Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS200647_0005
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 Phase	Phase II
Investigational Medicinal Product(s)	M7824 (Bintrafusp alfa)
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Approval Page

Integrated Analysis Plan: M200647_0005

A Multicentre, 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

Approval of the IAP by all Merck Data Analysis Responsible has to be documented within BREEZE via eSignature. With the approval within BREEZE, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

Merck Data Analysis Responsible	Date	Signature
PPD, Study Biostatistician, EMD Serono	Via BREEZE approval process	Via BREEZE approval process

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADA	Anti-drug Antibody
AE	Adverse event
AESI	Adverse events of special interest
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
CCI	[redacted]
BMI	Body mass index
BSA	Body surface area
cCRT	Concomitant Chemoradiotherapy
COVID-19	Coronavirus Disease 2019
C_{eoi}	Concentration observed immediately at the end of infusion
CR	Complete response
CrCL	Creatinine clearance
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
C_{trough}	Concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing)
CCI	[redacted]
CCI	[redacted]

DOR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
[redacted]	CCI [redacted]
CCI [redacted]	[redacted]
FAS	Full (analysis set)
FDA	Food and Drug Administration
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
FWER	Family wise error rate
GCP	Good clinical practice
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLT	High level term
HR	Hazard ratio
CCI [redacted]	[redacted]
IAP	Integrated analysis plan
ICH	International Council for Harmonisation
IDMC	Independent data monitoring committee
CCI [redacted]	[redacted]

imAE	Immune-mediated adverse event
IMM	Immunogenicity (analysis set)
IMRT	Intensity-modulated radiotherapy
INR	International normalized ratio
IPD	Important protocol deviation
irAE	Immune-related adverse event
IRC	Independent review committee
IRR	Infusion-related reactions
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intention-to-treat
IVRS/IWRS	Interactive voice/web response system
KA	Keratoacanthomas
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event,
NSCLC	Non-small cell lung cancer
CCI	[redacted]
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
CCI	[redacted]
PFS	Progression-free survival
PFTs	Pulmonary function tests
PK	Pharmacokinetics

PKAS	Pharmacokinetic (analysis set)
PR	Partial response
CCI	[redacted]
PT	Prothrombin time
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RT	Radiation therapy
SAE	Serious adverse event
SAF	Safety (analysis set)
SCC	Squamous cell carcinoma
SCR	Screening (analysis set)
SD	Stable disease
TBILI	Total bilirubin
TEAE	Treatment-emergent adverse event
CCI	[redacted]
CCI	[redacted]
TSH	Thyroid-Stimulating Hormone
ULN	Upper limit of normal
VAS	Visual analogue scale
CCI	[redacted]

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	09 October 2019	PPD	First Release
2.0	22 February 2022	PPD	Updated with new PPD Statistical Team Lead name and new Merck Biostatistician name Updated the list of reviewers with new Medical and Safety Leads at Merck Added "COVID-19" in the list of abbreviations. Fixed typos across the document. **Section 6.3:** Added PD-L1 status at screening. **Section 6.5:** Replaced text with a reference to section 15.5. **Section 7**: Added section 7.1 COVID-19 Impact **Section 9:** 1) Updated definition of baseline to specify that it will be based on the pre-randomization values (text added by Muriel). 2) Error: replaced "time of first study intervention" with "time of randomization" in the "Time since documented, locally advanced or inoperable disease diagnosis (months)" definition. 3) Added the µmol/L → mg/dL conversion factor. 4) Added definition of pre, during, post pandemic period for COVID-19 impact assessment. **Section 10.1:** 1) Added the following bullet points as per the disposition table finally agreed with Sponsor: - Number of randomized participants who completed all study interventions by treatment arm. - Number of randomized participants with any study intervention ongoing by treatment arm. - Number of randomized participants allocated to each chemotherapy regimen overall and by treatment arm. - Number of randomized participants who discontinued the study, grouped by treatment arm and main reason (as reported on "Study termination" page of the eCRF). 2) Updated including COVID-19 analyses details **Section 10.2**: Updated including COVID-19 analyses details **Section 11.1:** Added PD-L1 status at screening and Kaplan-Meier plot of time to treatment discontinuation. **Section 11.3.2**: Added stage at study entry and known history of one or more renal/cardiac insufficiency, severe nausea or hearing impairment. **Section 11.3.5:** Added details for the overview table for PD-L1 status at screening. **Section 13:** 1) Added details on the total duration of chemotherapy regimen calculation. 2) Added details on the carboplatin mg conversion.

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
			3) Added split by immunotherapy drug for cumulative dose, DI and RDI reporting in unblinded deliveries. **Section 14.1.1:** Updated PFS rules to consider 2 scheduled tumor assessments and added details in PFS definition **Section 14.4:** 1) Table7: added the correspondent "*" description in footnote. 2) Updated across the whole document (as per protocol): • No post-Baseline assessments due to death within 8 ~~6~~ weeks after randomization • PD too late (i.e. tumor assessment of PD was >16 ~~12~~ weeks after randomization and there was no evaluable tumor assessment in between) **Section 14.4.1:** Added waterfall plots for best percent change and change at first scan and unconfirmed BOR by investigator spider plot. Section 14.9.1: Updated definition of BOR according to irRECIST **Section 15.2.3.3:** Added Lip Squamous Cell Carcinoma and Bowen´s Disease to Broad definition of skin AEs possibly related to TGFβ inhibition. **Section 15.2.3.4:** Added the Overview Anemia TEAEs table. **Section 15.3**: Added corrected calcium formula **Section 17**: added GFR and carboplatin conversion references. DRAFT 2 Updates: Approval page: ELDORADO/CARA system has been replaced by BREEZE Section 4: Purpose of the integrated analysis plan: removed interim analyses as protocol amendment (v.4.0) Section 5: Objective and endpoints updated as protocol amendment (v.4.0): • updated all objectives based on response according to RECIST 1.1: they will be assessed by investigator rather than IRC CCI [redacted] • Removed objective based on irRECIST criteria Section 6: overview of planned analyses updated as protocol amendment (v.4.0): • Removed interim analyses, OS final analysis and sequential testing procedure from the overview of planned analyses. • Updated efficacy analyses at PA as per new study objectives Section 6: Added "Overview of Planned Analyses after Trial Discontinuation" Section 8.2 and across the document: ITT analysis set has been renamed as FAS as per as protocol amendment (v.4.0) Section 9: Significance level section removed as not anymore applicable per protocol amendment (v.4.0) Section 9: Added imputation rules for nicotine consumption dates

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
			Section 9: Added computation of duration of nicotine consumption and years since quitting Section 10.1: Added categories in patient disposition table Section 11.1: Added pooled region and EEA in demographics as per BOA 10 Section 11.1: plot of time to immunotherapy discontinuation has been moved in Section 10.1 Section 11.3.4: Added nicotine consumption section Section 12.3: Added description of overview table of concomitant procedures Section 13: Added further details for listing of chemotherapy switch Section 14: Efficacy analyses updated as per protocol amendment (v.4.0): • Removed sequential testing procedure and interim analyses as not anymore applicable per protocol amendment (v.4.0) • Removed hypothesis test for OS • Updated the event triggering the PA as date when 70 PFS events + 15 months f-up will be reached • updated all analyses based on response according to RECIST 1.1 as per IRC: they will be assessed by investigator rather than IRC • PFS according to RECIST 1.1 as assessed by investigator will not anymore be a sensitivity analysis but rather the primary analysis • Removed analyses based on irRECIST criteria Section 14: updated reason for non-evaluable BOR. SD of insufficient duration has been set at 6 weeks rather than 8 weeks as greed with Merck Bios. SD (or better) specified for confirmed response. Section 15: Safety analyses updated as per protocol amendment (v.4.0): • Addition of bleeding events as an AESI • Skin Adverse Events renamed as "TGF-Beta inhibition mediated skin reactions" • Removed Radiation/immune mediated pneumonitis as AESI • Removed Three tier approach analysis Section 15: Added description of list of MedDRA Preferred Terms considered as AESI Section 15: Removed Evaluation of Potential Effect of ADA on M7824 Safety Section 15.1: Added overview table of treatment-emergent AEs associated to COVID-19 Section 15.3: Added further details on listings of Hemostaseology, Urinalysis/Urinalysis Microscopic Evaluation, Hormonal Tests, Serology, Pregnancy Test Section 15.4 Added further details on listing of maximum change from baseline in vital signs Section 15.5 Added details on analyses on pulmonary functions tests.

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
			Section 16.4: Immunogenicity analyses updated as per last Merck requirements: • Added ADA categories "Treatment emergent (ALL)" and "ADA non-treatment emergent" • Missing values considered in the computation of numerator and denominator of treatment emergent category and category renamed as "Treatment emergent (baseline induced)" • Added listing of ADA results Section 18: Added appendix for list of outputs, wording updates. Section 16.3: Removed PRO analyses description as no analyses will be provided for the abbreviated CSR Section 16.4: Removed immunogenicity analyses description as no analyses will be provided for the abbreviated CSR Section 16.1: Removed PK analyses description as no analyses will be provided for the abbreviated CSR Appendix: Removed PRO Scoring Guidelines appendix as no analyses on PRO will be provided for the abbreviated CSR Minor adjustments across the document in order to align it with shells BOR was partially changed to ORR across the document to be consistent with Merck guidance v.3.0 "Definition and Analysis of Objective Response in Oncology Studies from GBS Perspective"

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the primary analysis of data collected for protocol MS200647_0005.

Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned primary analysis identified in this IAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon Section 9 (General Specifications for Data Analyses) of the study protocol and is prepared in compliance with International Council for Harmonization (ICH) Guideline E9. Details of the Independent Data Monitoring Committee (IDMC) analyses are provided in appendices.

5 Objectives and Endpoints

Objective	Endpoint	SAP Section
Primary Objective		
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	Efficacy Analysis: Section 14.1.1
Secondary Objectives		
To evaluate the safety in participants treated with M7824 plus cCRT followed by M7824 or cCRT plus placebo followed by durvalumab	• Occurrence of TEAEs and treatment-related AEs	Safety Analysis: Section 15
To evaluate OS in participants treated with M7824 plus cCRT followed by M7824 or cCRT plus placebo followed by durvalumab	• OS	Efficacy Analysis Section 14.2
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 •	Efficacy Analysis Section 14.4
To evaluate duration of response in participants treated with M7824 plus cCRT 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	Efficacy Analysis Section 14.5
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	Analysis of Other Endpoints Section 16.1
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	Analysis of Other Endpoints Section 16.4
CCI [redacted]		

Objective	Endpoint	SAP Section
CCI		

CCI , ADA=anti-drug antibody, cCRT=concomitant chemoradiation therapy; C_{eoi}=concentration immediately at the end of infusion, CR=complete response, CCI , C_{trough}=concentration immediately before next dosing; CCI , EoT=End of Treatment, CCI , IHC=immunohistochemistry, CCI , OS=overall survival, PD=progressive disease, PFS=progression-free survival, CCI PK=pharmacokinetics, PR=partial response, CCI , TEAE=treatment-emergent adverse event, CCI .
Note: analysis of CCI endpoints will be contingent on the outcomes of primary and secondary endpoints.

6 Overview of Planned Analyses

This IAP will be focused on primary analysis. Table 1 below displays an overview of the analyses to be provided and the timing of the primary analysis that will be triggered by the data cut-off points specified.

Table 1 Overview of Planned Analyses

Analysis	Data cut-off point
Primary Analysis	To be conducted when 70 PFS events per investigator assessment are reached and after a minimum follow-up of 15 months after randomization of the last participant.
Regular IDMC safety meetings	To be conducted at the following timepoints: During the safety run-in part • After the first 18 Non-Japanese participants have completed cCRT phase. • After the first 30 Non-Japanese participants have completed cCRT phase. • After the 12 Japanese subjects have completed cCRT phase. During the expansion part • 3 months after the start of the expansion phase and 6 months thereafter See more details in the IDMC Charter.

cCRT=Concomitant chemoradiation, IDMC=Independent data monitoring committee, PFS=Progression-free survival,

A separate Statistical Analysis Plan will be provided for the IDMC regular safety meetings (see Appendix 1).

6.1 IDMC

An IDMC will be formed and will be responsible for periodic safety evaluations of the study. Details for the IDMC reviews are stated in the IDMC SAP (see Appendix 1).

After the prospectively determined data cut-off date is reached for the periodic safety evaluations, the data center statistician will prepare the outputs (using programs prepared by the blinded team based on dummy treatment arms) in agreement with the IDMC charter and transmit the analyses, tabulations, and listings to the IDMC for the meeting. The data center statistician will be available at the IDMC meeting should any questions from the IDMC members arise regarding the data and/or analyses.

6.2 Primary Analysis

The Primary Analysis will be triggered by the data cut-off date displayed in Table 1 and will include the following:

- Subject disposition, time to follow-up since randomization, and important protocol deviations
- Demographics, medical history and other Baseline characteristics
- PD-L1 Status at screening

- Previous and concomitant medications and procedures
- Previous anti-cancer treatments for NSCLC and subsequent anti-cancer treatments
- Premedications for immunotherapy and chemotherapy
- Subsequent anti-cancer treatments
- Treatment exposure and compliance (e.g. duration of treatment, number of infusions and dose intensity)
- Efficacy analyses:
    - PFS according to RECIST 1.1 criteria as assessed by Investigator

CCI [redacted]

    - Objective Response Rate (ORR) per RECIST 1.1 criteria as assessed by Investigator
    - Time to response
    - Duration of response (DOR)
    - OS
    - Pulmonary function tests overview

CCI [redacted]

- Safety analyses (overview of AEs, SAEs, TEAEs, treatment-related AEs, AESI and bleeding events), Eastern Cooperative Oncology Group Performance Status [ECOG PS], vital signs, clinical laboratory evaluations, electrocardiograms [ECG])

CCI [redacted]

- Immunogenicity and pharmacokinetic (PK) profile

CCI [redacted]

- Tumor volume shrinkage

Radiomics analysis of images for digital features potentially predictive of prognosis and/or future treatment benefit analysis will only be performed retrospectively if deemed as appropriate.

The Sponsor study team will be unblinded at the time of the PA while the Investigators and participants remain blinded until End of Study as specified in the IDMC Charter.

6.3 Overview of Planned Analyses after Trial Discontinuation

Following review and analysis of data available from MS200647_0005 in September 2021, and in accordance with the IDMC recommendation, the Sponsor made the decision to discontinue the clinical study due to a low likelihood that the study will achieve superiority in the efficacy endpoints vs. the standard of care.

Therefore, the analyses described in Section 6.2 will not be performed as planned, but one primary analysis will be performed for reporting purpose (abbreviated CSR). The analyses considered relevant for this purpose are listed below:

- Participant disposition
- Important protocol deviations
- Enrollment details (difference between planned and actual treatment arm and re-screened subjects)
- Demographics, medical history and other baseline characteristics (height, weight, BSA and BMI at baseline, disease history, skin status history, nicotine consumption, PD-L1 expression at screening)
- Previous and concomitant procedures, follow-up treatments
- Treatment exposure and compliance (e.g. duration of treatments, number of infusions/fractions, cumulative dose, dose intensity and relative dose intensity, chemotherapy dose reductions)
- Efficacy analyses:
    - PFS per RECIST 1.1 as assessed by Investigator
        - PFS per RECIST 1.1 as assessed by Investigator by subgroups
    - Overall survival (OS)
        - OS by subgroups
    - Follow-up time (PFS and OS)
    - ORR per RECIST 1.1 as assessed by Investigator
        - ORR per RECIST 1.1 as assessed by Investigator by subgroups

- Overall Response per RECIST 1.1 as assessed by Investigator at the end of cCRT
- Percentage change from baseline in sum of longest diameters (overall and by PD-L1 and histology subgroups)
- Duration of response

- Safety analyses (overview of treatment-emergent adverse events (TEAEs), serious TEAEs (SAE), treatment-related TEAEs, TEAEs leading to treatment discontinuation/interruption/modification, TEAEs Leading to death, adverse events of special interest (AESI), vital signs, ECOG, clinical laboratory evaluations, pulmonary function tests: DLCO, Slow spirometry, FEV_1, FVC and 6-minutes walking test)

Data from the cutoff of 21 July 2021 were the basis for the decision to discontinue the trial and will be used for the primary analysis.

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

7 Changes to the Planned Analyses in the Clinical Study Protocol

The statistical methods as described in the study protocol will be adopted. There are no changes to the planned analyses, except additional outputs that will be generated to assess the potential impact of COVID-19 pandemic and described in the Section 7.1 below.

7.1 COVID-19 Impact

No changes to the planned analysis of the efficacy endpoints will be performed due to the impact of COVID-19 outbreak. Instead, additional outputs (summary tables and listings) will be generated to assess potential impacts of COVID-19 to this study.

- An overview table of the impact by COVID-19
- An overview table of participants who started the treatment pre/during COVID-19 study period
- A table of treatment-emergent adverse events associated to COVID-19
- A listing of COVID-19 impact
- A listing of COVID-19 related protocol deviations

Details of the categorization of participants for COVID-19 impact assessment is provided in Section 9 and details of the analyses are provided in Sections 10.1, 10.2. 15.1.1.

