
Abbreviations: CTCAE=Common Toxicity Criteria for Adverse Events (Version 5.0).					

Cardiotoxicity

There are many forms of RT-induced cardiac toxicities and usually occur as late onset adverse events. Radiation can affect the pericardium, muscle, the electrical conduction system, valves and

vasculature, among other structures. Mechanistically, the effects of RT on vasculature may be most important for pathophysiologic correlations of heart toxicity. The effects of RT on small vessels, regardless of location, are that of fibrosis (possibly preceded by some level of chronic inflammation) and endothelial injury (potentially a partially obliterative endarteritis phenotype). This not only can predispose to arterial disease from preexisting causes (e.g. lipid dysregulation and atherosclerosis), but is also an independent risk factor for chronic ischemia and future cardiac events. In event of cardiotoxicity, cardiologist should be consulted and managed per local guidance.

6.11 Adverse Drug Reactions Requiring Treatment Discontinuation

Adverse drug reactions (ADR) are defined in this study as any AEs related to study treatment assessed by the Investigator and / or Sponsor. Serious adverse reactions (SARs) 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.

Details of management of adverse drug reactions including permanent treatment discontinuation should follow the following sections:

- For suspected irAEs, irAE management and guidance in Section 6.9.2.
- Infusion-related reactions and hypersensitivity reactions guidance in Section 6.9.1.
- Anemia guidance in Section 6.9.4
- Bleeding adverse event guidance in Section 6.9.5
- Guidance and management for potentially TGF-β inhibition mediated skin reactions are discussed in Section 6.9.3
- Guidance and management for radiotherapy and chemotherapy AEs are discussed in Section 6.10.

For general guidance, refer to section 6.8.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

7.1.1 Permanent Discontinuation

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

- Participants with progression per RECIST 1.1 and subsequent confirmation with the exception that participant may continue past the determination of PD if the ECOG PS has remained stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment. See Section 4.1.1 for study intervention beyond progression. In case of premature withdrawal

from the study intervention for reasons other than PD, the participants will be asked to attend scheduled visits including tumor assessment and other assessments as planned until confirmed PD, End of Study or death.

- The participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons (e.g., disruption of operations due to natural disasters, interruption of laboratory or facility accreditation, participant moving to another country, resignation of key staff).
- Significant clinical deterioration (clinical progression), defined as new symptoms that are deemed by the Investigator to be clinically significant or significant worsening of existing symptoms.
- Unacceptable toxicity (See Section 6.8 for additional details)
- Therapeutic failure requiring urgent additional or alternative anticancer treatment.
- Occurrence of AEs resulting in the permanent discontinuation of the study intervention being desired or considered necessary by the Investigator and/or the participant (see Sections 6.8, 6.9, and 6.10). Participants who experience AEs are allowed to skip up to 3 consecutive doses of M7824, placebo, or durvalumab at any time during the entire study intervention. In case participants recover from AEs within the allowed time (up to 3 doses of M7824, placebo, or durvalumab) and are able to resume study intervention, they will not be withdrawn from study intervention. Treatment may be resumed in participants who have experienced an AE with a prolonged dose hold (> 3 consecutive doses) and in the opinion of the Investigator will benefit from restarting treatment. Such cases must be discussed with the Medical Monitor prior to resuming treatment. See Section 6.9.5 for specific guidance on bleeding adverse events, for which dose reductions may be appropriate.
- Occurrence of pregnancy in the participant.
- Use of a prohibited concomitant drug, as defined in Section 6.5.2, where the predefined consequence is withdrawal from the study intervention if considered necessary by the Investigator or the Sponsor.
- Noncompliance (See Section 6.4)

In case of withdrawal from study intervention the assessments scheduled for this visit should be performed, if possible with focus on the most relevant assessments.

7.1.2 Rechallenge

Rechallenges in terms of treatment re-initiation (post discontinuation) are not allowed in this study.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time, at his/her own request (i.e., withdrawal of consent) 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 SoA (Section 1.3). The SoA 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 will document this in the site study records.

In case of participant discontinuation/withdrawal from the study:

- The appropriate electronic case report forms (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, patient reported outcomes questionnaires, 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.

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7.3 Lost to Follow-Up

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

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

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

- Should the participant continue to be unreachable, he/she will be deemed lost to follow-up.

8 Study Assessments and Procedures

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

8.1 Efficacy Assessments and Procedures

Contrast-enhanced computed tomography (CT) of chest/abdomen and pelvis covering the area from the superior extent of the thoracic inlet to the symphysis pubis is the first choice of imaging modality to assess treatment efficacy. The CT scan of the pelvis may be omitted for radiation protection reasons if it is not part of the standard of care and CT of the abdomen includes the entirety of the liver and both adrenal glands, as well as all other known sites of disease. If a participant cannot receive iodinated contrast, or if regional radiation regulations prevent full CT scan, magnetic resonance imaging (MRI) of the same area, using macrocyclic gadolinium enhancement 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. The +5 days end of cCRT visit window does not apply to the tumor assessment at this timepoint.

A brain CT/MRI (MRI preferred) scan is required at Baseline, at the end of cCRT and during study intervention after cCRT every 12 weeks and as clinically indicated in case of development of new specific symptoms. In case of suspected skin metastasis during study intervention a biopsy must be performed to confirm PD. The same modality, and preferably the same scanner, should be used per participant throughout the study.

Investigators will read and interpret some or all CT / MRI data and treatment decisions will be made by the treating Investigator based on Investigator tumor assessments. Tumor responses to study intervention assessed according to RECIST 1.1 by the Investigator will be documented in the eCRF (all measurements should be recorded in metric notation). Response will be defined according to RECIST 1.1 (refer to RECIST 1.1 instructions in Appendix 8). As per RECIST 1.1 criteria, tumor lesions situated in a previously-irradiated area, or in an area subjected to other loco-regional therapy are not usually considered measurable, however, excluding measurable target lesion(s) within the radiation field is not justified for patients with Stage III NSCLC. In fact, participants in this study will all receive cCRT as SoC treatment and tumor assessments will include irradiated lesion(s). Localized post-radiation changes which affect lesion sizes may occur and there may be high levels of necrosis/fibrosis with little or no active tumor in recently irradiated lesions. However, accepting these limitations in this patient population with prior curative radiation treatment, irradiated lesions may be considered measurable and selected as target lesions providing they fulfil the other criteria for measurability.

Baseline scans are taken within 21 days (ideally, within 14 days) prior to randomization. All the scans performed at Baseline, unless otherwise specified in the SoA, 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 scans during-study intervention are to be repeated using the same method at the subsequent assessment time points.

Participants will be evaluated every 8 weeks with radiographic imaging of chest, abdomen, and pelvis, to assess response to study intervention for up to 24 months after the participant's first dose unless progression or withdrawal from the study whichever occurs first. Subsequent scans will be done every 8 to 12 weeks up to progression, start of new treatment or death. To evaluate tumor volume shrinkage, and radiomic features of images in participants, radiomics analysis of images for digital features potentially predictive of prognosis and/or future treatment benefit will only be performed retrospectively if deemed appropriate.

In the case of a PR or CR, a confirmatory CT or MRI scan should be performed at the scheduled 8-week interval or no sooner than 4 weeks from the assessment. After PD, confirmation of PD is also required and should be performed preferably and if clinically feasible, at the regularly scheduled 8 weekly assessment intervals, but no sooner than 4 weeks after the initial documentation. For investigational assessments, the date of progression will be determined based on the earliest of the RECIST assessment/scan dates of the component that indicates progression.

Diagnosis of disease progression based solely on nodal enlargement within 8 weeks of coronavirus vaccination should be made with extreme caution, particularly if in axillary and/or supraclavicular nodes on the ipsilateral side to vaccination, and verified with hindsight if possible. Participants who start subsequent treatment should be monitored for response to that treatment according to RECIST 1.1. Tumor scans should be performed following local clinical practice for monitoring disease status on subsequent lines of therapy. The study team encourages and requests scans to be performed every 8 to 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 in the eCRF. A participant's progression may involve the following: objective radiological progression

or death due to advancing disease. This should be documented every 8 to 12 weeks until initiation of the next treatment, withdrawal of consent, or death.

For participants who discontinue study intervention due to toxicity or a reason other than radiological confirmed PD, objective tumor assessments should be continued every 8 weeks for up to 24 months from the participant's first dose or until progression, start of new treatment or death, whichever occurs first.

Administration of M7824 or durvalumab can continue beyond PD as outlined in Section 4.1.1

Participants will be monitored for survival every 12 weeks in the Long-term Follow-up period. Participants will be contacted shortly before the data cut-off for the primary analyses to provide complete survival data.

Lung function is also assessed as described in Section 1.3 to evaluate the potential changes induced by M7824 when administered with cCRT and after cCRT compared with cCRT followed by durvalumab. High-resolution CT scans are as scheduled in Section 1.3 and may be evaluated for Radiation Induced Pulmonary Fibrosis (RIPF) by an Independent review committee as outlined in the HRCT Charter.

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, adverse events (AEs), physical examination findings, vital signs, electrocardiograms, 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.

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems at Screening. Height and weight will also be measured and recorded (see Section 1.3).

Subsequent focused physical examinations to be performed as per local standard practice and as clinically indicated. Due to the increased risk of pneumonitis with cCRT and M7824 or durvalumab, performing thorax examination at each visit and according to the SoA is required (see Table 1 and Table 3).

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

8.2.2 Vital Signs

Temperature, pulse rate, respiratory rate, resting pulse oximetry, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed in semi-supine position 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 must be reported in the eCRF.

8.2.3 Electrocardiograms

A single 12-lead ECG will be obtained as outlined in the SoA.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 5, at the time points listed in the SoA (see Section 1.3). All samples should be clearly identified.

Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.

The tests will be performed by local laboratory.

The Sponsor will 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 designated organization.