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations and Analysis Sets

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

Important protocol deviations include:

- Participants who are dosed on the study despite not satisfying the inclusion criteria
- Participants who develop withdrawal criteria whilst on the study but are not withdrawn
- Participants who receive an incorrect dose
- Participants who receive an excluded concomitant medication
- Deviations from Good Clinical Practices (GCP).

The following important protocol deviations will be identified and confirmed prior to or at each Cross-Functional Protocol Deviation Review Meetings and will include:

- Deviations from the inclusion and exclusion criteria
- Deviations post inclusion.

All important protocol deviations will be documented in SDTM datasets whether identified through site monitoring, medical review, or programming.

Important protocol deviations will be defined in a specific document (see Appendix 4), and deviations to be checked programmatically will be identified in this list.

Further Considerations for PK

Examples of important protocol deviations or important events for PK for this study include, but are not limited to, the following:

- Dose delayed outside the allowed window (and actual dosing time not recorded)
- Pre-dose sample collected after the actual start of infusion
- End-of-infusion sample collected before the actual end of infusion
- Sample processing errors that may lead to inaccurate bioanalytical results.

For the above important protocol deviations or important events for PK, the relevant PK data will be excluded from summaries and the PK Analysis Set (PKAS).

8.2 Definition of Analysis Populations and Subgroups

Screening (SCR) Analysis Set

The SCR analysis set will include all participants who provided informed consent regardless of the participant's randomization and study intervention status in the study.

Full Analysis Set (FAS)

The FAS will include all participants who were randomized to study treatment. Analyses performed on the FAS will take into account participants' allocation to treatment groups as randomized.

Non-Japanese Safety (SAF-nJ) Analysis Set

The SAF-nJ analysis set will include the first 30 non-Japanese participants who were administered any dose of any study intervention. Analyses will consider participants as treated.

Japanese Safety (SAF-J) Analysis Set

The SAF-J analysis set will include the first 12 Japanese participants who were administered any dose of any study intervention. Analyses will consider participants as treated.

Safety (SAF) Analysis Set

The SAF analysis set will include all participants who were administered any dose of any study intervention. Analyses will consider participants as treated.

Pharmacokinetic Analysis Set (PKAS)

The PKAS will include all participants who completed at least 1 infusion of M7824, and who provided at least 1 sample with a measurable concentration of M7824, without important protocol deviations or events deemed to affect PK evaluation.

Immunogenicity (IMM) Analysis Set

The IMM analysis set IMM will include all participants who completed at least 1 infusion of M7824 and have at least 1 valid IMM result. All IMM analyses will be based on this analysis set.

CCI [redacted]

CCI [redacted]

CCI [redacted]

Error! Reference source not found.2 displays the use of the analysis sets in the different a nalyses.

Table 2 Overview of the Analysis Set Used in the Different Analyses

Analyses	SCR	FAS	SAF-nJ/ SAF-J/SAF	PKAS	IMM	C [redacted]	[redacted]
Subject disposition status	✓	✓					
Randomization details		✓					
Summary of timeliness/cleanliness of data			✓				
Protocol deviations		✓					
Demographic and Baseline characteristics		✓	✓				
Treatment duration			✓				
Efficacy		✓					
Safety and Tolerability			✓				
Pharmacokinetics				✓			
Immunogenicity					✓		
CCI [redacted]						■	
CCI [redacted]							■

CCI [redacted] IMM=Immunogenicity analysis set, FAS = Full analysis set, PKAS=Pharmacokinetics analysis set, CCI [redacted], SAF=Safety analysis set, SAF-J=Japanese Safety analysis set, SAF-nJ=Non-Japanese Safety analysis set, SCR=Screening analysis set

Treatment Allocation

Participants will be allocated to the actual treatment arm where first planned medication and prepared medication, as reported in the randomization list, match.

Additional Subgroup Analysis Population

Analysis of efficacy variables will also be performed on subgroups of interest specified below (see Table 33).

In order to include Baseline variables into Cox's proportional hazards model and logistic models, the following parameterization will be used. For variables with more than two categories, an indicator variable will be defined for each category except for the first category, which always defines the reference. In case of low participant numbers within a category (i.e. 20 participants), categories may be pooled.

All the subgroup analyses will be CCI [redacted] no adjustment for multiplicity will be performed. The subgroups used are defined in Table 33.

Table 3 Subgroup Definition (with Reference Level)

Variable	Levels
Sex	Male (reference level) Female
Age	<65years (reference level) ≥65 years
	<75years (reference level) ≥75 years
Smoking history	Never smoker (reference level) Ever smoker
Histology	Squamous cell carcinoma (reference level) Non-squamous cell carcinoma
EGFR mutation	Mutated Wild type (reference level)
Overall Response at cCRT end	CR+PR SD PD (reference level)
Radiotherapy dose	<60 Gy (reference level) ≥60 Gy
Type of chemotherapy	Cisplatin/etoposide (reference level) Paclitaxel/carboplatin Pemetrexed/cisplatin
Race	Caucasian/White (reference level) Black or African American Asian Other
Ethnicity	Japanese Not Japanese (reference level)
	Hispanic or Latino Not Hispanic or Latino (reference level)
ECOG PS	ECOG PS 0 (reference level) ECOG PS 1
NSCLC stage	IIIA (reference level) IIIB IIIC
PD-L1 (SP263)	<1% (reference level) ≥1% Unknown
Pooled Region	North America (reference level) Latin America Europe Asia Australia and Oceania

ADA=Anti-drug antibody, cCRT=Concomitant chemoradiotherapy, CR=Complete response, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EGFR=Epidermal growth factor receptor, NSCLC=Non-small cell lung cancer, C[redacted], PR=Partial response, SD=Stable disease CI

Overall response at cCRT end will be excluded from the Cox model and only be displayed for descriptive purposes.

9 General Specifications for Data Analyses

Unless otherwise indicated all analyses will be presented separately for the two treatment arms (Arm 1 - cCRT plus bintrafusp alfa followed by bintrafusp alfa or Arm 2 - cCRT plus placebo

followed by durvalumab). The specifications for PK data analysis are presented in Section 16.1, and, in case of discrepancies, Section 16.1 shall supersede this section for the purpose of PK data handling, analysis, and presentation.

Data Handling After Cut-off Date

Data after the cut-off will not undergo data cleaning, and will be cut at SDTM level, i.e. before the process of ADAM creation. These data will not be displayed in any listings or used for summary statistics, e.g. laboratory values of samples taken after data cut-off, AEs with onset date after data cut-off, etc. will not be included in any analysis or listing.

Pooling of Centers

Because of the high number of participating centers and the anticipated small number of participants randomized in each center, data will be pooled across centers, and the factor center will not be considered in statistical models or for subgroup analyses.

Unscheduled Assessments

As per database definition, unscheduled safety assessments are always linked to a scheduled time point (each unscheduled assessment is linked to the previous scheduled time point). Safety data retrieved from an unscheduled time point (vital signs, ECOG PS, ECG and laboratory data) will be analyzed as follows:

- For shift tables, data will be taken into account in the definition of the worst assessment during the study
- For description at each post-Baseline time point, the first available result (in chronological order) will be taken into account in the analysis in case of multiple values.

For IMM analysis, unscheduled visits will also be taken into account in the analysis.

For PKAS, unscheduled samples will not be linked to a scheduled time point and will be excluded from summaries.

For description at Baseline, the last available/non-missing result before first study intervention will be taken into account in the analysis in case of multiple values.

Presentation of Continuous and Qualitative Variables

Continuous variables, other than PK, will be summarized using descriptive statistics, i.e.:

- Number of subjects (N), number of subjects with missing values
- Mean, standard deviation (StD)
- Median, 25th percentile - 75th percentile (Q1-Q3)
- Minimum and maximum.

If there are no missing values, this will be indicated by a 0.

Pharmacokinetic variables (concentrations and parameters) will be summarized as described in Section 16.1.

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated, the calculation of proportions will be based on the number of subjects of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

Where an analysis refers only to certain visits, percentages will be based on the number of subjects still present in the study at that visit, unless otherwise specified.

Reporting Conventions

Mean, median, Q1, Q3, minimum and maximum will have the same precision as SDTM data (number of digits) for non-derived data, and standard deviation will be displayed to one digit more than the mean. Statistics on derived data will be rounded to reasonable digits, whereas maximal digits should be available in CDISC ADaM data sets. Percentages will be reported to one decimal place. The rounding will be performed to the closest integer/first decimal using the common mid-point between the two consecutive values. For example, 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

Definition of Study Intervention

In this study, immunotherapy, chemotherapy and radiotherapy are all considered study interventions. The date of first study intervention will be defined as the earliest date of any treatments (immunotherapy, chemotherapy or radiotherapy). The date of last study intervention will be defined as the latest date of any treatments (immunotherapy, chemotherapy or radiotherapy).

Definition of Baseline

The last available assessment prior to randomization will be defined as "Baseline" value or "Baseline" assessment for efficacy analyses. If an assessment is planned to be performed prior to randomization and the assessment is performed on the same day as randomization, it will be assumed that it was performed prior to randomization, if the assessment time point is not collected or is missing. If no such a value is available, the last measurement prior to the first study intervention will be used as the baseline measurement except for pre-randomization assessments used for the derivation of efficacy endpoints (e.g. tumor assessment at Baseline, which will be set to missing, if not done prior to randomization).

For safety analyses, the last measurement prior to the first study intervention will be used as the Baseline measurement. If an assessment is planned to be performed prior to the first dose of any study intervention as per protocol and the assessment is performed on the same day as the first dose of any study intervention, it will be assumed that it was performed prior to study intervention, if the assessment time point is not collected or is missing.

The same baseline values should be used for the description of baseline characteristics for the FAS and safety population. This should be in general the pre-randomization values. Those values should be also used for subgroup classification.

Definition of On-treatment Period

On-treatment period is defined as the time from the first study intervention to the last study intervention date + 30 days OR the earliest date of subsequent anticancer therapy minus 1 day, whichever occurs first, unless otherwise stated. For participants with treatment ongoing at cut-off date, all data from the first study intervention up to the cut-off date will be considered under the on-treatment period. Any systemic anticancer therapy, any anticancer surgery and any anticancer radiotherapy, will be considered as subsequent anticancer therapy.

Definition of Duration

Duration will be calculated as the difference of start and stop date + 1 (e.g. survival time (days) = date of death – date of randomization + 1), if not otherwise specified.

The time since an event (e.g. time since first diagnosis) will be calculated as the reference date minus date of event.

Conversion Factors

The following conversion factors will be used to convert days into months or years:

- 1 month = 30.4375 days
- 1 year = 365.25 days

In order to allow the estimated Glomerular Filtration Rate (GFR) for the carboplatin conversion from AUC to mg, creatinine units collected in eCRF as µmol/L need to be converted into mg-dL as per the Cockroft-Gault equation (National Comprehensive Cancer Network, Templates Appendix B: Carboplatin conversion. Retrieved from: https://www.nccn.org/professionals/OrderTemplates/PDF/appendix_B.pdf - last accessed 04th February 2021).

Nephrol Dial Transplant (2004) 19 [Suppl 2]: ii42–ii43. "Appendix C: Tables, conversions and abbreviations"

).

The conversion factor used will be the following (Nephrol Dial Transplant (2004) 19 [Suppl 2]: ii42–ii43. "Appendix C: Tables, conversions and abbreviations"

):

- To convert µmol/l to mg/dl, multiply by 0.0113

Handling of Missing Data

Unless otherwise specified in this IAP, missing data will not be imputed.

Missing statistics, e.g. when they cannot be calculated, should be presented as "nd" for not determined. For example, if n=1, the measure of variability (StD) cannot be computed and should be presented as "nd".

Unless otherwise specified, CCI [redacted] will be scored using their published administration and scoring manual. For items with missing responses, the response will be managed as per the scoring manual. See Appendix 3 for details.

Handling of Incomplete Dates

Incomplete dates (date of informed consent, date of birth) for the calculation of age will be imputed as follows:

- In case of missing day for at least one date, but month and year available for both dates: the day of informed consent and the day of birth will be set to 1.
- In case of missing month for at least one date, but year available for both dates, the day and the month of informed consent and the day and month of birth will be set to 1.
- In all other cases, the incomplete dates will not be imputed.

Incomplete dates for disease history (date of initial cancer diagnosis, date of documented, locally advanced or inoperable disease diagnosis) and dates of nicotine consumption:

- If the day is missing, it will be imputed to the 1st day of the month.
- If both day and month are missing, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

Incomplete prior/concomitant medication dates will be imputed as follows:

For start date of medication

- If the day is missing, it will be imputed to the 1st day of the month.
- If both day and month are missing, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

For end date medication:

- If the day is missing, it will be imputed to the last day of the month.
- If both day and month are missing, the month and day will be imputed as December 31st.
- If the date is completely missing, no imputation will be performed.

Note: In case the imputation results in a date later than the date of patient's death, then the date of death will be used to impute the incomplete stop date.

Incomplete dates for start date of subsequent anti-cancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of on-treatment period:

- If only day is missing, it will be imputed as the last day of the month unless the end date of subsequent anti-cancer therapy is before that date. In that case, the incomplete anti-cancer therapy start date will be imputed as the end date of the anti-cancer therapy.
- If both day and month are missing, no imputation will be performed.
- Incomplete subsequent anti-cancer therapy stop dates will not be imputed.

Incomplete AE-related dates will be imputed as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of study intervention, the onset date will be replaced by the minimum of start of study intervention and AE resolution date (if not missing).
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case, the date of death, will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed.

For the purpose of survival analyses (PFS and OS), partially missing death dates will be imputed as follows:

- If only the day is missing, the death date will be imputed to the maximum of the (non-imputed) day after the date of last known alive date and the 15th day of the month.
- Otherwise it will not be imputed.

Incomplete date for tumor assessments will be imputed as follows:

- If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

Partial dates, which are not to be imputed according to the IAP, will be presented in the format "____YYYY". If values are imputed according to the IAP, imputed values will be presented in participant data listings and imputed information will be flagged.

Specifications for Computation

- Age (years): (date of given informed consent - date of birth + 1) / 365.25

- Body Mass Index (BMI) (kg/m^2): weight(kg)/[height(m)]^2
- Body Surface Area (BSA) (m^2): ([height (cm) x weight (kg)] / 3600) ^ ½
- Time since initial cancer diagnosis (months) = (date of randomization – date of initial cancer diagnosis)/30.4375
- Time since documented, locally advanced or inoperable disease diagnosis (months) = (date of randomization – date of documented, locally advanced or inoperable disease diagnosis)/30.4375.
- The duration of nicotine consumption is computed as follows:
  - If a subject is a former smoker, the difference in years between end date and start date of nicotine consumption is computed (end date of nicotine consumption – start date of nicotine consumption+1) / 365.25
  - If a subject is a current smoker, the difference in years between nicotine consumption collection date and start date of nicotine consumption is computed. (nicotine consumption collection date – start date of nicotine consumption+1) / 365.25
- Years since quitting of nicotine consumption is computed for former smokers only as (collection of nicotine consumption date - end date of smoking+1)/365.25.

Preferred Term for Analysis of World Health Organization's Drug Dictionary (WHO-DD) Coded Data

For data coded according to WHO-DD (e.g. concomitant medications), summaries will be presented at the preferred term (PT) level where the preferred term corresponds to codes ending in 01001. With this approach, variations of salt forms of active ingredients will be analyzed under the same term, e.g. diphenhydramine and diphenhydramine hydrochloride will be analyzed as the same preferred term, diphenhydramine.

Re-screened Participants

Re-screened participants will only be counted once in the SCR analysis set, considering the latest screening (screening with latest informed consent). If a participant is re-screened several times, they will be counted only once in the disposition table in the number of re-screened participants.

Definition of Pre-, During-, Post-pandemic Time Periods

Participants will be categorized based on the COVID-19 study period defined as:

- Pre-pandemic time period: subjects who started the treatment (earliest dose of any study intervention) before the start of COVID-19 pandemic.
- During-pandemic time period: subjects who started the treatment (earliest dose of any study intervention) on the same date or after the start of COVID-19 pandemic.
- Post-pandemic time period: the end of pandemic is considered not yet reached anywhere at the time of this IAP version redaction, consequently no participant will be grouped into the post COVID-19 study period for this study and no post-pandemic date will be defined.

The start of COVID-19 pandemic is defined by country as the earliest date of either the date of the first death from COVID-19 occurred in each country according to the published data by European Centre for Disease Prevention and Control on 26th June 2020 (https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide) or 11th March 2020 (when the WHO declared COVID-19 pandemic).

Software

All analyses will be performed using SAS 9.4 or higher in the SAS Grid environment.

10 Study Participants

The subsections in this section include specifications for reporting subject disposition and treatment/study discontinuations. Additionally, procedures for reporting protocol deviations are provided in Section 10.2.

10.1 Disposition of Participants and Discontinuations

Descriptive statistics will be used to summarize subject disposition and reason for discontinuation, based on the electronic case report form (eCRF) data. All participants within the SCR analysis set will be considered.

The following information will be reported:

- Total number of screened participants.
- Total number of re-screened participants.
- Number of participants who discontinued from the study prior to randomization overall and grouped by the main reason (as reported in on "Study Entry" page of the eCRF).
- Number of participants who completed the screening (main ICF signed), but have not been randomized yet
- Number of randomized participants overall and by treatment arm.
- Number of randomized participants who did not receive any study intervention by treatment arm.
- Number of randomized participants who completed or discontinued all study interventions by treatment arm.
- Number of randomized participants but not treated and still in study
- Number of randomized participants with any study intervention ongoing by treatment arm.
- Number of randomized participants allocated to each chemotherapy regimen overall and by treatment arm.
- Number of randomized participants who completed/discontinued immunotherapy grouped by main reason, death or progressive disease by treatment arm.

- Number of randomized participants who completed chemotherapy by main reason, death or progressive disease by treatment arm.
- Number of randomized participants who completed radiotherapy by treatment arm.
- Number of randomized participants with immunotherapy ongoing in each treatment arm.
- Number of randomized participants with chemotherapy ongoing in each treatment arm.
- Number of randomized participants with radiotherapy ongoing in each treatment arm.
- Number of randomized participants who completed cCRT phase and immunotherapy treatment as per protocol and are still in the study for follow-up, grouped by treatment arm.
- Number of randomized participants who have finalized cCRT phase as per protocol and discontinued immunotherapy but are still in the study for follow-up, grouped by treatment arm.
- Number of randomized participants who discontinued cCRT phase but completed immunotherapy treatment as per protocol and are still in the study for follow-up, grouped by treatment arm.
- Number of randomized participants who discontinued both cCRT phase and immunotherapy and are still in the study for follow-up, grouped by treatment arm.
- Number of subjects off-treatment and in follow-up with last known to be alive date within 1 month, between 1 and 2 months, between 2 and 3 months and more than 3 months before cut-off date
- Number of randomized participants who discontinued/completed the study, grouped by treatment arm and main reason (as reported on "Study termination" page of the eCRF).

The number of participants in each analysis set defined in Section 8.2 will also be summarized by treatment arm and by region and country. The discrepancies between planned and treated groups will be cross-tabulated and provided in a listing. The number of randomized subjects (IWRS) by region and country will be provided, as well as the number of subjects by randomization strata (IWRS).

The listing of individual disposition will include all participants (i.e. including screening failures.). The listing will include the following information (if applicable): planned arm (subjects having actual arm different from planned arm will be flagged and displayed in a separate listing), participant identifier, date of informed consent, included in the trial and reason for exclusion (if applicable), randomization date, first/last treatment date (for immunotherapy, chemotherapy and radiotherapy), reason off-treatment, date (relative day) and reason off-study, population flags. When the reasons, such as the reason off-treatment is categorized as "Other, specify" or "Withdrew consent from treatment, specify", the verbatim text as entered in the eCRF will be presented in the listing.

If any re-screened participants are observed, the listing of re-screened participants will be provided and will include the following information: planned arm, subject identifier, date of informed consent, date of randomization, subject identifier at screen failure, date of informed consent at screen failure, date of screening failure, reason of screening failure.

Additionally, a Kaplan-Meier plot of time to permanent immunotherapy discontinuation will be presented. Time to immunotherapy discontinuation is calculated as the time from randomization until the immunotherapy is discontinued or completed. Subjects who have immunotherapy ongoing are censored at last known to be alive date. This plot will be presented when at least 10 immunotherapy discontinuation events are observed, and it will exclude participants not treated by immunotherapy.

In addition, for the assessment of COVID-19 impact on this study, an overview table will be presented by treatment arm with the following information:

- Subjects potentially affected by COVID-19 (i.e. subjects who started treatment after start of the COVID-19 pandemic, or who started treatment prior to start of the COVID-19 pandemic and are still ongoing after the start of the pandemic)
- Subjects with at least one COVID-19 impact
- Subjects with at least one COVID-19 impact in the following categories: adverse events, death, protocol deviations, missed drug administration, treatment administration modifications, missed or delayed tumor assessments, missed visits, tele-visits replacing on-site visits, treatment discontinuation, study discontinuation.
- Number of subjects with missed or delayed tumor assessments, missed visits, tele-visits replacing on-site visits (1 / 2 / 3 / >3)

The frequency distribution of participants who started the treatment before or during the pandemic per country-specific start of COVID-19 study period (see Section 9 for details on the COVID-19 categorization by study period) will be also displayed.

A listing of COVID-19 impact will be provided with the following information: treatment arm, participant identifier, first and last date of treatment administrations, date of the event, visit, category, event, event description/reason.

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

Important protocol deviations will be determined for all participants by either medical review processes, site monitoring or programming based on the inclusion/exclusion criteria or other criteria presented in the protocol and documented in SDTM.

The following summary tables and listings of important protocol deviations will be provided (separately for pre-/post inclusion deviations):

- Frequency table per reason of important protocol deviations.
- Listing of important protocol deviations.

Summaries will be performed on the FAS

Further considerations for PK

Examples of IPDs or important events for PK in terms of this study may include, but are not limited to, the following:

- Dose delayed outside the allowed window (and actual dosing time not recorded)
- Dose change or missed dose
- Pre-dose sample collected after the actual start of infusion
- End-of-infusion sample collected before the actual end of infusion
- Sample processing errors that may lead to inaccurate bioanalytical results

For the above IPDs or important events for PK, the relevant PK data will be excluded from summaries based on the PK analysis set.

Refer to Section 16.1 for more details of protocol deviations and handling relevant to PK.

Impact of COVID-19 pandemic

Potential impact of COVID-19 pandemic in MS200647-0005 will be evaluated by an analysis of protocol deviations:

The listing of important protocol deviations will be enriched by the variable "COVID-19 Related Protocol Deviations" flagging all protocol deviations due to COVID-19.

10.2.2 Reasons Leading to the Exclusion from an Analysis Population

Clinically important protocol deviations which that will lead to the exclusion of a participant of the PK analysis set will be described case by case at the time of the PK analysis.

11 Demographics and Other Baseline Characteristics

If not stated otherwise, summaries will be presented for the FAS by treatment arm and overall. In case of IDMC, demographics will be presented using SAF analysis set.

11.1 Demographics

Demographic characteristics will be summarized using the following information from the "Demographics" eCRF page.

- Demographic characteristics
  - Sex: male, female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not collected at this site and Other

    - For participants reporting several races, all combinations will be reported under 'More than one race" category.
  - Ethnicity: Hispanic or Latino/Not Hispanic or Latino; Japanese/Not Japanese
  - Age (years): summary statistics
  - Age categories:
    - < 65 years, ≥ 65 years
    - 65-<75, 75-<85, ≥85 years
- Pooled Region:
  - North America
  - Europe
  - Asia
  - Rest of the World
- Geographic Region:
  - North America
  - Europe
  - Asia
  - Latin America
  - Australia and Oceania
- EEA (European Economic Area)
  - Yes
  - No
- PD-L1 status at screening
  - <1%
  - ≥1%

Specifications for computation are detailed in Section 9 and in Section 11.3.6 for PD-L1 status at screening.

A listing of individual demographics will be also provided with the following information: planned arm, subject identifier, sex, race (including all reported races in case of "multiple" races, and details in case of "other" race), ethnicity, geographic region, age, and age category, body mass index, body surface area, weight and height at Baseline and PD-L1 status at screening.

11.2 Medical History

Relevant past and ongoing medical conditions at Baseline will be summarized from the "Medical History Details" eCRF page, using the latest available version of Medical Dictionary for Regulatory Activities (MedDRA), PT as event category and MedDRA system organ class (SOC) body term as Body System category.

Medical history will be displayed in terms of frequency tables by treatment arm and overall: ordered by SOC and PT in alphabetical order. Each participant will be counted only once within each PT or SOC.

The related listing will provide the following information: planned arm, ethnicity (Japanese, Non-Japanese), participant identifier, age, sex, race, PT, reported medical history term, start date, end date, related to study condition, ongoing, and grade. This listing will be sorted by treatment arm, subject identifier, start date, end date, and PT.

11.3 Other Baseline Characteristics

Other Baseline characteristics include disease history, ECOG PS (see Section 15.6), vital signs, and skin status history. ECG and laboratory results at Baseline will be presented together with the results of all other assessments performed during the study in Section 15.6 and Section 15.3 respectively.

11.3.1 Vital Signs at Baseline

The following vital signs at Baseline will be collected from the "Vital signs" eCRF page and will be summarized:

- Height (cm)
- Weight at Baseline (kg)
- BMI (kg/m^2)
- BSA (m^2)

Specifications for computation of BMI and BSA are specified in Section 9.

11.3.2 Disease History

Information on disease characteristics collected on the "Disease History" eCRF page will be summarized as follows by treatment arm and overall:

- Tumor histology: adenocarcinoma, squamous cell carcinoma, large cell carcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, neuroendocrine carcinoma, diffuse idiopatic carcinoma, other
- Time since initial cancer diagnosis (months) computed as follows:

  (date of randomization – date of initial cancer diagnosis)/30.4375

- Time since documented, locally advanced or inoperable disease diagnosis (months) computed as follows:

  (date of randomization – date of documented, locally advanced or inoperable disease diagnosis)/30.4375

- Tumor, Node and Metastasis (TNM) classification at study entry: each T, N, M category will be described (TX, T0, N1, etc.)
- Molecular abnormalities:
  - Epidermal growth factor receptor (EGFR) (not done, mutated, wild type)
  - Anaplastic lymphoma kinase (ALK) translocation (not done, yes, no, not applicable)
  - ROS1 rearrangement (not done, yes, no, not applicable)
  - BRAF V600E mutation (not done, yes, no, not applicable)
  - Other molecular abnormalities (normal, abnormal)
- Stage at study entry (according to IASLC staging manual v8)
  - IIIa
  - IIIb
  - IIIc
- Has the subject a known history of one or more of the following (with or without the use of cisplatin)?
  - Renal insufficiency
  - Cardiac insufficiency
  - Severe nausea and/or vomiting
  - Hearing impairment
  - No

A dedicated listing will also be provided with the following information:

- Tumor histology, date of initial cancer diagnosis and time since initial cancer diagnosis (months), date of documented, locally advanced or inoperable disease and time since documented, locally advanced or inoperable disease (months), TNM classification at study entry, stage at study entry and known history of renal or cardiac insufficiency, severe nausea, hearing impairment.

- Molecular abnormality (result for EGFR (not done/mutated/wild type), presence of ALK translocation (not done/yes/no/not applicable), presence of ROS1 rearrangement (not done/yes/no/not applicable), presence of BRAF 600E mutation rearrangement (not done/yes/no/not applicable), other molecular abnormalities (normal/abnormal).

This listing will be sorted by planned treatment arm and participant identifier, and will also display age, sex, and race.

11.3.3 Skin Status History

Skin status history collected on the "Skin Status History" eCRF page will be summarized by the frequency and percentage of participants having the following skin status history:

- Personal history of frequent sunburn (yes, no, unknown)
- Personal history of easy sunburn (yes, no, unknown)
- Personal history of skin cancer (yes, no, unknown)
- Personal history of significant exposure to ultraviolet light (yes, no, unknown)
- Personal history of photosensitivity due to skin disorder (yes, no, unknown)
- Personal history of photosensitivity due to medication (yes, no, unknown)
- Family history of skin cancer in first degree relative (i.e. parents, siblings and/or children) (yes, no, unknown)
- Participants having history of skin conditions (0, 1, 2, >=3 conditions listed)

This table will use FAS and presented by treatment arm.

11.3.4 Nicotine Consumption

The nicotine consumption information will be collected from the "Nicotine consumption" e-CRF page and it will be described as follows:

- Nicotine use: Never smoker, Ever smoker (including further breakdown: former / current) as collected in e-CRF
- Smoking exposure (pack-years): 0, <20, 20-<40, ≥40 and summary statistics
- Years since quitting: <5, 5-<10, ≥10 and summary statistics
- A listing of nicotine consumption, including treatment arm, participant identifier, age, sex, race, will also be produced with the following data: nicotine consumption collection date (days), nicotine use status, start/end date of nicotine consumption, and duration of consumption (years).

11.3.5 Tumor Biopsy

Information regarding tumor biopsy collected on the "Tumor Biopsy (Block or Slides)" eCRF page will be displayed on a listing, including the following information: planned treatment arm, participant identifier, age, sex, race, specimen identifier, visit, block or slide available, tumor biopsy (block/slide) date, block sample type (archival/fresh), block method type, and number of

slides collected. This listing will be sorted by planned treatment arm, participant identifier, and sample collection date.

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12 Previous or Concomitant Medications/Procedures

Summaries will be performed on the FAS.

12.1 Previous Anti-Cancer Treatments for Non-small Cell Lung Cancer

Previous anti-cancer treatments for NSCLC are collected under the "Prior Anti-cancer Drug Therapies for NSCLC Details", "Prior Anti-cancer Radiotherapy for NSCLC Details", and the "Prior Anti-cancer Surgeries for NSCLC Details" eCRF pages.

Previous anti-cancer drug therapy, previous radiotherapy, and previous anti-cancer surgery will be presented in a listing as follows:

- The previous anti-cancer drug listing will contain planned treatment arm, participant identifier, age, sex, race, PT, medication name, start date, end date, route, intent of therapy and line number in case of metastatic/locally advanced, best response and documented progression disease date. This listing will be sorted by treatment arm, subject identifier, anti-cancer drug start date, end date, and PT.

- The previous radiotherapy listing will contain planned treatment arm, subject identifier, age, sex, race, start date, end date, location of radiotherapy, total dose, and number of fractions. This listing will be sorted by treatment arm, subject identifier, radiotherapy start date, radiotherapy end date, and location.
- The previous anti-cancer surgery listing will contain planned treatment arm, subject identifier, age, sex, race, date of surgery, name and location of surgery, curative intent of surgery (yes, no), and outcome of surgery. This listing will be sorted by treatment arm, subject identifier, surgery date, name of surgery, and location.

12.2 Previous and Concomitant Medications

Previous medications are medications, other than study intervention and pre-medications for study intervention, which started prior to the date of the first dose of the first study intervention. In case the date values will not allow to unequivocally allocate a medication to previous medication, the medication will be considered as previous medication.

Concomitant medications are medications, other than study interventions and pre-medications for study intervention, which are taken by participants at any time during the on-treatment period (see definition of on-treatment in Section 9). Medications taken on the first day of study intervention will be considered on-treatment. In case the date values clearly indicate that the medication cannot be allocated to previous medication and do not allow to unequivocally allocate it to concomitant medication, the medication will be considered as concomitant medication.

Specific rules will be used to define if a medication/procedure is considered as a previous, concomitant or both previous and concomitant medication/procedure as detailed in Appendix 5.

Concomitant medications will be summarized from the "Concomitant Medication Details" eCRF. Anatomical Therapeutic Chemical (ATC)-2nd level and PT will be tabulated according to the current version of the WHO-DD dictionary. In case multiple ATCs are assigned to a drug, all ATC-2nd level will be used for reporting.

A participant will be counted only once within a given drug class and a given drug name, even if he/she received the same medication at different times. The summary will be sorted by Drug Class and preferred term in alphabetical order.

Previous and concomitant medications will be presented in listings including planned treatment arm, participant identifier, age, sex, race, preferred term, medication name as provided by the Investigator, start/end date, dose, dose units, frequency, route, and reason for the medication. These listings will be sorted by treatment arm, subject identifier, start date, end date (note that entries with a missing end date will be considered as ongoing and will be displayed after non-missing date in case of same start date), and preferred term.

12.3 Concomitant Procedures

All concomitant procedures, which were undertaken any time during on-treatment period (see definition of on-treatment in Section 9), will be summarized according to the CRF page "Concomitant Procedures Details".

An overview table of concomitant procedures will be presented with the following information:

- Subjects with at least one Concomitant Procedure and type of procedure
- Subjects with concomitant procedures, starting prior to first dose of any study intervention and type of procedure
- Subjects with concomitant procedures, starting during the on-treatment period and type of procedure

Concomitant procedures will be presented in a listing including planned treatment arm, subject identifier, age, sex, race, name of procedure (as provided by the investigator in case of "Other, please specify"), start date, end date, ongoing (yes, no), indication (as provided by the investigator), and reason for procedure. The listing will be sorted by treatment arm, participant identifier, start date, end date (note that entries with a missing end date will be considered as ongoing and will be displayed after non-missing date in case of same start date), and procedure name.

12.4 Subsequent Anti-Cancer Treatment

Subsequent anti-cancer treatment is collected under the "Anti-Cancer Treatment After Discontinuation Details", "Radiotherapy After Discontinuation Details" and "Surgery After Discontinuation Details" eCRF pages.