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

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

8.3 Adverse Events and Serious Adverse Events

The definitions of an Adverse Event (AE) and a Serious Adverse Event (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 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

AEs are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 and are assessed for their outcome during the Long-term Follow-up. All SAEs ongoing at the End-of-Treatment Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is given in Appendix 4.

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 IEC/IRB that approved the study.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the

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

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

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

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

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

8.3.5 Pregnancy

Only pregnancies the Investigator considers to be related to the study intervention (e.g., resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 must be recorded in the AE page/section of the CRF 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.

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

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

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

8.4 Treatment of Overdose

For this study, any dose of immunotherapy greater than 2 times more than the planned dose administered within a 24-hour time period will be considered an overdose.

For chemotherapeutic agents used in this study, any single dose exceeding 20% of recommended chemotherapy dose regimen will be considered overdose. For radiation, refer to the Radiotherapy Guidelines that will be provided to the site. Prior to initiating RT, the radiation treatment plan must be submitted by the Investigator to the radiation oncology vendor for review. Consult will Medical Monitor as deemed necessary.

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

In event of overdose, infusion should be discontinued, and participants should be observed closely for any signs of toxicity. Supportive treatment should be provided if clinically indicated.

If an AE occurs resulting from overdose, it should follow SAE reporting criteria as indicated in Appendix 4.

The Sponsor does not recommend specific treatment for an overdose.

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

8.5 Pharmacokinetics

PK samples will be collected according to SoA (Table 1 and Table 3).

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

- C_{eoi}
- C_{trough}

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

The following PK parameters will be calculated, when appropriate:

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

Whole blood samples of approximately 3.5 mL will be collected for measurement of serum concentrations of investigational medicinal product, as specified in Table 1 and Table 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 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.

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

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

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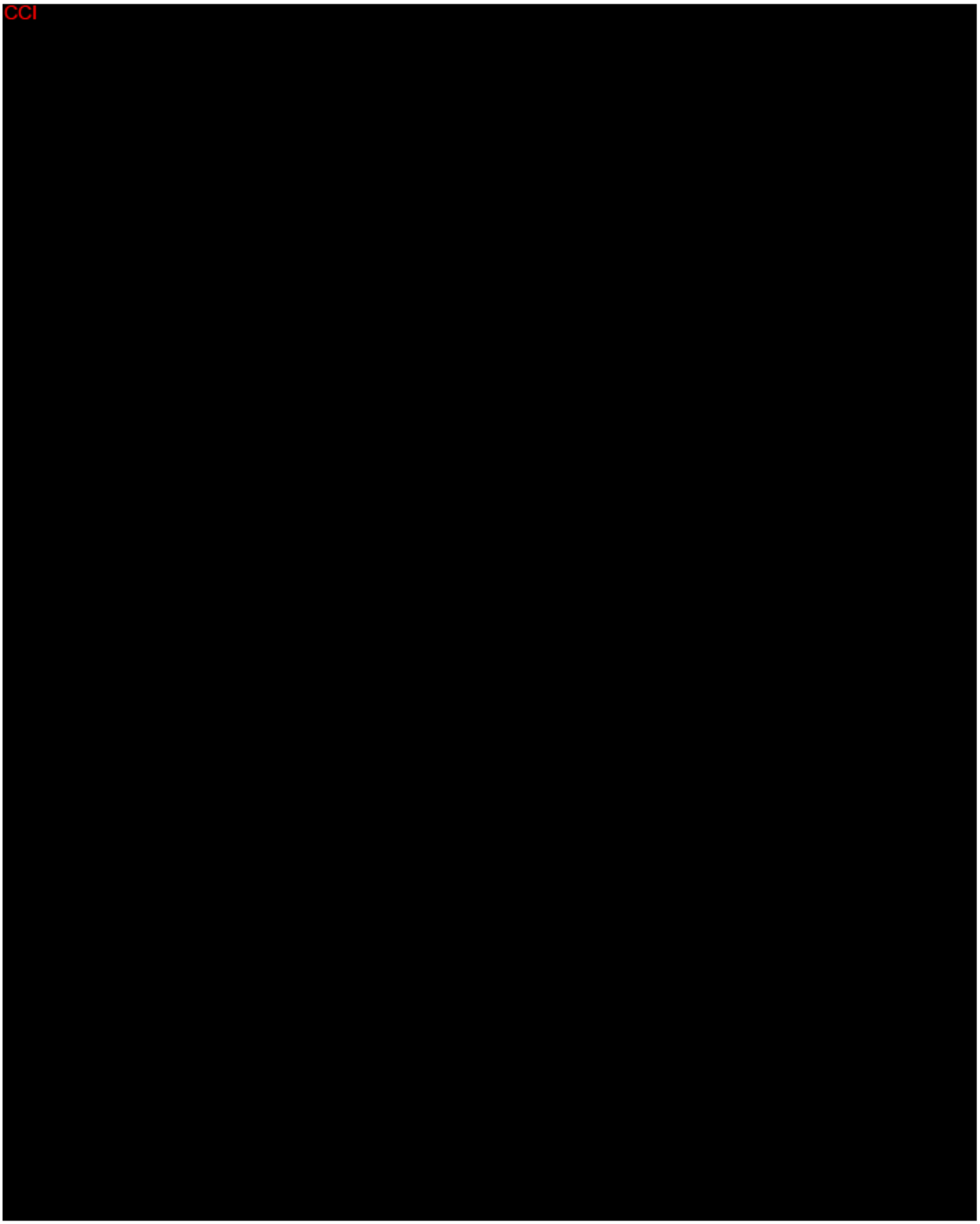
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8.8 Immunogenicity Assessments