The number of participants with at least one subsequent anti-cancer treatment or procedure (drug therapy, radiotherapy or surgery), at least one subsequent anti-cancer drug therapy, at least one subsequent radiotherapy, and at least one subsequent surgery will be tabulated. Best response across all subsequent anti-cancer treatments will be included.

Subsequent anti-cancer treatment (medication, radiotherapy and surgery) will be presented in a listing including planned treatment arm, participant identifier, age, sex, race, treatment type, preferred term/medication name, regimen name (if medication), best response (if medication), start date, end date (if medication or radiotherapy), radiotherapy site/name of surgery/location (if radiotherapy or surgery). This listing will be sorted by treatment arm, subject identifier, start date, end date, medication type, preferred term, and medication name.

12.5 Premedication

Premedication are defined as medications administered per protocol on the same day as, but prior to, study intervention.

Premedication for immunotherapy will be based on the "Premedication Immunotherapy" eCRF page (participants for whom the question "Has the subject received premedication before immunotherapy infusion?" is answered "Yes" at the corresponding visit). Premedication for chemotherapy will be based on the "Premedication Chemotherapy" eCRF page (participants for whom the question "Has the subject received premedication before chemotherapy infusion?" is answered "Yes" at the corresponding visit).

The number of participants receiving premedication for immunotherapy and the number of participants receiving premedication for chemotherapy will be summarized for each treatment visit. Percentages will be calculated on the number of participants who actually received a dose of immunotherapy dose (or a chemotherapy dose, respectively) at the associated visit.

Listings of premedication for immunotherapy and of premedication for chemotherapy will be provided. These listings will include planned treatment arm, participant identifier, age, sex, race, name of medication, visit, date of administration (for immunotherapy), start and end date (for chemotherapy) , dose, unit, and route. These listings will be sorted by treatment arm, subject identifier, start date/time of premedication, end date/time of premedication, and medication name.

13 Study intervention Compliance and Exposure

Summaries will be performed on the SAF analysis set by treatment arm.

Participants will be treated with immunotherapy (M7824 for Arm 1 and Placebo for Arm 2) in combination with concomitant chemo-radiotherapy (cCRT), followed by immunotherapy (M7824 for Arm 1 and durvalumab for Arm 2). Administration details of all study interventions are given in Section 6 of the study protocol. In case of chemotherapy switchers, information after their switch will not be provided.

Duration of treatment and number of infusions (or fractions in case of radiotherapy) summaries will be based on "Immunotherapy Administration Details" and "Radiotherapy Administration Details" eCRFs pages. For chemotherapy, each component has a unique administration eCRF page so dosing details will be collected from: "Paclitaxel Administration Details", "Carboplatin Administration Details", "Cisplatin Administration Details", "Etoposide Administration Details", and "Pemetrexed Administration Details" eCRF pages. Dosing calculations for chemotherapy and radiotherapy will also be based on the corresponding eCRF pages mentioned previously whether for immunotherapy, the planned dose (prepared by the unblinded pharmacist) will be captured in the drug preparation form.

Duration of Therapy (Weeks) and Number of Infusions/Fractions for Immunotherapy, Chemotherapy and Radiotherapy

An infusion is regarded as being administered if the actual dose received is > 0.

Duration of treatment will be calculated, as follows:

- Immunotherapy:

Duration of immunotherapy (weeks) = (date of last immunotherapy dose – date of first immunotherapy dose + 14)/7

- Cisplatin (50 mg/m^2)/etoposide (50 mg/m^2) regimen:

Duration of cisplatin (weeks) = (date of last cisplatin dose – date of first cisplatin dose + 21)/7

Duration of etoposide (weeks) = (date of last etoposide dose – date of first etoposide dose + 24)/7

- Carboplatin (AUC 2)/paclitaxel (45 mg/m^2) regimen:

Duration of carboplatin (weeks) = (date of last carboplatin dose – date of first carboplatin dose + 7)/7

Duration of paclitaxel (weeks) = (date of last paclitaxel dose – date of first paclitaxel dose + 7)/7

- Cisplatin (75 mg/m^2) / pemetrexed (500 mg/m^2) regimen:

Duration of cisplatin (weeks) = (date of last cisplatin dose – date of first cisplatin dose + 21)/7

Duration of pemetrexed (weeks) = (date of last pemetrexed dose – date of first pemetrexed dose + 21)/7

- Radiotherapy:

Duration of radiotherapy (weeks) = (date of last dose – date of first radiotherapy dose +1) / 7

In case of chemotherapy total regimen calculations, the date of the first component to be administered and the date of the last dose of the last component to be administered will be considered as first and last dose respectively. For total duration of the regimen:

Total duration of chemotherapy regimen (weeks): (date of last dose – date of first dose + cycle length) / 7

Considering as the regimen cycle length 28 days for cisplatin/etoposide regimen, 7 days carboplatin/paclitaxel regimen and 21 days for cisplatin/pemetrexed regimen.

The following summary tables will be provided:

- Duration of therapy (weeks) for each treatment (immunotherapy, chemotherapy – by regimen and by component – and radiotherapy)
- Number of infusions/fractions received for each treatment (immunotherapy, chemotherapy – cisplatin, etoposide, pemetrexed, paclitaxel or carboplatin – and radiotherapy)

Cumulative Dose, Dose Intensity and Relative Dose Intensity

Immunotherapy and chemotherapy calculations and summaries will be based on the "Administration Details" eCRF page for each therapy. In case of chemotherapy, each individual component administration eCRF page will be used.

Due to the double-blind design of the study, in order to determine the actual dose of immunotherapy infused to the participant, the following calculation will be performed:

$$\text{Actual } \textit{immunotherapy} \text{ dose infused (mg)} = \frac{\text{Dose prepared} \times \text{Volume infused}}{\text{Volume prepared}}$$

Additionally, for carboplatin administration, the planned dose is reported as AUC and the actual dose is reported in mg, hence the Calvert equation will be used to convert the planned dose to mg, in order to calculate RDI:

$$\textit{Maximum Carboplatin Dose } (mg) = \textit{Target AUC } (\text{mg} \cdot \text{min/mL}) \times (\text{Glomerular Filtration Rate/ min} + 25)$$

The Glomerular Filtration Rate (GFR) value will be capped at 125 ml/min for use in the carboplatin planned dose formula, following the Cockroft-Gault equation:

$$\textit{Estimated GFR } = \frac{(140 - \textit{age (years)}) * \textit{weight (kg)} * (0.85 \textit{ for females only})}{(72 * \textit{creatinine}(mg/dL))}$$

In case of missing age, weight or creatinine values at a given visit, the value from the previous visit will be used.

Actual dose of chemotherapy will be calculated considering BSA at each visit:

$$\textit{Actual chemotherapy dose infused } (mg/m^2) = \frac{\textit{Actual dose } (mg)}{\textit{BSA } (m^2)}$$

- Cumulative dose:

The cumulative dose of immunotherapy and chemotherapy per participant in a time period will be the sum of the actual dose levels that the participant received within that period (i.e. total dose administered [mg – for immunotherapy; mg/m^2 - for chemotherapy]).

Separate cumulative doses by immunotherapy drug will be displayed in unblinded deliveries (placebo, durvalumab, bintrafusp alfa).

For radiotherapy, total dose (Gy) as collected in the eCRF will be displayed.

- Dose Intensity:

Dose intensity (DI) of immunotherapy (mg/cycle) and chemotherapy (mg/m^2/cycle) per participant in a time period will be defined as:

$$\text{Dose Intensity } (units) = \frac{\text{Cumulative Dose } (unit)}{\frac{Duration\ of\ treatment\ (weeks)}{Cycle\ length\ (weeks)}}$$

Separate DI by immunotherapy drug will be displayed in unblinded deliveries (placebo, durvalumab, bintrafusp alfa).

DI for each individual chemotherapy component (cisplatin, etoposide, carboplatin, pemetrexed, and paclitaxel) will be calculated according to their chemotherapy regimen administration scheme.

DI will not be calculated for radiotherapy.

As cycle length differs between study interventions (immunotherapy and chemotherapy), **Error! Reference source not found.** specifies which value should be used in each case.

Table 4 Cycle Length Specifications

Study intervention	Regimen (chemotherapy components)	Cycle length	Number of planned doses per cycle
Immunotherapy	Not Applicable	2 weeks	1 dose
Chemotherapy	Cisplatin (50 mg/m^2) / etoposide (50 mg/m^2)	4 weeks	Cisplatin: 2 doses Etoposide: 5 doses
	Carboplatin (AUC 2) / paclitaxel (45 mg/m^2)	1 week	1 dose
	Cisplatin (75 mg/m^2) / pemetrexed (500 mg/m^2)	3 weeks	1 dose

AUC = Area Under the Curve

- Relative Dose Intensity:

The Relative Dose Intensity (RDI) for immunotherapy and chemotherapy will be defined as the actual DI divided by the planned dose per week and expressed as a percentage:

$$\text{Relative Dose Intensity (\%)} = \frac{\text{Dose Intensity } per\ cycle}{\text{Planned dose per } cycle} \times 100$$

Planned dose per cycle (mg – for immunotherapy; mg/m^2 - for chemotherapy), will be determined as follows:

$$\text{Planned dose per } cycle\ (units) = Sum\ of\ planned\ doses\ in\ 1\ cycle$$

For carboplatin and durvalumab, the dose administered at week 1 day 1 will be used as planned dose.

Separate RDI by immunotherapy drug will be displayed in unblinded deliveries (placebo, durvalumab, bintrafusp alfa).

RDI for each individual chemotherapy component (cisplatin, etoposide, carboplatin, pemetrexed, and paclitaxel) will be calculated according to their chemotherapy regimen administration scheme.

RDI will not be calculated for radiotherapy.

A summary table will be provided for immunotherapy and chemotherapy (cisplatin, carboplatin, pemetrexed, etoposide, and paclitaxel) displaying: Cumulative dose, DI, and RDI. Radiotherapy total dose will be also summarized.

A listing of treatment compliance and exposure will include treatment arm, participant identifier, age, sex, race, radiotherapy start and stop date, radiotherapy dose, visit, infusion start date and time, infusion end date and time, type of study intervention, if administration was completed (yes, no), if administration was modified (yes, no), modification description and reason for modification, actual dose infused. This listing will be sorted by treatment arm, participant identifier, infusion start date, and infusion end date.

An additional listing of treatment exposure will include treatment arm, participant identifier, age, sex, race, duration of therapy (weeks), total number of infusions/fractions received, cumulative dose of therapy, DI, and RDI (%). This listing will be sorted by treatment arm and participant identifier.

Therapy Delays

Delays of therapy will be defined by infusion as follows:

- For immunotherapy administrations as the number of days since last infusion – 14
- For chemotherapy administrations:
    - If the participant is receiving cisplatin (50 mg/m^2) / etoposide (50 mg/m^2) regimen:
        - Delays of therapy for cisplatin will be derived by infusion as the number of days since the start of last infusion –7 if the last infusion was the first infusion within a cycle, otherwise as the number of days since the start of last infusion – 21.
        - Delays of therapy for etoposide will be derived by infusion for cycle day 1 as the number of days since start of last infusion -24, for day 2, 3, 4 and 5 within a cycle as the number of days since last infusion -1.
    - If the participant is receiving carboplatin (AUC 2) / paclitaxel (45 mg/m^2) regimen:
        - Delay in carboplatin as the number of days since last infusion – 7.
        - Delay in paclitaxel as the number of days since last infusion – 7.
    - If the participant is receiving cisplatin (75 mg/m^2) / pemetrexed (500 mg/m^2) regimen:
        - Delay in cisplatin as the number of days since last infusion – 21.
        - Delay in pemetrexed as the number of days since last infusion – 21.

Delay on radiotherapy administration will not be provided.

If the value above is > 0 days, this will be classed as a delay. A participant may have more than one treatment delay throughout the course of treatment.

The following will be summarized in a table:

- Number of subjects with at least one delayed infusion
- Number of subjects with delays (1-2 days, 3-8 days, 9-15 days, ≥ 16 days)
- Number of delays per subject (1 delay, 2 delays, 3 delays, ≥ 4 delays).

A summary table will be provided displaying for immunotherapy and chemotherapy (cisplatin, carboplatin, pemetrexed, paclitaxel, etoposide).

Dose Reductions

Chemotherapy dose reductions as recorded on the "Cisplatin Administration Details", Etoposide Administration Details", "Carboplatin Administration Details", "Paclitaxel Administration Details" and "Pemetrexed Administration Details" pages of the eCRF (i.e. answer to the question "Is there a change in dose?" = "Dose adjusted") will be used for analysis. The number of participants with at least one dose reduction, reasons for dose reduction, as well as a categorization of the number of infusions with dose reduced (1 / 2 / ≥ 3) will be summarized.

Summary tables will be provided for each chemotherapy (cisplatin, etoposide, carboplatin, paclitaxel, and pemetrexed). No dose reduction is allowed for immunotherapy or radiotherapy.

Treatment Temporary Interruption

Temporary interruptions to immunotherapy and chemotherapy infusion as recorded on the "Treatment Administration Details" pages of the eCRF will be used for analysis. The number of subjects with at least one infusion interruption, reason for temporary infusion interruptions, as well as a categorization of the number of study intervention interruptions (1 / 2 / ≥ 3) will be summarized.

Chemotherapy Switch

A listing of participants who had a chemotherapy switch will be provided based on the "Chemotherapy Switch" eCRF page and it will include: treatment arm, participant identifier, age, sex, race, initial chemotherapy regimen, new chemotherapy regimen, reason for switch.

13.1 Radiotherapy Plan Compliance

Compliance or non-compliance with the radiotherapy plan will be categorized as follows:

- **Participants with compliant plans**: are those radiotherapy plans with a final score of 'Pass". This will include plans that have no variations from the RT guidelines (ie, which pass the initial Certified Medical Dosimetrist (CMD) case review) **and** those that have acceptable variations from guidelines based on the determination of the Medical Doctor (MD) reviewer.

- **Participants with non-compliant plans**: are those radiotherapy plans with a final score of "Fail". All of these plans will have been escalated for MD review and scored as a 'Fail" due to unacceptable variations from guidelines.

A summary table displaying the proportion of participants with compliant and non-compliant radiotherapy plans per treatment arm will be provided.

14 Efficacy Analyses

The primary endpoint of this study is based on PFS according to RECIST 1.1 criteria assessed by investigator. Evidence of efficacy (study success) is entitled when the stratified log rank test is significant at the primary analysis (when 70 PFS events and a minimum follow-up of 15 months after randomization of the last participant are reached).

The hypothesis regarding the primary PFS endpoint is:

$H_0^{PFS}: \lambda_M^{PFS}(t) = \theta\lambda_D^{PFS}(t), \theta \geq 1$ *versus* $H_1^{PFS}: \lambda_M^{PFS}(t) = \theta\lambda_D^{PFS}(t), \theta < 1$; $\alpha^{PFS} = 2.5\%$ one-sided; where $\lambda^{PFS}(t)$ represents the hazard at time (t) and θ the unknown constant of proportionality of hazards in the treatment groups M (Arm 1) and D (Arm 2).

Efficacy analysis will be performed using the FAS.

14.1 Progression-Free Survival

14.1.1 Primary Objective: PFS According to RECIST 1.1 Assessed by investigator

The PFS time is defined as the time from randomization to the date of the first documentation of objective Progressive Disease (PD) as assessed by the investigator according to RECIST 1.1 criteria or death due to any cause, whichever occurs first. Death will be considered as event if reported within:

- 16 weeks (112 days) after the last tumor assessment without progression or the randomization (whichever occurs later) – during the first 24 months of follow-up
- 24 weeks (168 days) after the last tumor assessment without progression or the randomization (whichever occurs later) - after 24 months of follow-up.

PFS time in months will be computed as follows:

PFS = (date of PD or death/censoring – date of randomization + 1) / 30.4375 (months) The following censoring rules, summarized in Table 5, will be applied for the PFS computation:

- Participants with neither assessment of tumor progression, nor death date within two scheduled tumor assessments intervals after last tumor assessment or date of randomization will be

censored on the date of the last tumor assessment or at the randomization date, whichever is later. For two scheduled tumor assessments intervals it is meant:

- during the first 24 months from randomization, 16 weeks
- after the first 24 months from randomization, 24 weeks

- Participants with an event after two scheduled tumor assessment intervals after the last evaluable response assessment will be censored at the date of the last evaluable response assessment or at the randomization date, whichever comes later. For event after two scheduled tumor assessment intervals it is meant:
  - during the first 24 months from randomization, event after 16 weeks without assessments
  - after the first 24 months from randomization, event after 24 weeks without assessments
- Participants who start new anti-cancer treatment prior to an event will be censored on the date of the last evaluable assessment before anti-cancer therapy is given or at the randomization date, whichever comes later.

  Note that in this study, palliative bone radiotherapy can be given while the patient is still receiving the study drug (as per protocol, see section treatment beyond progression) but disease progression must have been documented and the participant will not be censored.
- Participants with non-evaluable Baseline assessment or with all post-Baseline assessments stated as non-evaluable will be censored at the randomization date unless death occurred on or before the time of the second planned tumor assessment (i.e.16 weeks), in which case the death will be considered an event.

Table 5 Definition of date of PFS event/censoring

Status		Censoring	Date of event / censoring
Progressed or died	Within two subsequent scheduled tumor assessments after last evaluable response assessment of CR, PR, SD, or randomization	Event	Minimum (date of PD, date of death)
	Otherwise	Censored	Date of last evaluable assessment with outcome CR, PR, SD, or date of randomization, whichever is later
Neither progressed nor died		Censored	Date of last evaluable assessment before the start of a new anti-cancer-treatment or date of randomization, whichever is later
Baseline or all post-Baseline assessments non-evaluable		Censored	Randomization date

CR = Complete response, PR=Partial response, SD=Stable disease, PD=Progressive disease

The last tumor assessment date is defined as the last available and evaluable tumor assessment performed prior to the cut-off date or prior to subsequent anti-cancer therapy. If no evaluable tumor assessment date is available, this date will be replaced by the randomization date.

Primary Analysis

The primary analysis (PA), will be conducted when at least 70 PFS events and a minimum follow-up of 15 months after randomization of the last participant have been reached. It will focus on evaluating the differences between Arm 1 (cCRT + M7824 followed by M7824) and Arm 2 (cCRT + placebo followed by durvalumab) in terms of PFS.

Kaplan-Meier Analysis

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics (PFS rates at 6, 9, 12, 18, 24, 36, 48, and 60 months) including the corresponding two-sided 95% CIs.

The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) and CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (1980) (CONFTYPE=loglog default option in SAS Proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula. A Kaplan-Meier plot will also be displayed.

Frequency (number and percentage) of participants with each event type (PD or death) and censoring reasons will be presented by treatment arm. Censoring reasons are as follows:

- Ongoing in the study without an event
- No Baseline assessment
- No evaluable post-Baseline assessment
- Start of new anti-cancer therapy before and event
- Event after two scheduled tumor assessment intervals after the last evaluable response assessment
- Withdrawal of consent
- Lost to follow-up:

  Lost to follow-up will include the following participants:

  - Lost to follow-up status will be collected on the eCRF treatment termination page or eCRF study termination page or end of assessment visit page prior to the analysis cut-off.
  - Participants with the last date known to be alive > 14 weeks prior to the analysis cut-off date (survival follow-up will take place every 12 weeks ± 2 weeks)

A listing of PFS according to RECIST 1.1 assessed by investigator will be provided with the following information: planned treatment arm, subject identifier, age, sex, race, date of randomization, date of last tumor assessment, censored (yes/no), date of event/censoring, event/censoring reason, and time to event. This listing will be sorted by planned treatment arm and subject ID.

Cox's Regression Model

The Cox's regression model will be applied in addition to the Kaplan-Meier method in order to compare the PFS time between the randomization groups (Arm 1 *vs* Arm 2).

Stratified analyses will use the stratification factors: chemotherapy regimen and PD-L1 expression in tumor cells (< 1% *vs* ≥ 1%). PD-L1 expression will be determined retrospectively during the safety run-in and prospectively during the expansion phase by the Ventana PD-L1 (SP263) investigational use only (IUO) assay in central laboratories.

The treatment effect will be estimated using a Cox's Proportional Hazard model stratified by PD-L1 expression status and chemotherapy regimen to calculate the hazard ratio (HR). Each stratum will define a separate Baseline hazard function (using the 'STRATA' statement in SAS PROC PHREG), i.e. for the i-th stratum, the hazard function is expressed as: $h(i;t) = h(i,0;t) \exp(\beta X)$, where h(i,0;t) defines the Baseline hazard function for the i-th stratum and x defines the treatment group (0=Arm 2, 1=Arm 1) and beta is the unknown regression parameter.

Ties will be handled by replacing the proportional hazards model by the discrete logistic model. With this ties option, the Score test in the Cox's proportional hazards model is identical to the log-rank test.

For the PA, a table including the Kaplan-Meier estimates and the Cox's proportional hazards model results will be provided, together with a Kaplan-Meier plot.

14.1.2 Sensitivity Analyses for PFS

To assess the robustness of the PA, the following sensitivity analyses will be conducted:

- PFS according to RECIST 1.1 as assessed by investigator considering all deaths as events without applying the censoring rule for death.
- PFS according to RECIST 1.1 as assessed by investigator considering all PD and deaths as events without applying the censoring rules for PD or death.
- PFS according to RECIST 1.1 as assessed by investigator considering the initiation of any subsequent anti-cancer therapies as PD instead of censoring.
- Unstratified PFS according to RECIST 1.1 as assessed by investigator , considering death and PD 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.
- In case 10% or more participants switch chemotherapy, the analysis for PFS will be repeated using PD-L1 expression and the chemotherapy regimen that was given mostly for stratification.

Multivariable Cox Regression

Multivariable Cox regression analysis will be carried out to assess and adjust the treatment effect for relevant Baseline factors of potential prognostic impact. The subgroup variables defined in Section 8.2 "Definition of Analysis Sets and Subgroups" will be included in the model. A stepwise selection procedure will serve to identify explanatory variables of potential prognostic values additional to the randomization strata, which will be included in all models during the selection procedure. The stepwise selection method in SAS (PROC PHREG) will be used. The level of significance for an explanatory variable to enter the model is set to 0.15 (boundary for p-value of Score test for inclusion) and the significance level for removing it is set to 0.40 (boundary for p-value of Wald test for exclusion). Once the selection procedure is finalized, the treatment group

will be added to the effect of treatment on PFS when adjusted for the selected explanatory variables.

The Cox's Proportional Hazard model is defined as: $h(t) = h(0;t) \exp(Xb)$, where $h(0;t)$ defines the Baseline hazard function, X defines the vector of explanatory variables and b the unknown vector of regression parameters. The HR of all selected explanatory variables and of treatment effects will be reported including 2-sided 95% CIs. No interactions will be considered. Post-Baseline factors will not be considered for the model.

Methods for Evaluating the Validity of Model Assumptions

The proportional hazards assumption will be checked visually for the PA by plotting log(-log(PFS)) versus log(time) within each randomization stratum. Schoenfeld residuals including a LOESS curve will be plotted to investigate graphically violations of the proportional hazard's assumption. Schoenfeld residuals will be computed in SAS using the PHREG procedure and using the OUTPUT statement and the keyword RESSCH. With proportional hazards the LOESS curve should be parallel to the x-axis.

14.1.3 Subgroup Analysis for PFS

The subgroup variables defined in Section 8.2 "Definition of Analysis Sets and Subgroups" will be considered for the following analyses:

- The PFS time between Arm 1 and Arm 2 will be compared using a two-sided unstratified log rank test per subgroup level; and the unstratified HR and its corresponding 95% CI will be computed per subgroup level. The HR and its corresponding 95% CI of all subgroups will also be presented in a forest plot.

  To assess the heterogeneity of treatment effects across the subgroup levels, two Cox regression models will be fitted with the PFS time as the dependent variable; subgroup, treatment arm, and with and without the treatment arm-by-subgroup interaction as explanatory variables:

  Model 1: treatment arm + subgroup

  Model 2: treatment arm + subgroup + treatment arm*subgroup-variable

  A p-value for the interaction test will be provided together with the HR and corresponding 95% CI of the interaction model parameter.

14.2 Overall Survival

Overall survival (OS) will be tested as a secondary endpoint of this study. The same methodology as used for the PFS analysis will apply to OS (see Section 14).

The OS time is defined as the time from the date of randomization to the date of death due to any cause:

OS = (date of event/censoring – date of first study intervention + 1)/30.4375 (months).

For participants alive at the time of the data cut-off date or who are lost to follow up, OS will be censored at the last date known to be alive.

The date of event/censoring is defined in the following table:

Table 6 Survival Event/Censoring rules for OS

Survival status	Date of event / censoring	Censoring
Participants alive or lost to follow-up before or at cut-off date	Last date known to be alive	Censored
Participants who died before or at cut-off date	Date of death	No censoring

The following complete dates will be used to determine the last date known to be alive. Only those that are before or at the data cut-off shall be used in the derivation. Dates after the data cut-off will be ignored by the derivation:

- All participant assessment dates (blood draws [laboratory, PK], vital signs, performance status, ECG, tumor assessments, PRO assessments).
- Start and end dates of anti-cancer therapies administered after study intervention discontinuation
- AE start and end dates
- Last known alive date collected on the 'Subject Status / Survival Follow-Up" eCRF page (do not use the follow up date).
- Study interventions start and end dates
- Randomization date
- Date of discontinuation from the "Study Termination" eCRF page (do not use if reason for discontinuation is lost to follow-up or death)

Only dates associated with actual examinations of the participant reported in the eCRF will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed will not be used.

The analysis of OS time will be performed using the Kaplan-Meier method and the same approach described for PFS in Section 14.1. Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including corresponding two-sided 95% CIs. They will be estimated at 12, 18, 24, 36, 48, and 60 months.

A Cox model will be used with the same approach as for PFS described in Section 14.1.

A subject listing will provide the following information: treatment arm, participant identifier, age, sex, race, date of randomization, date of event/censoring, event/censoring reason, and time to event.

14.2.1 Sensitivity Analyses for OS

To assess the robustness of the OS analysis, the following sensitivity analyses will be conducted:

- Unstratified OS analysis
- In case 10% or more participants switched chemotherapy, the analysis for OS will be repeated using PD-L1 expression and the chemotherapy regimen that was given mostly for stratification.

14.2.2 Subgroup Analysis for OS

The OS analysis as described in Section 14.1.3 will be conducted in the subsets of participants defined in Section 8.2.

14.3 Follow-Up Time

14.3.1 Follow-Up Time (PFS)

A Kaplan-Meier analysis for PFS assessed by investigator follow-up will be generated to assess the follow-up time in the treatment arms reversing the PFS censoring and event.

Kaplan-Meier estimates will be presented by treatment group together with the median time of follow-up for PFS. In particular, the follow-up rate at 6, 9, 12,18, 24, 36, 48, and 60 months will be estimated with corresponding two-sided 95% CIs. A Kaplan-Meier plot will also be displayed.

14.3.2 Follow-Up Time (OS)

The analyses performed in Section14.3.1 will be conducted on OS data. A Kaplan-Meier plot will also be displayed.

14.4 Objective Response Rate According to RECIST 1.1 as Assessed by Investigator

The confirmed Objective Response Rate (ORR) is defined as the number of participants having a confirmed best overall response assessment of CR or PR, out of the total number of participants belonging to the analysis set of interest. Unconfirmed ORR will also be presented.

Best overall response will be assessed based on the tumor response at different evaluation time points from randomization until the first documented PD according to RECIST 1.1. Only tumor assessments performed before the start of any further anti-cancer treatment will be considered in the assessment of best overall response. Clinical deterioration will not be considered as documented PD.

The best overall responseaccording to RECIST 1.1 as assessed by investigator can be CR, PR, non-CR/non-PD, SD, PD, or NE.

The following requirements are taken into account for unconfirmed best overall response:

- CR = at least one determination of CR before disease progression
- PR = at least one determination of PR before disease progression (and not qualifying for a CR)
- SD = at least one SD assessment ≥ 6 weeks after the first study intervention and before disease progression (and not qualifying for CR or PR)
- Non-CR/Non-PD = at least one non-CR/non-PD assessment ≥ 6 weeks after start date and before progression with no measurable disease at baseline (and not qualifying for CR or PR)
- PD = at least one PD assessment (and not qualifying for CR, PR, SD or non-CR/non-PD)
- If a subject has a missing Baseline tumor assessment and/or no (or NE) tumor assessments on-treatment, best overall response will be "Not Evaluable" (NE).
- In the case the single response is SD, SD must have been assessed no less than 6 weeks (at least 42 days) after randomization, otherwise, the best response will be NE.

Table 77 summarizes the derivation rules described by Eisenhauer, et al. (2009) for the best overall response when confirmation from subsequent assessment is needed. For subjects who have non-target lesions only at Baseline, the timepoint tumor assessment of "Non-CR/non-PD" will be evaluated with the same criteria as SD (minimum criteria for SD duration) in deriving the overall best overall response.

Table 7 Confirmation Rules for Best Overall Response

Overall response at 1st time point	Overall response at subsequent time point	Best Overall Response
CR	CR*	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met; otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met; otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR*	PR
PR	PR*	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = non-evaluable

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to Baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best overall response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best overall response is PR.

*The second assessment should be at least 4 weeks after the first one to confirm response.

The following requirements are taken into account for confirmed best overall response:

- CR = at least two determinations of CR at least 4 weeks apart (with no PD in between)
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart (and not qualifying for a CR), with no PD in between
- SD = at least one SD assessment (or better) $\geq$ 6 weeks after randomization date and before progression (and not qualifying for CR or PR)
- Non-CR/Non-PD = at least one non-CR/non-PD assessment (or better) $\geq$ 6 weeks after start date and before progression with no measurable disease at baseline (and not qualifying for CR or PR)
- PD = progression $\leq$ 16 weeks after randomization date (and not qualifying for CR, PR, SD or non-CR/non-PD).
- Not Evaluable (NE): all other cases.

The Disease Control Rate (DCR) is defined as the proportion of participants with confirmed best overall response according to the evaluation criteria of CR, PR, or SD out of the total number of participants belonging to the analysis set of interest. DCR for unconfirmed best overall response will also be presented.

The number and percentage of participants with confirmed and unconfirmed best overall response of CR, PR, SD, PD, and NE will be tabulated for both treatment arms. Tables will include DCR.

A listing will be provided with the following information: treatment arm, subject identifier, age, sex, race, each study intervention first/last dose, confirmed/unconfirmed best overall response, date of subsequent anti-cancer therapy, date of death, visit, date(s) of imaging (days since randomization), lesion type (target lesion, non-target lesion, new lesion), description of target lesions (size, site, method, response), non-target lesions (status, site, method, response) and new lesions (site, method), sum of lesion diameters, percent change in target lesions from Baseline, and overall response. This listing will be sorted by treatment arm, participant identifier, visit, date of imaging and lesion ID.

The confirmed and unconfirmed best overall response (including ORR and DCR) will be calculated per treatment arm with a two-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).Overall Response at the end of cCRT phase assessed by investigator will also be tabulated. For the computation overall response at the end of ccRT phase, assessments at "Evaluation visit 1"/ "Unscheduled evaluation visit 1" occurring within 47 and 67 days from randomization and before the start of any subsequent anticancer treatment will be considered. Subjects with missing assessment/missing date of assessment/assessment out of range/ assessment performed after the start of the subsequent anticancer treatment will be classified in the "Missing" category.

A summary table of the following reasons for non-evaluable confirmed best overall response as adjudicated by the investigator by treatment arm will be provided:

- No Baseline assessment

- No post-Baseline assessments due to death within 8 weeks after randomization
- No post-Baseline assessments due to other reasons
- All post-Baseline assessments have overall response 'Non-evaluable'
- New anti-cancer therapy started before first evaluable post-Baseline assessment
- SD (or better) of insufficient duration (< 6 weeks after randomization without further evaluable tumor assessment) - Note: Special and rare cases where best overall response is NE due to both early SD and late PD will be classified into this category
- PD too late (i.e. tumor assessment of PD was >16 weeks after randomization and there was no evaluable tumor assessment in between)
- Non-CR/non-PD of insufficient duration (< 6 weeks after randomization without further evaluable tumor assessment)

A waterfall plot for best percent change from Baseline in sum of diameters of all target lesions and for the percentage change of sum of longest diameter at first scan of all target lesions will be provided. Participants with missing/non-evaluable baseline and/or post-baseline tumor assessment will be excluded from the plot.

Additionally, a spider plot will be displayed by treatment arm. The unconfirmed best overall response assessed by Investigator will be showed in the plot and color code will be used to differentiate responses: "CR", "PR" vs "SD, PD or NE". Subjects with missing/non-evaluable baseline and/or post-baseline tumor assessment will not be included in this analysis. Timepoints for the first occurrence of a new lesion and of treatment discontinuation (all study interventions – immunotherapy, chemotherapy and radiotherapy – have their treatment termination pages filled) will be shown in the plot.

14.4.1 Subgroup Analysis for ORR

Logistic models will be fitted to assess the heterogeneity of treatment effect across subgroup levels for the confirmed ORR (using subgroups defined in Section 8.2). A logistic regression model will be fitted with best overall response as dependent variable (1 for subjects with best overall response of PR or CR, 0 otherwise) subgroup, treatment, and with and without the treatment by subgroup interaction as explanatory variables. A p-value for the interaction term will be provided together with the odds ratio and corresponding 95% CI of the interaction model parameter. A forest plot of odds ratios and their corresponding 95% Cis will be displayed.