Whole blood samples of approximately 5 mL will be collected for detection of antibodies against M7824 in serum, as specified in Table 1 and Table 3. Samples will be collected prior to M7824, placebo or durvalumab administration on the same Study Day.

The detection of antibodies to M7824 will be performed using a validated method with tiered testing of screening, confirmatory and titration. Confirmed positive antibodies will be tested for the presence of neutralizing antibodies when the methods are validated and may be further characterized.

Remaining samples collected for analysis of anti-M7824 antibodies may also be used to evaluate drug concentration or exploratory biomarkers during or after the study.

Details on processes for collection and shipment of these samples will be in Laboratory Manual. Retention time and possible analyses of samples after the End of Study are specified in the respective ICF.

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9.3 Populations for Analyses

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

For purposes of analysis, the analysis populations are defined in Table 23.

Table 23 Analysis Populations

Analysis Population	Description
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's randomization and study intervention status in the study.
Full analysis set (FAS)	All participants, who were randomized.
Safety (SAF-nJ [non-Japanese])	First 30 non-Japanese participants who were administered any dose of any study intervention.
Safety (SAF-J [Japanese])	First 12 Japanese participants who were administered any dose of any study intervention.
Safety (SAF)	All participants, who were administered any dose of any study intervention.
PK	All participants who complete at least 1 infusion of M7824, and who provide at least 1 sample with a measurable concentration of M7824.
ADA	All participants who complete at least 1 infusion of M7824 and have at least one valid ADA result. All ADA analyses will be based on this analysis set.

9.4 Statistical Analyses

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

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

In general, continuous variables will be summarized using number (n), mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. Proportions are calculated based on the number of participants in the analysis set of interest, unless otherwise specified in the IAP. If not explicitly stated, no imputation is used in the analyses. All safety and efficacy endpoints will be summarized by treatment arm. The Japanese safety cohort will be summarized separately.

9.4.1 Efficacy Analyses

All analyses on efficacy endpoints are primarily done on the full analysis set (FAS). The framework in Table 24 below describes the analysis of Primary and Secondary endpoints.

Stratified analyses will use the chemotherapy regimen and PD-L1 expression in tumor cells (< 1% versus ≥ 1%, retrospective test results for participants from the safety run-in part and prospective test results for participants in the expansion part) as stratification factors.

Table 24 Efficacy Endpoints and Statistical Analysis Methods

Endpoint	Statistical Analysis Methods

Primary Endpoint
PFS according to RECIST 1.1 as assessed by the Investigator
	• FAS population is used for analyses of the primary endpoint
	• Estimation of the treatment effect (HR θ) by a Cox proportional hazards model (stratified by chemotherapy regimen and PD-L1 expression, each stratum defines separate baseline hazard function); ties handled by replacing the proportional hazards model by the discrete logistic model; 95% Confidence intervals for the hazard ratio will be calculated
	• Progression-free survival is defined as the time from randomization to the date of the first documentation of objective PD as assessed by the Investigator according to RECIST 1.1 or death due to any cause in the absence of documented PD, whichever occurs first
	• Progression or death, which occurred later than two scheduled tumor assessment intervals after the last evaluable response assessment will be censored at the date of the last evaluable response assessment for PFS analyses
	• PFS time will be censored the last evaluable assessment date before the start of a new anti-cancer-treatment if no event occurred so far; In case of not evaluable Baseline assessment or all post-Baseline assessments are non-evaluable the participant will be censored at the randomization date.
	• Graphical check of the proportional hazards assumption
	• Kaplan-Meier estimates and associated statistics (PFS rates at 6, 9, 12, 18, 24, 36 months; median PFS) and corresponding 95% confidence intervals will be presented by treatment group.
	• Sensitivity analyses taking other factors and analysis populations into account as specified in IAP, in particular but not limited to
	  • different PD-L1 expression levels
	  • alternative censoring rules and unstratified analyses (including an analysis which counts death and progression according to RECIST 1.1 as PFS event regardless of the start of a new anti-cancer therapy and ignoring the number of missing evaluable tumor assessments before progression or death)
	• Subgroup analyses as defined in IAP.