14.5 Duration of Response

DOR is defined as the time from first documentation of objective response (CR or PR) to the date of first documentation of objective PD or death due to any cause, whichever occurs first. The analysis of DOR will be performed on confirmed and unconfirmed objective response of CR or PR according to RECIST 1.1 as adjudicated by investigator. The censoring rules for DOR are as described for PFS (see Section 14.1).

DOR = (date of PD or death/censoring – date of objective response + 1)/30.4375 (months).

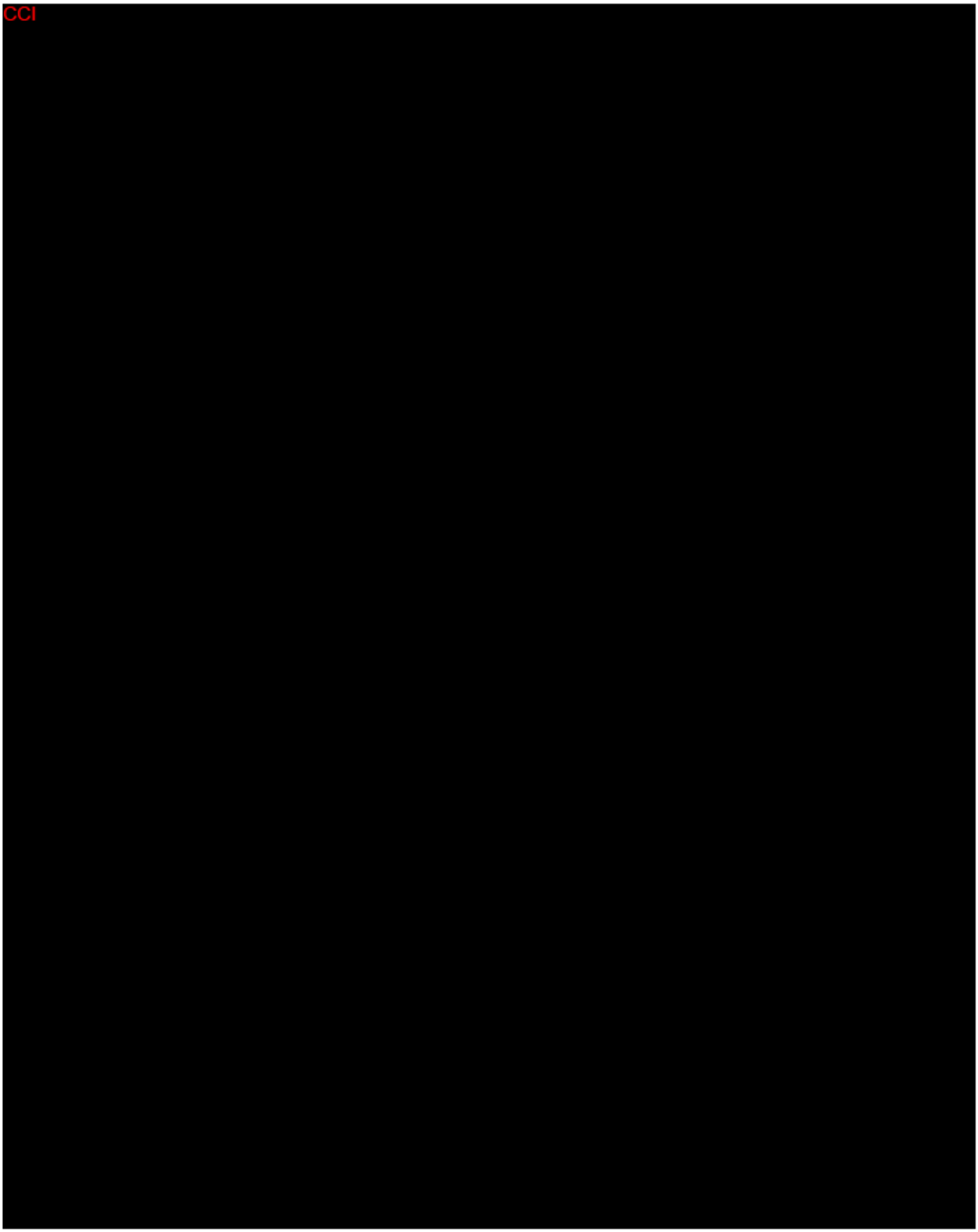
The analysis of DOR will be performed with a Kaplan-Meier method (product-limit estimates) and a summary of associated statistics will be presented including corresponding two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) and CIs for the survival function estimates at 6, 9, 12, 18, 24, 36, 48, and 60 months will be derived using the log-log transformation according to Kalbfleisch and Prentice (1980) (CONFTYPE=loglog default option in SAS PROC LIFETEST). The estimate of standard error will be computed using Greenwood's formula.

A participant listing will provide the following information: treatment arm, participant identifier, age, sex, race, date of randomization, date of first response, time to response, date of last tumor assessment, censored (yes, no), date of event/censoring, event/censoring reason, and DOR.

The Time to Response will be calculated for each participant with an unconfirmed response according to RECIST 1.1 as the time from randomization until first observation of response as determined by the investigator .

Time to response = (date of CR or PR– date of randomization + 1)/ 30.4375 (months).

Descriptive statistics of time to response will be provided.


CCI

CCI

14.10 Delayed Response after Initial Progression

A delayed response will be defined as a documented objective response (CR or PR) that occurred after the initial progression of disease. For those participants, the duration of delayed response (DoDR) will be defined as:

DoDR = (date of end of response – date of objective response + 1)/30.4375 (months),),

with end of response being the earliest date between PD occurring after response, death, start of new anticancer treatment or cut-off date.

A listing of duration of response for participants having a delayed response will be provided including: planned treatment arm, participant identifier, age, sex, race, date of first study intervention, date/study day of first PD, date/study day of first response (CR or PR), ongoing response at cut-off date (yes, no), date/study day of end of response (with reason for end of response being PD, death, new anticancer treatment, cut-off), duration of delayed response.

CCI

CCI

[redacted]

CCI

[redacted]

14.11.3 Cox Regression Models

Cox models will be used within the Landmark analysis setting to evaluate the treatment effect on subgroups as defined in Section 8.2 complemented by further subgroups as cCRT completion and radiologic compliance. Univariate or multivariate Cox models may be used upon discretion of the Sponsor to further evaluate the effects of baseline covariates and cCRT related covariates in addition to the treatment effect in the scope of the Landmark analysis.

15 Safety Analyses

The following subsections include specifications for summarizing safety endpoints that are common across clinical studies such as adverse events (AEs), laboratory tests and vital signs. Baseline values for safety analysis are defined in Section 9.

If not stated otherwise, summaries will be presented for the SAF analysis set by treatment arm and overall. For IDMC purposes during the Safety run-in phase of the study, SAF-nJ and SAF-J analysis sets will be presented separately.

15.1 Adverse Events

Treatment emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period (on-treatment period defined in Section 9) or if the worsening of an event is during the on-treatment period.

Changes in toxicity grade, seriousness or outcome of AEs are recorded as separate entries in the eCRF with associated end and start dates (start date equals end date of previous entry). Such entries reporting the same event in such immediately consecutive periods will be considered as one event in the analysis. These events will be kept as separate records in the database in order to maintain the full detailed history of the events. The start date of the initial record in the sequence is taken as start date of the entire event, similarly the end date of the last event in the sequence is taken as end date of the entire event. The overall outcome of the adverse event is the outcome of the last event in the sequence. Duration of the AE and the TEAE flag will be adjusted accordingly in the analysis.

All analyses described in this section will be based on TEAEs during the on-treatment period if not otherwise specified and will be described by treatment arm and overall. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

Incomplete AE-related dates will be handled as stated in Section 9.

Treatment-related Adverse Events

Immunotherapy related AEs are those AEs with relationship to immunotherapy reported by the Investigator as related (i.e. answer to the question "Relationship with immunotherapy" = "Related" on "Adverse Events Details" eCRF page).

Chemotherapy related AEs are those AEs with relationship to chemotherapy reported by the Investigator as related (i.e. answer to the question "Relationship with Carboplatin" = "Related", or "Relationship with Paclitaxel" = "Related", or "Relationship with Cisplatin" = "Related", or "Relationship with Pemetrexed" = "Related", or "Relationship with Etoposide" = "Related" on "Adverse Events Details" eCRF page).

If any of the chemotherapy compounds (Carboplatin, Paclitaxel, Cisplatin, Pemetrexed, or Etoposide) are marked as "Related", the AE will be considered as "Chemotherapy-related".

Radiotherapy related AEs are those AEs with relationship to radiotherapy reported by the Investigator as related (i.e. answer to the question "Relationship with radiotherapy" = "Related" on "Adverse Events Details" eCRF page).

If relationship to any study intervention is unknown or missing the AE will be considered as "Related".

Serious Adverse Events

Serious adverse events (SAEs) are those events reported on the "Adverse Events Details" eCRF page with the "Serious Adverse Event" field ticked "Yes".

Adverse Events Leading to Temporary Treatment Discontinuation

Adverse Events Leading to Temporary Discontinuation of Immunotherapy: AEs leading to permanent discontinuation of study intervention (i.e. answer to the question "Action(s) taken with Immunotherapy" = "Drug interrupted" on "Adverse Events Details" eCRF page).

Adverse Events Leading to Temporary Discontinuation of Chemotherapy: AEs leading to permanent discontinuation of study intervention (i.e. answer to the question "Action(s) taken with Carboplatin" = "Drug interrupted", or "Paclitaxel" = "Drug interrupted", or "Cisplatin" = "Drug interrupted", or "Pemetrexed" = "Drug interrupted", or "Etoposide" = "Drug interrupted" on "Adverse Events Details" eCRF page).

Adverse Events Leading to Temporary Discontinuation of Radiotherapy: AEs leading to permanent discontinuation of study intervention (i.e. answer to the question "Action(s) taken with Radiotherapy" = "Radiotherapy interrupted" on "Adverse Events Details" eCRF page).

Adverse Events Leading to Temporary Discontinuation of at Least One Chemotherapy: AEs leading to temporary discontinuation of Carboplatin, Paclitaxel, Cisplatin, Pemetrexed, or Etoposide, as defined above.

Adverse Events Leading to Temporary Discontinuation of at Least One Trial Drug: AEs leading to temporary discontinuation of immunotherapy (definition above) or AEs leading to temporary discontinuation of at least one chemotherapy (definition above) or temporary discontinuation of at least one radiotherapy (definition above).

Adverse Events Leading to Permanent Treatment Discontinuation

Adverse Events Leading to Permanent Discontinuation of Immunotherapy: AEs leading to permanent discontinuation of study intervention (i.e. answer to the question "Action(s) taken with Immunotherapy" = "Drug withdrawn" on "Adverse Events Details" eCRF page).

Adverse Events Leading to Permanent Discontinuation of Chemotherapy: AEs leading to permanent discontinuation of study intervention (i.e. answer to the question "Action(s) taken with Carboplatin" = "Drug withdrawn", or "Paclitaxel" = "Drug withdrawn", or "Cisplatin" = "Drug withdrawn", or "Pemetrexed" = "Drug withdrawn", or "Etoposide" = "Drug withdrawn" on "Adverse Events Details" eCRF page).

Adverse Events Leading to Permanent Discontinuation of Radiotherapy: AEs leading to permanent discontinuation of study intervention (i.e. answer to the question "Action(s) taken with Radiotherapy" = "Radiotherapy withdrawn" on "Adverse Events Details" eCRF page).

Adverse Events Leading to Permanent Discontinuation of at Least One Chemotherapy: AEs leading to permanent discontinuation of Carboplatin, Paclitaxel, Cisplatin, Pemetrexed, or Etoposide, as defined above.

Adverse Events Leading to Permanent Discontinuation of at Least One Trial Drug: AEs leading to permanent discontinuation of immunotherapy (definition above) or AEs leading to permanent discontinuation of at least one chemotherapy (definition above) or permanent discontinuation of at least one radiotherapy (definition above).

Adverse Events Leading to Death

AEs leading to death (as recorded on the "Adverse Events Details" eCRF page, "Change in grade" = "No" and outcome = "Fatal", or "Grade" = "Grade 5 or death related to AE" or "serious adverse event" = "Yes" and seriousness criteria include "Results in death").

Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest (AESI) will be identified according to a pre-specified search list using the last available version of MedDRA Preferred Terms.

Categories of AESI considered include:

- Infusion-related reactions (IRRs) including immediate hypersensitivity: any infusion-related reaction, or hypersensitivity (regardless of grade).
- irAEs including autoimmune disorders
- CCI [redacted]
  - [redacted]
  - [redacted].
- Anemia AEs
- Pneumonitis (radiation-induced and immune-mediated), including:
  - Acute interstitial pneumonitis
  - Interstitial lung disease
  - Pneumonitis
  - Autoimmune lung disease
  - Radiation-induced pneumonitis

  Note that immune-mediated pneumonitis will be reported twice: once under "irAE" and secondly under "Pneumonitis (radiation-induced and immune-mediated)".
- Bleeding Events

  Bleeding events are defined as those AEs with a preferred term according to the MedDRA for Hemorrhage terms (excluding laboratory terms). See Section 15.2.3.6 for more details.

15.1.1 All Adverse Events

Adverse events will be summarized by worst severity according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 per participant, using the last available version of MedDRA preferred term as event category and primary SOC body term as Body System category.

Unless otherwise stated, AEs will be displayed in terms of frequency tables: preferred term and primary SOC, in alphabetical order.

If an AE is reported for a given participant more than once during the on-treatment period, the worst severity and the worst relationship to study treatment will be tabulated. In case a participant has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

A table presenting the overall summary of TEAEs, as defined in Section 15.1, will be presented by treatment arm with the following information:

- TEAEs
- Immunotherapy related TEAEs
- Chemotherapy related TEAEs (by regimen)
- Radiotherapy related TEAEs
- Serious TEAEs
- Immunotherapy related serious TEAEs
- Chemotherapy related serious TEAEs (by regimen)
- Radiotherapy related serious TEAEs
- TEAEs by NCI-CTCAE severity grade (≥ 3, ≥ 4)
- Immunotherapy related TEAEs NCI-CTCAE severity grade (≥ 3, ≥ 4)
- Chemotherapy related TEAEs NCI-CTCAE severity grade (≥ 3, ≥ 4) (by regimen)
- Radiotherapy related TEAEs NCI-CTCAE severity grade (≥ 3, ≥ 4)
- TEAEs leading to death
- Immunotherapy related TEAEs leading to death
- Chemotherapy related TEAEs leading to death (by regimen)
- Radiotherapy related TEAEs leading to death
- Adverse Events of Special Interest (related or non-related as assessed by investigator):
    - IRR
    - irAEs

  - TGFβ inhibition mediated skin reactions
  - Anemia AEs
  - Radiation/immune -mediated pneumonitis AEs
  - Bleeding AEs
- Immunotherapy-related Adverse Event of special interest (relationship with immunotherapy as assessed by investigator in the "Adverse Events Details" eCRF page):
  - IRR
  - irAEs
  - TGFβ inhibition mediated skin reactions Anemia AEs
  - Radiation/immune mediated pneumonitis AEs
  - Bleeding AEs

Tables for TEAEs frequency corresponding to each category below will be provided by MedDRA primary SOC (ordered alphabetically) and preferred term (ordered alphabetically). Each participant will be counted only once within each preferred term or SOC.

- TEAEs
- Immunotherapy related TEAEs
- Chemotherapy related TEAEs (by compound)
- Radiotherapy related TEAEs
- TEAEs leading to death
- Immunotherapy related TEAEs leading to death
- Chemotherapy related TEAEs leading to death (by compound)
- Radiotherapy related TEAEs leading to death

The following frequency tables will be provided by worst grade, SOC, and preferred term:

- TEAEs
- Immunotherapy related TEAEs
- Chemotherapy related TEAEs (by compound)
- Radiotherapy related TEAEs
- Bleeding Events
- Immunotherapy related Bleeding events

Evaluation of COVID-19 effects on AEs

The direct effect of COVID-19 for AEs will be assessed by means of:

- An overview table of treatment-emergent AEs associated to COVID-19 by MedDRA primary SOC, high level terms (HLT) and PTs (ordered alphabetically).

COVID-19 AEs will be identified using the MedDRA SMQ 'COVID-19'.

Clinicaltrials.gov and EudraCT -Requirements

Summary tables for non-serious TEAEs excluding SAEs applying frequency threshold of 5% will be provided.

A listing of AEs will contain the following information: treatment arm, participant identifier, age, sex, race, preferred term, reported term for the AE (Investigator term), start and end date for immunotherapy, chemotherapy, and radiotherapy and their cumulative dose and number of infusions/fractions, duration of AE (in days), event start or change date and end date, day since most recent administration prior to AE onset/change, relationship to study treatment (immunotherapy, chemotherapy, and radiotherapy), toxicity grade, action(s) taken on immunotherapy, chemotherapy and radiotherapy, outcome, seriousness (yes, no), and AESI (yes, no). AEs which lead to chemotherapy switch will be flagged. This listing will be sorted by treatment arm, participant identifier, start date of AE and AE preferred term.

Listings will also be provided with the relevant information:

- TEAEs
- AEs with onset or worsening date after the on-treatment period.

The following figures will be displayed:

- TEAEs with risk difference $\geq$ 5% between treatment arms
- Serious TEAEs with risk difference $\geq$ 5% between treatment arms

Evaluation of Potential Effect of ADA on M7824 Safety

The overall summary of the AEs table as described above will also be provided by ADA status (ever positive, never positive).

A listing of all AEs (including IRR) for ever-positive ADA participants (pre-existing, transient treatment-emergent, persistent-treatment emergent) will be prepared including participant identifier and showing the date(s) of the positive ADA result together with the AEs or IRRs. For the AEs and IRRs, start and stop date will be shown along with grade. Adverse events recorded during the period of 2-weeks prior to the positive ADA value till two weeks after the positive ADA value will be flagged.

15.1.2 Adverse Events Leading to Study Intervention Discontinuation

The following frequency tables, as defined in Section 15.1, will be prepared for the TEAEs actions overall and by primary SOC and preferred term in alphabetical order:

- TEAEs leading to temporary discontinuation of at least one study drug
- TEAEs leading to temporary immunotherapy discontinuation
- TEAEs leading to temporary chemotherapy discontinuation
- TEAEs leading to temporary radiotherapy discontinuation
- Immunotherapy related TEAEs leading to temporary immunotherapy discontinuation
- Chemotherapy related TEAEs leading to temporary chemotherapy discontinuation (by regimen)
- Radiotherapy related TEAEs leading to temporary radiotherapy discontinuation
- TEAEs leading to permanent discontinuation of at least one study intervention
- TEAEs leading to permanent immunotherapy discontinuation
- TEAEs leading to permanent chemotherapy discontinuation
- TEAEs leading to permanent radiotherapy discontinuation
- Immunotherapy related TEAEs leading to permanent immunotherapy discontinuation
- Chemotherapy related TEAEs leading to permanent chemotherapy discontinuation (by regimen)
- Radiotherapy related TEAEs leading to permanent radiotherapy discontinuation.
- TEAEs leading to dose reduction of chemotherapy
- Chemotherapy related TEAEs leading to dose reduction of chemotherapy

The listing of AEs leading to permanent treatment discontinuation will provide relevant information (as described in Section 15.1.1), sorted by participant identifier, start date of AE and AE preferred term.

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

All deaths, deaths within 30 days after last dose of study intervention, death within 60 days after first dose as well as reason for death, will be tabulated based on information from the "Death" page.

- Number of deaths
- Number of deaths within 30 days after last dose of study intervention
- Number of deaths within 60 days after first dose of study intervention
- Primary reason for death:
    - Progressive disease and/or disease related condition

- Event unrelated to study intervention.
- Event related to study intervention, including:
  - Event related to immunotherapy
  - Event related to chemotherapy
  - Event related to radiotherapy
- Unknown.

In addition, date and cause of death will be provided in an individual subject data listing together with treatment arm, participant identifier, sex, race, age, selected dosing information (study intervention received, date of first/last administration, and dose and number of infusions/fractions) and will include columns for:

- AEs with fatal outcome (list of preferred terms for AEs with outcome=fatal, Grade 5 or Serious resulting in death).
- Autopsy performed (yes, no, unknown)
- Flag for death within 30 days of last study intervention.
- Flag for death within 60 days of first study intervention.

15.2.2 Serious Adverse Events

The number of subjects with SAEs will be described by SOC and preferred term:

- SAEs
- SAEs related to immunotherapy, chemotherapy or radiotherapy

The listing of SAEs will also provide the relevant information (as described in Section 15.1.1).

15.2.3 Adverse Events of Special Interest

A listing summarizing AESI will be displayed containing the following information: treatment arm, participant identifier, age, sex, race, preferred term, reported term for the AE (Investigator term), start and end date for immunotherapy, chemotherapy, and radiotherapy and their cumulative dose and number of infusions/fractions, duration of AE (in days), event start or change date and end date, day since first administration of study drug (days), day since most recent administration prior to AE onset/change (days), toxicity grade, outcome, seriousness (yes, no), AESI: IRR (yes, no), IRR: reaction (yes, no), IRR: sign and symptom (yes, no), immune-related reaction (yes, no), skin AESI (yes, no), anemia (yes, no), pneumonitis (radiation/immune mediated) (yes, no), bleeding (yes, no). This listing will be sorted by treatment arm, participant identifier, start date of AE, and AE preferred term.

A Pre-specified Search List of MedDRA Preferred Terms considered as AESI will be provided.

15.2.3.1 Infusion-related Reactions Including Immediate Hypersensitivity

IRRs are defined as AEs with preferred terms on a pre-specified list of MedDRA preferred terms and divided into Reactions *vs* Signs and Symptoms.

Reactions of IRR: should be considered when onset is on the day of immunotherapy and/or chemotherapy infusion (during or after the infusion) or the day after the infusion (irrespective of resolution date) for any infusion-related reaction, drug hypersensitivity, anaphylactic reaction, hypersensitivity and/or Type 1 hypersensitivity.

Signs and symptoms of IRRs and hypersensitivity/allergic reactions: should be considered when onset is on the day of immunotherapy and/or chemotherapy infusion (during or after the infusion) and resolved completely with the end date within 2 days after onset.

IRR will be summarized by the following variables per subgroup of IRR and overall:

- Number of participants with at least one IRR by the worst NCI-CTCAE toxicity grade (Grade 1/ Grade 2/ Grade 3/ Grade 4/ Grade 5/ missing grade)
- Number of participants with IRR leading to permanent immunotherapy discontinuation
- Time related to first onset (Infusion 1/ Infusion 2/ Infusion 3/ Infusion 4 or later).

The events should be assigned to the actual drug infusions that the participant received, not to the planned dates. An IRR is assigned to a drug infusion if its onset is at the same date (but not before dosing) or the following day of drug infusion.

A frequency table of IRR AEs by worst grade, SOC, and preferred term will be provided.

A listing of IRRs for both reactions and signs and symptoms will also be provided with the relevant information (as described in Section 15.1.1).

15.2.3.2 Immune-related Adverse Events

irAEs will be identified programmatically. AEs which satisfy all of the following criteria will be flagged as immune-related:

1- The AE PT matches a PT on the list of pre-selected MedDRA terms

2- The AE onset or worsening occurs after the first immunotherapy administration and no more than 90 days after immunotherapy last dose

3- On the "Adverse Events Details" eCRF page, the question "Were Corticosteroids, Immunosuppressants, or Hormonal Therapy (Eg. Thyroid) Applied?" has the answer "Yes" selected

4- On the "imAE Specific Questions" eCRF page, either:

a) The question "Does any of the following provide a clear etiology for the event?" has the answer "No" selected, indicating that the AE is not attributable to underlying cancer disease/PD, prior or concomitant medications/procedures, nor another medical condition such as an infection or pre-existing disease

OR

b) The "imAE Specific Questions" eCRF page indicates that a biopsy was performed and the question "Is the histopathology/biopsy consistent with an immune-mediated event?" has the answer "Yes" selected.

In the case that criteria (1) through (3) are met, and entries for condition (4) are missing, the following rules will be applied:

- If the answer to "Does any of the following provide a clear etiology for the event?" (4a) is missing, the event will be considered as irAE (irrespective of biopsy results).

- If the answer to "Is the histopathology/biopsy consistent with an immune-mediated event?" (4b) is missing, or if no biopsy was performed, and condition (4a) is not satisfied (i.e. "Yes" is selected as the answer to the question "Does any of the following provide a clear etiology for the event?"), the event will be considered as a non-irAE.

PTs will be compiled into categories: Immune-mediated rash, Immune-mediated colitis, Immune-mediated pneumonitis, Immune-mediated hepatitis, Immune-mediated nephritis and renal dysfunction, Immune-mediated endocrinopathies (Adrenal insufficiency, Hypogonadism, Pituitary dysfunction, Type 1 Diabetes Mellitus, Thyroid disorders), Other immune-mediated myositis, Other immune-mediated adverse events.

An overview table of irAEs containing frequency of participants with:
- At least one irAE by worst grade
- At least one study intervention related irAE by worst grade
- Immune-related AESI leading to permanent treatment discontinuation
- Serious irAEs.

Frequency table of irAEs by worst grade, category, and PT will also be provided.

A listing of irAEs will also be provided with the relevant information (as described in Section 15.1.1).

15.2.3.3 TGF-β inhibition mediated Skin Reactions

TGFβ inhibition mediated skin reactions will be selected based on MedDRA preferred terms according to a pre-specified MedDRA search list:

Narrow Definition

- KA

- SCC of skin

Broad Definition

Broad definition has additional PTs:

- Hyperkeratosis
- Actinic keratosis
- Basal cell carcinoma
- Lip Squamous Cell Carcinoma
- Bowen´s Disease

A table for frequency of skin TEAEs will be provided by MedDRA PTs (including both narrow and broad definition PTs).

A listing of skin AEs will also be provided with the relevant information (as described in Section 15.1.1).

15.2.3.4 Anemia Adverse Events

The following HLTs and PTs (using the latest version of MedDRA available) will be used to select the anaemia AEs:

- Anaemias NEC (HLT)
- Anaemias haemolytic immune (HLT)
- Anaemias haemolytic NEC (HLT)
- Haemoglobin decreased (PT)

An overview table for on-treatment anaemia AEs will be provided, displaying the number of participants with:

- At least one anaemia by worst grade
- At least one immunotherapy related anaemia by worst grade
- Anaemia leading to permanent immunotherapy discontinuation
- Serious anaemia

The listing of anemia AEs will be provided with the relevant information (as described in Section 15.1.1).

15.2.3.5 Radiation/immune-mediated Pneumonitis Adverse Events

Radiation/immune mediated pneumonitis AEs are defined on a pre-specified list of Medical Dictionary for Regulatory Activities terms (MedDRA latest version) and in the "immune-related pneumonitis" category in the general irAE list. It includes the following terms: acute interstitial pneumonitis, interstitial lung disease, pneumonitis, autoimmune lung disease and radiation-induced pneumonitis.

The listing of Radiation/immune mediated pneumonitis AEs will be provided with the relevant information (as described in Section 15.1.1).

15.2.3.6 Bleeding Adverse Events

Bleeding events are defined as AEs with PTs according to the MedDRA for Hemorrhage terms (excluding laboratory terms). Bleeding events and study drug related bleeding events will be summarized in a frequency table presenting SOC and PT sorted by alphabetical order. The worst grade per participant, per SOC, and per PT will be reported:

- Any grade (including missing grade)
- Grade 1
- Grade 2
- Grade 3
- Grade 4
- Grade 5

15.3 Clinical Laboratory Evaluation

On-treatment laboratory values (including corresponding normal ranges) converted to standard units will be used for summary statistics and shift tables (on-treatment period defined in Section 9).

A summary table over time by treatment arm will be displayed, including absolute values and absolute change from Baseline values per visit. Only parameters and visits with at least 2 observations available will be displayed.

Laboratory results will be classified according to the NCI-CTCAE Version 5.0 and as specified in Appendix 2. Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: low, normal and high (according to the laboratory normal ranges).

Quantitative data will be examined for trends using descriptive statistics (mean, StD, median, Q1, Q3, min, and max) of actual Baseline values, on-treatment values, and changes from Baseline to each on-treatment visit over time. The changes computed will be the differences from Baseline. Qualitative data based on reference ranges will be described according to the categories (i.e. low, normal, and high).

Laboratory Parameters with NCI-CTC Grades Available

Laboratory parameters with NCI-CTC grades available will be analyzed with their respective NCI-CTC name and direction of abnormality. For parameters which are graded with both low and high values, the toxicities will be summarized separately. Low direction toxicity grades at Baseline and post-Baseline will be set to 0 when the variables are derived for summarizing high direction toxicity, and vice versa.

For gradable parameters, the following summaries will be displayed by treatment arm:

- Number and percentage of participants by worst on-treatment grade ($\geq 1, \geq 3, \geq 4$)
- Shift in toxicity grading from Baseline to highest on-treatment grade.

The definitions of the NCI-CTCAE toxicity grade Version 5.0 for each parameter are provided in Appendix 2.

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO), if available. Corrected Calcium is calculated from Albumin and Calcium as follows:

- Corrected calcium (mmol/L) = measured total calcium (mmol/L) + 0.02 (40 − serum albumin [g/L])

Creatinine Clearance (CrCl) will be derived through the Cockcroft-Gault formula (Cockcroft and Gault, 1976), from the serum creatinine measurements in the "FULL SERUM CHEMISTRY PANEL A" and "CORE CHEMISTRY" e-CRF pages, the weight in the "VITAL SIGNS" e-CRF page and the age re-calculated at the sampling date as follows:

- $CrCl = FACTOR * (140 - AGE) * \frac{WT}{S_{CREA} * 0.8136}$

- where FACTOR is gender-dependent with value 1 (male) or 0.85 (female), AGE is the subject age in years, WT is the subject weight in kg and S_{CREA} is the observed serum creatinine in umol/l.

- Toxicity grading for creatinine clearance will be defined as per NCI-CTCAE toxicity grading version 5.0, the following normal ranges will be considered: 110 to 150 mL/min in males and 100 to 130 mL/min in females.

Laboratory Parameters with NCI-CTC Grades Not Available

For all non-gradable parameters, the following summaries will be displayed by treatment arm:

- Shift from Baseline to lowest on-treatment value (classified as normal, high, low)
- Shift from Baseline to the highest on-treatment value (classified as normal, high, low)
- Number and percentage of participants by worst on-treatment value (classified as normal, high, low).

Liver Function Tests

The number and percentage of participants within each of the following liver function categories (based on alanine aminotransferase [ALT], aspartate aminotransferase [AST], upper limit normal [ULN] and total bilirubin values) during the on-treatment period will be described:

- ALT < 3 × ULN, ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10 × ULN, ALT ≥ 20 × ULN
- AST < 3 × ULN, AST ≥ 3×ULN, AST ≥ 5xULN, AST ≥ 10 × ULN, AST ≥ 20 × ULN
- (ALT and AST) < 3 × ULN, (ALT or AST) ≥ 3 × ULN, (ALT or AST) ≥ 5 × ULN, (ALT or AST) ≥ 10 × ULN, (ALT or AST) ≥ 20 × ULN
- Total bilirubin < 2×ULN, total bilirubin ≥ 2 × ULN
- Concurrent ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN
- Concurrent AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN
- Concurrent (ALT or AST) ≥ 3 × ULN and total bilirubin ≥ 2 × ULN
- Concurrent (ALT or AST) ≥ 3 × ULN and total bilirubin ≥ 2 × ULN and ALP > 2 × ULN
- Concurrent (ALT or AST) ≥ 3 × ULN and total bilirubin ≥ 2 × ULN and (ALP ≤ 2 × ULN or missing)

Concurrent measurements are those occurring on the same date. Categories will be cumulative, i.e., a participant with an elevation of AST ≥ 10 × ULN will also appear in the categories ≥ 5 × ULN and ≥ 3 × ULN.

A plot of peak ALT versus peak total bilirubin (TBILI), both relative to the ULN will be provided. This eDISH plot (evaluation of drug-induced serious hepatotoxicity) will be divided into 4 quadrants by the lines through ALT ≥ 3×ULN and TBILI ≥ 2×ULN. The left lower quadrant is then considered normal or insignificant elevations in liver chemistries; the upper quadrants indicate patients with possible Gilbert's cholestasis; the right upper quadrant are the possible Hy's Law patients; the right lower quadrant is possible Temple's Corollary (patients with ALT ≥ 3xULN but not satisfying Hy's Law). A plot of peak AST versus peak total bilirubin, both relative to the ULN will be also provided.

A plot of peak AST versus peak total bilirubin, both relative to the ULN will be also provided.

Separate listings of hematology and biochemistry will be created. Each listing will include treatment arm, participant identifier, age, sex, race, weight, each study intervention first and last dose, cumulative dose and number of infusions/fractions, laboratory parameter (units), visit, date, value, change from Baseline, lower limit of normal (LLN), ULN, indicator of normal range (low, normal, high), toxicity grade according to NCI-CTCAE, and highest/lowest on treatment value flag. These listings will be sorted by treatment arm, subject identifier, laboratory measurement date, and parameter. The Baseline values and post-Baseline values after the on-treatment period will be flagged.

In addition, a listing of all TBILI, ALT, AST and alkaline phosphatase (ALP) values for subjects with a post-Baseline TBILI ≥ 2×ULN, ALT ≥ 3×ULN or AST ≥ 3×ULN will be provided,

including values expressed as multiples of ULN. The same information as hematology and biochemistry listings will be provided.

Hemostaseology, Urinalysis/Urinalysis Microscopic Evaluation, Hormonal Tests, Serology

All test results for hemostaseology, urinalysis /urinalysis microscopic evaluation, hormonal tests, serology will be listed.

Hemostaseology listing will include treatment arm, participant identifier, age, sex, race, each study intervention first and last dose, collection date and time (or not done), prothrombin time (sec), prothrombin time/standard (% or ratio), activated partial thromboplastin rime (sec), activated PTT/standard (% or ratio), prothrombin international normalized ratio.