Secondary Endpoint
OS
	• OS analysis applies the same methodology as PFS analysis, conducted on FAS population
	• OS is defined as the time from randomization to the date of death due to any cause
	• For participants alive, the OS will be censored at the last date known to be alive.
	• Sensitivity analyses taking other factors and analysis populations into account as specified in IAP, in particular but not limited to
	  • different PD-L1 expression levels
	  • different pulmonary function baseline characteristics
	  • unstratified analyses
	• Subgroup analyses of OS and other potential endpoints or its derivations (e.g., duration of response or time to response) as defined in IAP (e.g., subgroup by amount of cCRT received)

CCI [redacted]	

Endpoint	Statistical Analysis Methods
	CCI [redacted]

Analysis of CCI [redacted] endpoints will be contingent on the outcomes of primary and secondary endpoints.

9.4.1.1 Tumor Assessment by IRC

The primary endpoint in this study is PFS according to RECIST 1.1 assessed by the Investigator. If a clinically relevant PFS benefit is observed at the primary analysis, an additional analysis of PFS per IRC assessment may be conducted. Details will be defined in a separate statistical analysis plan.

9.4.2 Safety Analyses

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

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

Table 25 Safety Endpoints and Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Occurrence of TEAEs and treatment-related AEs	Safety will be analyzed on the SAF population and will be based on all safety analysis reporting outcomes like adverse events, AESIs and laboratory tests outcomes. The safety endpoints will be tabulated using descriptive statistics. Safety will also be tabulated by subgroups (e.g., ethnicity Japanese and non-Japanese). The incidence of TEAEs which includes AESIs, regardless of attribution, will be summarized by Preferred Term and System Organ Class for each treatment arm, and described in terms of intensity and relationship to treatment. The IDMC correspondingly evaluates the safety on the SAF-J and SAF-nJ analysis population in the safety run-in, whereas details are specified in the IDMC charter. Further details of safety analyses will be provided in the IAP
CCI [redacted]	

9.4.3 Other Analyses

PK analysis and CCI [redacted] analyses will be specified in the Integrated Analysis Plan finalized before database lock. The population PK analysis and exposure-response may be performed using combined data from several M7824 clinical studies and will be specified in a separate IAP. PopPK, exposure-response and CCI [redacted] analyses will be presented separately from the main clinical study report (CSR).

9.4.4 Sequence of Analyses

- Regular safety analyses conducted by the IDMC
- Primary analysis (conducted once 70 PFS events per Investigator assessment have been reached and after a minimum follow-up of 15 months after randomization of the last participant).

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11 Appendices

Appendix 1 Abbreviations

ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BOR	Best overall response
β-hCG	Beta human chorionic gonadotropin
CR	Complete response
CrCL	Creatinine clearance
cCRT	Concomitant Chemoradiotherapy
CNS	Central nervous system
CRO	Contract Research Organization
cSCC	Cutaneous squamous cell carcinomas
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circular Tumor DNA
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
CCI [redacted]	[redacted]
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]

FN	Febrile Neutropenia
CCI	[redacted]ity
FDA	Food and Drug Administration
CCI	[redacted]
1L	First-line
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
CCI	[redacted]
IAP	Integrated Analysis Plan
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
CCI	[redacted]
Ig	Immunoglobulin
IL	Item library
ILD	Interstitial lung disease
IMRT	Intensity-modulated RT
INR	International normalized ratio
irAE	Immune-related AE
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-related reactions
ITT	Intention-to-Treat
IUO	Investigational use only
IV	Intravenous

IWRS	Interactive Voice/Web Response System
LDH	Lactate Dehydrogenase
LLN	lower limit of normal
KA	Keratoacanthomas
mAb	Monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NSCLC-SAQ	Non-small cell lung cancer symptom assessment questionnaire
ORR	Objective response rate
mOS	Median Overall survival
PD	Progressive disease
CCI	[redacted]
PFS	Progression-free survival
PFTs	Pulmonary Function Tests
mPFS	Median Progression-free survival
PK	Pharmacokinetics
popPK	Population pharmacokinetic
PR	Partial response
CCI	[redacted]
PT	Prothrombin time
q2w	Every 2 weeks
q3w	Every 3 weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RMP	Risk Management Plan
RP2D	Recommended Phase II Dose
RT	Radiation therapy
SAE	Serious adverse event

SAF	Safety (analysis population)
SCR	Screening (analysis population)
CCI [redacted]	[redacted]
SUSAR	Suspected unexpected serious adverse reactions
CCI [redacted]	[redacted]
TGFβRII	Transforming growth factor β receptor II
TEAE	Treatment-emergent Adverse Event
CCI [redacted]	[redacted]
ULN	Upper limit of normal
VAS	Visual analog scale
WOCBP	Woman of childbearing potential

Appendix 2 Study Governance

Financial Disclosure

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

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative (where allowed by local laws and regulations) and answer all questions on the study.
- Participants must be informed that their participation is voluntary.
- Participants or their legally-authorized representative (where allowed by local laws and regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; the Japanese ministerial ordinance on GCP; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, participants must be re-consented to the most current, approved version.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

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

- The Investigator will complete the participant registration form and fax it to the registration center. If the participant meets all inclusion criteria and does not meet any of the exclusion criteria, the participant registration center will receive confirmation, register the participant and inform the Investigator and the Sponsor of the registration number by fax. If the participant is ineligible for the study, a participant number will be allocated and documented.