Urinalysis/Urinalysis Microscopic Evaluation listing will include treatment arm, participant identifier, age, sex, race, laboratory parameter (units), visit, collection date and time (or not done), value.

Hormonal Tests listing will include treatment arm, participant identifier, age, sex, race, each study intervention first and last dose, collection date and time (or not done), Thyrotropin (Thyroid-Stimulating Hormone; TSH) (unit), Thyroxine Free (Free T4) (unit).

Serology listing will include treatment arm, participant identifier, age, sex, race, each study intervention first and last dose, information on Hepatitis B Virus / Hepatitis C Virus Testing and (i.e. collection date and time (or not done), method and result) , information on Hepatitis B DNA / Hepatitis C RNA (i.e. collection date and time (or not done) and result).

Pregnancy Test

All pregnancy test results as collected on the "Pregnancy Test" eCRF page will be listed. Pregnancy listing will include treatment arm, participant identifier, age, sex, race, each study intervention first and last dose, laboratory parameter, visit, date (days), specimen type, value, reasons for test not done.

15.4 Vital Signs

On-treatment vital signs values will be used for summary statistics and shift tables (on-treatment period defined in Section 9).

The following summaries will be prepared for vital signs parameters as collected in the "Vital Signs eCRF page" considering only participants with post Baseline values:

- Summary statistics over time by treatment arm. This table will include absolute values and absolute change from Baseline values per visit (only parameters and visits with at least 2 observations available will be displayed)
- Listing of maximum change from Baseline per participant. The listing will include treatment arm, participant identifier, parameter, visit, date, value, unit, baseline value and maximum change from baseline.

The following potentially clinically significant abnormalities in vital signs will be also summarized:

- ≤ 95 mmHg and decrease from Baseline ≥ 20 mmHg in systolic blood pressure
- ≥ 140 mmHg and increase from Baseline ≥ 20 mmHg in systolic blood pressure
- ≤ 45 mmHg and decrease from Baseline ≥ 20 mmHg in diastolic blood pressure
- ≥ 90 mmHg and increase from Baseline ≥ 20 mmHg in diastolic blood pressure
- ≤ 50 bpm and decrease from Baseline ≥ 20 bpm in pulse
- ≥ 100 bpm and increase from Baseline ≥ 20 bpm in pulse
- ≥ 10% weight increase
- ≥ 10% weight decrease
- Respiration Rate: <20 breaths/min and decrease from baseline ≥ 5 breaths/min
- Respiration Rate: ≥ 20 breaths/min and decrease from baseline ≥ 5 breaths/min
- Oxygen saturation: < 90% or a decrease from baseline ≥ 10%

All vital signs will also be listed, Baseline values and Post-Baseline values collected after the on-treatment period will be flagged in the listing. The listing will include treatment arm, participant identifier, age, sex, race, vital sign parameter, unit, visit, date, on-treatment flag, value and change from Baseline. Listings will be sorted by treatment arm, participant identifier, vital sign parameter, and vital sign measurement date and time.

15.5 Pulmonary Function Tests

Pulmonary Function Tests (PFTs), including DLCO, Slow spirometry, HRCT, FEV_1, FVC and 6-minutes walking test will be analyzed using the absolute change at a prespecified time point regarding to Baseline (as defined in Section 9 "Definition of Baseline") for each participant.

A summary table over time by treatment arm will be displayed, including absolute PFTs values and absolute change from Baseline values per visit. A boxplot of PFTs values over time will be displayed too.

A summary listing of PFTs will be provided, the following information will be included: treatment arm, participant identifier, ethnicity (Japanese/Non-Japanese), age, sex, race, visit, date, repetition number, absolute and relative change from baseline of CCI [redacted].

In addition, for CCI [redacted] parameters (i.e. CCI [redacted], Alveolar volume, Inspiratory vital capacity, Breath hold time, Inspiration time, Maximal vital capacity) a specific listing will be displayed including treatment arm, participant identifier, age, sex, race, visit, date, parameter value and its absolute and relative change from baseline.

Specific listings will be also provided for Slow spirometry, CCI [redacted]

15.6 Other Safety or Tolerability Evaluations

ECOG Performance Status

The ECOG Performance Status will be derived from the data collected on the "ECOG Performance Status" eCRF page and will be summarized in a listing including treatment arm, participant identifier, age, sex, race, ECOG PS values at screening and per visit, date of visit (days).

ECG

A listing of ECG values will provide the following information: treatment arm, subject identifier, age, sex, race, ECG parameter and unit, visit, ECG date and value, and change from Baseline. The listing will be sorted by treatment arm, subject identifier, ECG parameter, and ECG date. It will include ECG values collected at screening and at safety follow-up visits.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

The analyses described in this section will be performed by the Clinical PK/PD group (CPK) of Translational Medicine, Merck Healthcare KGaA, Darmstadt, Germany, or by a Contract Research Organization selected by the Sponsor. Pharmacokinetic listings and individual data will be presented for the Safety Analysis Set. Summaries and statistical analyses will be based on the PK Analysis Set.

Pharmacokinetic concentrations/parameters refer to M7824 concentrations/PK parameters.

16.1.1 Missing/non-quantifiable Pharmacokinetic Data Handling

Concentrations Below the Lower Limit of Assay Quantification

Pharmacokinetic concentrations below the lower limit of quantification will be set to zero for calculating parameters and descriptive statistics.

Unscheduled Samples

For PK analysis, unscheduled samples will not be linked to a scheduled timepoint and will be excluded from summaries.

Deviations, Missing Concentrations and Anomalous Values

There will be no imputation of missing data. Concentrations will be set to missing in summary tables if the value is reported as no result. Pharmacokinetic concentrations which are erroneous due to a protocol violation (as defined in the clinical study protocol), documented handling error, or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed upon prior to performing a statistical analysis. In this case the rationale for

exclusion will be provided in the CSR. Any other PK concentrations that appear implausible to the Pharmacokineticist/PK Data Analyst must not be excluded from the analysis. Any implausible data will be documented in the CSR.

If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (not calculated). (Note that NC values will not be generated beyond the day that a participant discontinues the treatment). For statistical analyses, PK parameters coded as NC will be set to missing.

If an individual participant has a known biased estimate of a PK parameter (due for example to a deviation from the assigned dose level), this participant/value will be excluded from the descriptive statistics, and instead the result will be listed only.

Relevant decisions on participant inclusion in the PK analysis set will be made before database lock in the Database Review Meeting.

16.1.2 Descriptive Pharmacokinetic Analysis

Presentation of Pharmacokinetic Concentration Data

A by-participant listing will present PK sample times, time deviations, and concentrations. Concentration listings will be based on the SAF analysis set. Concentrations will be reported with the same precision as the source data. Actual elapsed sample collection times will be rounded to two decimal places with units of hours for reporting purposes in listings.

Presentation of Pharmacokinetic Parameter Data

The PK parameters listed below will be taken directly from the observed M7824 concentration-time data.

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

Individual PK parameters will be listed by nominal study day. Individual PK parameters will be reported with the same precision as the source data.

Pharmacokinetic parameter data will be presented in tables and descriptively summarized for the PKAS by nominal study day using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (StD), coefficient of variation (CV%), minimum (Min), median (Median), maximum (Max), geometric mean (GeoMean), the geometric coefficient of variation (GeoCV%), and the 95% CI for the GeoMean. Additional table(s) will summarize with further stratification by ADA subsets ever positive and never positive.

In export datasets, as well as in the SDTM PP domain, PK parameters will be provided with full precision and will not be rounded. Descriptive statistics of PK parameter data will be calculated using full precision values and rounded for reporting purposes only.

The following conventions will be applied when reporting descriptive statistics of PK parameter data:

- Mean, Min, Median, Max, GeoMean, 95% CI: 3 significant digits
- StD: 4 significant digits
- CV%, GeoCV%: 1 decimal place.

Individual PK C_{trough} and C_{eoi} values will be plotted versus actual study day on a linear scale, for all participants. Individual data will be presented based on the SAF

Arithmetic mean (± StD) and median C_{trough} and C_{eoi} will be plotted versus nominal study day on a linear scale. Summaries will be based on the PKAS. Additional figure(s) will be presented with further stratification by ADA subsets ever positive and never positive.

16.2 Pharmacodynamics

Not applicable.

CCI [redacted]

16.4 Immunogenicity

The IMM analysis set will be used to evaluate the immunogenicity of M7824. As per protocol, the bioanalyst may have access to the randomization list, but neither the randomization details nor the analysis results described below will be shared before unblinding.

ADA will be assessed prior to study intervention infusions. Samples collected after the on-treatment period (e.g. safety follow-up) will be included in the analysis as well. If the sample is positive for ADA, it will be re-analyzed to determine the titer. The ADA results will be derived based on the algorithm in **Error! Reference source not found.**8.

Table 8 Algorithm for the Derivation of ADA Results

Sample Screen Result	Confirmatory	Titer	ADA Result
Negative	NA	NA	Negative
NR	NA	NA	NR
Positive	Negative	NA	Negative
Positive	NR	NA	NR
Positive	Positive	Number	Number
Positive	Positive	NR	Positive-TNR

ADA=anti-drug antibody, NA=not applicable, NR=no result, TNR=titer no result.

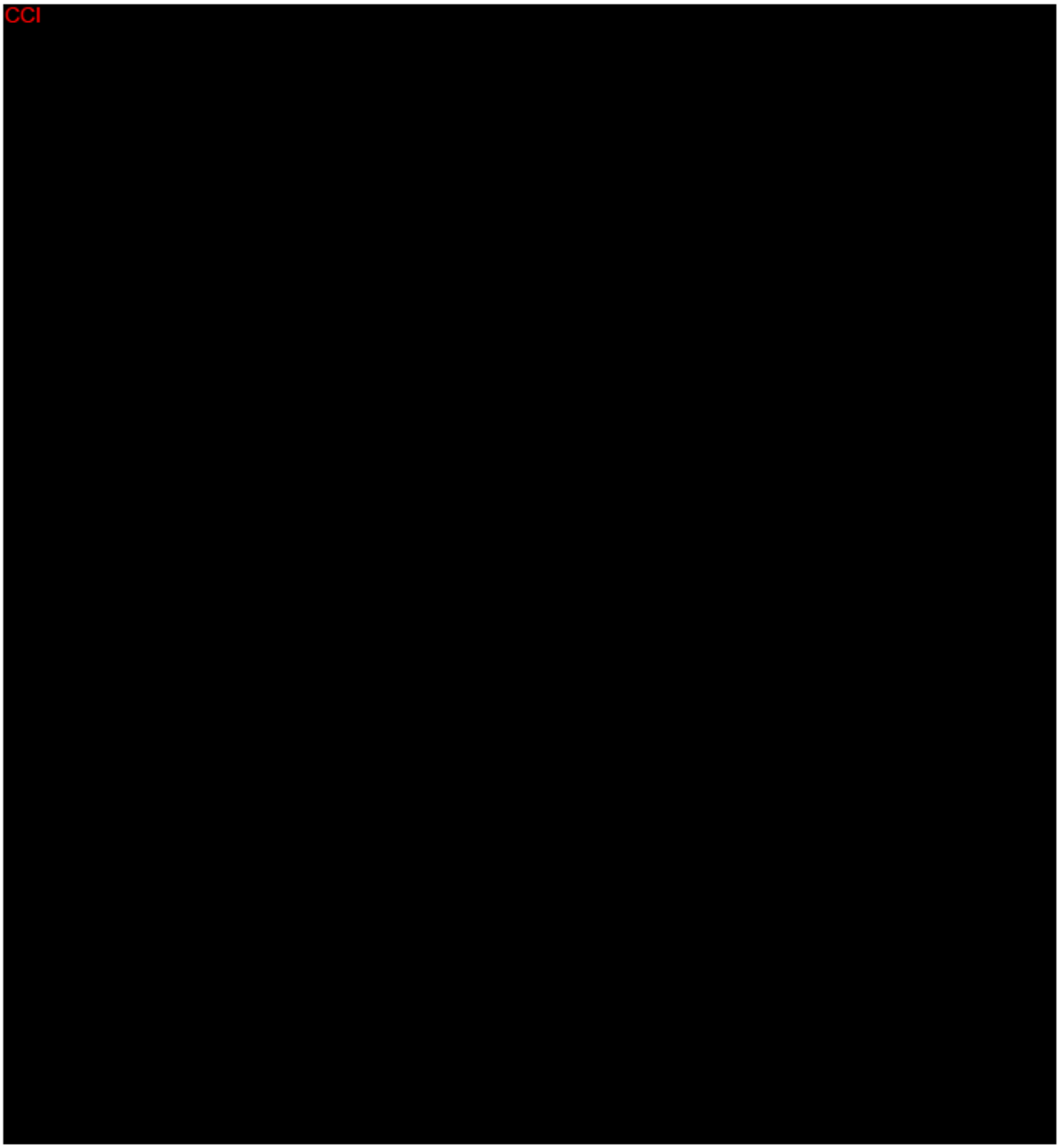
Negative, number, or positive-TNR are valid results while number and positive-TNR are considered as positive. Participants will be characterized into different categories based on the criteria in Table 99.

Table 9 Participants Characterized Based on ADA Results

Category	Definition	Participant at Risk (Denominator for Incidence)
Never positive	No positive results at any time point	Number of participants with at least one valid result at any time point
Ever positive	At least one positive result at any time point, including Baseline	Number of participants with at least one valid result at any time point
Pre-existing	A positive ADA result prior to treatment with M7824	Number of participants with valid Baseline result
Treatment boosted	A positive ADA result prior to treatment with M7824 and the titer ≥ 8*Baseline titer at least one post-Baseline value	Number of participants with valid Baseline result and at least one valid post-Baseline result
Treatment emergent	Not positive prior to treatment with M7824 and with at least one positive post-Baseline result	Number of participants with at least one valid post-Baseline result and without positive Baseline result (including NR)
Transient positive	If treatment emergent participants have - a single positive evaluation, or - duration between first and last positive result <16 weeks and last assessment not positive	Number of participants with at least one valid post-Baseline result and without positive Baseline result (including NR)
Persistent positive	If treatment emergent participants have duration between first and last positive result ≥16 weeks or a positive evaluation at the last assessment	Number of participants with at least one valid post-Baseline result and without positive Baseline result (including NR)

ADA=anti-drug antibody, NR=no result

CCI


CCI

17 References

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Nephrol Dial Transplant (2004) 19 [Suppl 2]: ii42–ii43. "Appendix C: Tables, conversions and abbreviations"

18 Appendices

18.1 Appendix 1 – IDMC SAP

See separate Appendix of this IAP.

18.2 Appendix 2 – Definition of NCI-CTCAE grading

See separate Appendix of this IAP.

18.3 Appendix 3 – List of Important Protocol Deviations

See separate Appendix of this IAP.

18.4 Appendix 4 – Identification of Previous or Concomitant Medications/Procedures

For identification of previous or concomitant medications/procedures, rules presented in tables below will be used to define if a medication/procedure is considered as a previous, concomitant or both previous and concomitant medication/procedure.

Table 10 Stopping rules for medication/procedure end dates

End date of medication/procedure			Stopping rule
Day	Month	Year	
UNK	UNK	UNK	After treatment start (ongoing)
UNK	UNK	< Treatment start (year)	Before treatment start
UNK	UNK	>= Treatment start (year)	After treatment start
UNK	< Treatment start (month and year)		Before treatment start
UNK	>= Treatment start (month and year)		After treatment start
< Treatment start (complete date)			Before treatment start
>= Treatment start (complete date)			After treatment start

UNK: Unknown

Table 11 Rules to define previous and/or concomitant medications

Start date of medication/procedure			Stopping rule (see Table 100)	Medication/procedure
Day	Month	Year		
UNK	UNK	UNK	Before treatment start	Previous
UNK	UNK	UNK	After treatment start	Previous and concomitant
UNK	UNK	<= Treatment start (year)	Before treatment start	Previous
UNK	UNK	<= Treatment start (year)	After treatment start	Previous and concomitant
UNK	UNK	> Treatment start (year) and <= Treatment end [+ 30] days (year)	After treatment start	Concomitant
UNK	<= Treatment start (month and year)		Before treatment start	Previous
UNK	<= Treatment start (month and year)		After treatment start	Previous and concomitant
UNK	> Treatment start (month and year) and <= Treatment end [+ 30] days (month and year)		After treatment start	Concomitant
<= Treatment start (date)			Before treatment start	Previous
<= Treatment start (date)			After treatment start	Previous and concomitant
> Treatment start (date) and <= Treatment end [+ 30] days (date)			After treatment start	Concomitant

UNK= Unknown

18.5 Appendix 5 - IAP_MS200647-0005 List of outputs

See separate Appendix of this IAP.

Signature Page for VV-CLIN-287799 v1.0

Approval	PPD 24-Feb-2022 14:51:33 GMT+0000

Signature Page for CCI [redacted]