Study Administrative

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

The study will be conducted at approximately 100 centers in North and South America, EU, and Asia-Pacific. Approximately 20 to 30 sites will be in the USA.

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

The study will appear in the following clinical studies registries: clinicaltrials.gov and EudraCT. Details of structures and associated procedures will be defined in a separate Integrated Project Management Plan, which will be prepared under the supervision of the Clinical Study Leader.

Refer to the Study Organization and the Study Sites in Japan in supporting document.

An IDMC will be formed in this study.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- The Japanese ministerial ordinance on GCP
- Applicable laws and regulations
- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g, advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.
- The Sponsor initiates the study at a site after obtaining written approval from the Head of the study site, based on favorable opinion/approval from the concerned IRB.

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

Emergency Medical Support

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

Clinical Study Insurance and Compensation to Participants

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

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

Clinical Study Report

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

Publication

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

Dissemination of Clinical Study Data

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

Data Quality Assurance

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

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

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the following demographic and medical information for the participant, and should be as complete as possible:
- Participant's full name, date of birth, sex, height, 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 electronic CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The study monitors will use printouts of electronic files for source data verification. These printouts must be signed and dated by the Investigator and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Head of the study site ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in the eCRF guidelines.

Study and Site Start and Closure

First Act of Recruitment

- The study start date is the date when the clinical study will be open for recruitment.
- The first act of recruitment is when the first site is opened and will be the study start date.

Study Closure and Site Termination

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

Appendix 3 Contraception

Woman of Childbearing Potential (WOCBP)

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

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

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

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

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

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

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

User-Dependent

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

User-Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation*
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)

- Bilateral tubal occlusion
- Vasectomized partner: This is a highly effective contraception method only if the partner is the sole sexual partner of the WOCBP and he has received medical assessment of the surgical success.
- Sexual abstinence: This is a highly effective method only if the WOCBP refrains from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
- *Not approved in Japan.

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

Definitions

Adverse Event

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

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

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

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

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

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

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

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

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

The 5 general grades are:

Grade 1 or Mild

Grade 2 or Moderate

Grade 3 or Severe

Grade 4 or Life-threatening

Grade 5 or Death

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

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

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

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

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

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

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

Serious Adverse Events

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

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

do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

For Japanese sites where hospitalization is considered in the safety run-in for observational measures, any AE occurring during this hospitalization should not be reported as serious, unless seriousness criteria is met for AE reportability purpose.

Events that Do Not Meet the Definition of an SAE

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

Events Not to Be Considered as AEs/SAEs

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

AE/SAEs Observed in Association with Disease Progression

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

Adverse Events of Special Interest

Adverse events of special interest can be serious or nonserious events.

Categories of AESIs related to M7824 include:

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

For this study, pneumonitis (radiation or immune mediated) is considered an AESI.

Recording and Follow-Up of AE and/or SAE

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal

relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

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

Reporting Serious Adverse Events

Serious Adverse Events

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

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

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

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

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

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

Appendix 5 Clinical Laboratory Tests

Table 26 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 Schedules of Assessments if participant with infection history)	
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 women of nonchildbearing potential **only**) • Serum or highly sensitive urine human chorionic gonadotropin (β-hCG) pregnancy test (as needed for women of childbearing potential). • Serum KL-6, SP-A and SP-D			

ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = 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; RBC = red blood cell; RDW = red cell distribution width; T_4 = free thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell; TST = tuberculin skin test.

a Performed as indicated in the Schedules of Assessments.

Laboratory Assessments	Parameters
b	Performed at Screening only.


CCI

Appendix 7 Prohibited Traditional Chinese Medicine

	Name of Approved TCM with anticancer indication
	CCI English
1	Ai Di injection®
2	De Li Shen, Delisheng, injection
3	Kanglaite injection, or KLT
4	Ganfule, Gan Fu Le, GanFuLe tablet/capsules
5	Huaier, Huaier Keli, granules
6	Jinlong capsules
7	Cinobufacini injection
8	Jiedu Granules
9	Elemene injection, Elemenum emulsion, Injectio Emulsioni Elemeni
10	Xiaoaiping tablets
11	Chloroxoquinoline capsules
12	Kanglixin capsules
13	Kanglixin tablets
14	Sodium Cantharidinate For Injection
15	compound capsules cantharidin
16	Java brucea fruit oil emulsion
17	Java brucea fruit oil capsules
18	Java brucea fruit oil injection
19	Weimaining capsules
20	Shenyi Capsule
21	Shelian capsule
22	Kangai injection
23	Ubenimex
24	Xianchan tablet

	Name of chronic systemic immune treatment	
1	CCI [redacted]	Interleukin-2
2	[redacted]	interferon
3	[redacted]	Thymosin/thymopentin

Appendix 8 Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

The text below was obtained from the following reference: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer. 2009; 45: 228-247.

Definitions

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

Measurable Disease

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

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

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

Non-measurable Disease

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

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

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

Target Lesions

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

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

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

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

Non-target Lesions

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

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

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

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

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

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

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

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

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

RESPONSE CRITERIA

Evaluation of Target Lesions

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

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

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

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

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

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

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

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

Evaluation of Non-target Lesions

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

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

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

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

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

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

New Lesions

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

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

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

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

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

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

Evaluation of Best Overall Response

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

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

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

* CR = complete response; SD = stable disease; PD = progression of disease.
See text for more details.

Note:

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

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

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

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

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

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

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

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

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

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

Duration of Overall Response

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

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

Duration of Stable Disease

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

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

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

Appendix 9 Protocol Amendment History

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

Protocol Version [3.1] (05-Nov-2019)

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities and throughout the protocol	Reference to Section 6.9.1.5 is changed to Section 6.9.1.6	Corrected an error
Section 6.1 Study Intervention(s) Administration, Table 7	Clarified and added durvalumab supplier and manufacturer for Korea	Clarification and correction
Appendix 5 Recommendations for irAE Management	Added statement to Table 33, 8.5 Lymphopenia, to state that If the event is considered immune related but resolves to ≤ G1 within 14 days restarting treatment may be considered.	To clarify the criteria for the re-treatment on immune related lymphopenia

Protocol Version [3.0] (05-Jul-2019)

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale
Title page	Updated Sponsor Name and Legal Registered Address for Japan	Administrative update
	Updated the details for Medical Monitor and Contact Information	Administrative update
1.1 Synopsis	Added/updated the information regarding the IDMC safety reviews to the Overall Design and Involvement of Special Committee sections	To provide detailed information regarding the IDMC safety reviews
1.3 Schedule of Activities and throughout the document as applicable	Replaced information regarding the collection of the samples (from "48 hours" to "3 days") for the Laboratory Assessments	To update the window of lab tests collection and review prior dosing
	Included smoking information as part of medical history	To clarify that smoking/nicotine history is collected on the eCRF
	Added information regarding the Japanese participants for serum KL-6, SP-A, and SP-D measurements	To clarify the country where the tests are mandatory
	CCI [redacted]	CCI [redacted]
	CCI [redacted]	[redacted]
	Added information about the allowed window for the M7824 or placebo treatment	To clarify allowed window of treatment administration

Section # and Name	Description of Change	Brief Rationale
	Added information about the allowed window for the Cisplatin/Etoposide, Paclitaxel/Carboplatin, and Pemetrexed/Cisplatin treatments	To clarify allowed window of treatment administration
	Replaced text regarding premedication for all chemotherapy regimens	To provide clarity for use of corticosteroid as part of chemotherapy premedication and to align with latest NCCN recommendation
	Added information about the allowed window for the M7824 or Durvalumab treatments	To clarify allowed window of treatment administration
	Added window of ± 7 days for the Thorax Abdomen Pelvis CT (preferred) /MRI	For clarity and consistency
2 Introduction	Updated information with the current IB Bintrafusp alfa was included as the proposed international nonproprietary name for M7824	For consistency across the development program
3 Objectives and Endpoints	CCI [redacted]	[redacted]
4.1 Overall Design	Updated text regarding the IDMC safety reviews and about the period if participants require withholding of the study intervention due to toxicities.	To clarify the roles of the IDMC and when the period of cCRT can be extended
4.1.1 Study Intervention Beyond Progression	Added information for bone metastasis/lesion	To clarify that bone palliative radiotherapy is allowed during the study
5.2 Exclusion Criteria	Clarified the exclusion criteria #7	To exclude participants with history of bleeding diatheses or recent major bleeding events
6.1 Study Intervention(s) Administration	Added information regarding the sequence of treatment administration	To specify the sequence of treatment administration when the radiotherapy is delivered at a separate location
6.5.3 Permitted/Prohibited Procedures	Added information regarding the palliative radiotherapy	To clarify that palliative radiotherapy is allowed in participants who experience PD during the study
6.8.1 Additional Potential Risks	Included alterations in wound healing or repair of tissue damage, embryo-fetal toxicities, and mild to moderate mucosal bleeding events as additional potential risks	To align with newly identified potential risk as per current IB and protocol template across the program
6.9.1.1 Infusion-Related Reactions	Added information regarding administration of the study interventions	To clarify that the treatment should be administered in an outpatient basis unless hospitalization is required by health authorities or is part of the standard practice
6.9.1.3 Potential TGFβ-Mediated Skin Adverse Events	Replaced information regarding the management of potential TGFβ using skin toxicities guidelines	To provide guidelines for the management of potential TGFβ-related skin toxicities

Section # and Name	Description of Change	Brief Rationale
6.9.1.5 Management of Bleeding Events	Added text to describe management of bleeding events	To provide the guidelines for the management of bleeding events and indications for when patients should have study treatment held or discontinued
6.9.1.6 Risk Management for Chemoradiation	Added information regarding the treatment vs platelet and neutrophil counts	To clarify the conditions to resume the treatment
	Footnotes added to Tables 10, 11, 16, and 18 regarding the participant permanent discontinuation if the treatment withholding ≥ 2 weeks	To clarify treatment discontinuation in case of treatment withholding ≥ 2 weeks
8.3.2 Method of Detecting Adverse Events and Serious Adverse Events (including Appendix 4)	Modified nonserious AESI reporting	To discontinue expedited reporting of non-serious AESI
8.5 Pharmacokinetics	Correction of plasma to serum for the quantification of M7824.	To correct text.
8.6 Pharmacogenetics	Correction of "plasma sample" to "blood sample" for the pharmacogenetic research	To correct text
Appendix 5	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
Appendix 9	Updated information regarding protocol amendment history	For clarity and consistency
Throughout	Minor editorial and document formatting revisions	Minor text revisions are made for clarity, readability, consistency of language across the development program, and compliance with current Sponsor guidelines

Protocol Version 2.2 (21 May 2019)

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design	Added Phase II study in description	To clarify study design
4.4 End of Study Definition	Added reference to Appendix 2	To refer to further details for study and site closure
6.5.2.1 Medicines to Use with Caution	Amended text regarding anticoagulants	To clarify use of anticoagulants and provide example
6.9.1.5 Risk Management for Chemoradiation; 10 References	Added reference	To provide reference to detailed information on drug-drug interactions with sucralfate
7.1.1 Permanent Discontinuation	Added examples of reasons for participant withdrawal	To clarify reasons participant could be withdrawn from study
7.2 Participant Discontinuation/Withdrawal from the Study	Added examples of reasons for participant withdrawal	To clarify reasons participant could be withdrawn from study

Protocol Version 2.1 (08 May 2019)

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale
8.5 Pharmacokinetics	Correction of plasma to serum for the quantification of M7824.	To correct text.

Protocol Version 2.0 (05 March 2019)

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale
Synopsis, Overall Design; 4.1 Overall Design; 4.1.1.5 Stratification; 6.3.1 Study Intervention Assignment; 9.5.1 Efficacy Analyses	Added text regarding PD-L1 expression in tumor cells	To include PD-L1 expression in tumor cells as stratification factor in the expansion part of the study
1.3 Schedule of Activities	Addition of footnotes and corrections	To make corrections in the Schedule of Activities tables
4.1 Overall Design; 7.1.1 Permanent Discontinuation	Add text regarding adverse events resulting in permanent discontinuation of study intervention	To include instructions for resuming treatment
5.1 Inclusion Criteria	Updated Inclusion Criterion #3 and Inclusion Criterion #10	To include information regarding PD-L1 tumor expression and clarify inclusion criteria
6.1 Study Intervention(s) Administration	Added investigational and medicinal packaging and labeling information for durvalumab	To include correct information
9.5.1 Efficacy Analyses	Added Table 24	To add details on planned tests for overall survival analyses
Appendix 5 Recommendations for irAE Management	Updated immune-related adverse event management instructions	Updated for consistency with the IMFINZI product labelling

Appendix 10 Sponsor Signature Page

Study Title:	A Multicenter, Double Blind, Randomized, Controlled Study of M7824 with Concurrent Chemoradiation Followed by M7824 versus Concurrent Chemoradiation Plus Placebo Followed by Durvalumab in Participants with Unresectable Stage III Non-small Cell Lung Cancer
Regulatory Agency Identifying Numbers:	EudraCT 2018-003265-34 CCI
Clinical Study Protocol Version:	22 June 2021/Version 4.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	Medical Responsible
Institution:	Merck Biopharma Co., Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany)
Address:	Arco Tower, 1-8-1 Shimomeguro, Meguro-ku, Tokyo 153-8926, Japan
Telephone number:	PPD
Fax number:	Not applicable
E-mail address:	PPD

Appendix 11 Coordinating Investigator Signature Page

Study Title:	A Multicenter, Double Blind, Randomized, Controlled Study of M7824 with Concurrent Chemoradiation Followed by M7824 versus Concurrent Chemoradiation Plus Placebo Followed by Durvalumab in Participants with Unresectable Stage III Non-small Cell Lung Cancer
Regulatory Agency Identifying Numbers:	EudraCT 2018-003265-34 CCI [redacted]
Clinical Study Protocol Version:	22 June 2021/Version 4.0

I approve the design of the clinical study 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 [redacted]

Signature

PPD [redacted]

Date of Signature

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

Appendix 12 Principal Investigator Signature Page

Study Title:	A Multicenter, Double Blind, Randomized, Controlled Study of M7824 with Concurrent Chemoradiation Followed by M7824 versus Concurrent Chemoradiation Plus Placebo Followed by Durvalumab in Participants with Unresectable Stage III Non-small Cell Lung Cancer
Regulatory Agency Identifying Numbers:	EudraCT 2018-003265-34 CCI [redacted]
Clinical Study Protocol Version:	22 June 2021/Version 4.0
Site Number:	

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

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

_____ _____

Signature Date of Signature

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