Integrated Analysis Plan

Clinical Trial Protocol Identification No.	MS200647_0024
Title	A Phase Ib/II, Open-Label Study of Bintrafusp alfa (M7824) in Combination with Chemotherapy in Participants with Stage IV Non-small Cell Lung Cancer
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Integrated Analysis Plan Reviewers	PPD

PPD

Approval Page

Integrated Analysis Plan: MS200647_0024

A Phase Ib/II, Open-Label Study of Bintrafusp alfa (M7824) in Combination with Chemotherapy in Participants with Stage IV Non-small Cell Lung Cancer

Approval of the IAP by all Merck Data Analysis Responsible is documented within Eldorado. With the approval within Eldorado, the Merck/EMD Serono responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately. Approval by PPD

1 Table of Contents

Approval Page 3
1 Table of Contents....4
2 List of Abbreviations and Definition of Terms 8
3 Modification History 11
4 Purpose of the Integrated Analysis Plan....12
5 Objectives and Endpoints 13
6 Overview of Planned Analyses....14
6.1 Safety Monitoring Committee 15
6.2 Early Interim Analysis....15
6.3 Interim Analysis....16
6.4 Main Analysis....16
6.5 Follow-up Analysis....16
7 Changes to the Planned Analyses in the Clinical Trial Protocol....17
8 Analysis Populations and Subgroups....18
8.1 Definition of Analysis Populations....18
8.2 Subgroup definition and Parameterization 19
9 General Specifications for Data Analyses 21
9.1 Data Handling after Cut-off Date 23
9.2 Definition of Baseline and Change from Baseline 23
9.3 Study Day / Study Treatment Day....24
9.4 Definition of Duration and 'time since' Variables 24
9.5 Conversion Factors 24
9.6 Date of last Contact 24
9.7 Time Window 25
9.8 Definition of On-treatment Period....25
9.9 Imputation of Missing Data 25
9.10 Scoring of HRQOL Data 28
9.11 Data Collected after Re-initiated Treatment....28
10 Study Participants 28
10.1 Disposition of Participants and Discontinuations....28

10.2 Protocol Deviations / Exclusion from Analysis Populations.....31
10.2.1 Important Protocol Deviations.....31
11 Demographics and Other Baseline Characteristics.....32
11.1 Demographics.....32
11.2 Medical History.....33
11.3 Other Baseline Characteristics.....33
11.3.1 Disease History.....33
11.3.2 ECOG Performance Status at Baseline.....35
11.3.3 ECG at Baseline.....35
11.3.4 Vital Signs at Baseline.....35
11.3.5 Skin Status History.....36
11.3.6 Nicotine Consumption.....36
12 Previous or Concomitant Medications/Procedures.....36
12.1 Previous Anticancer Medications.....36
12.2 Previous and Concomitant Medications.....37
12.3 Concomitant Procedures.....38
12.4 Subsequent Anticancer Treatment.....38
12.5 Premedications.....39
13 Study Intervention Compliance and Exposure.....39
14 Efficacy Analyses.....43
14.1 Primary Endpoint Analysis.....44
14.2 Secondary Endpoint Analysis.....44
14.2.1 Confirmed Objective Response According to RECIST 1.1 as Assessed by Investigator.....44
14.2.2 Subgroup Analysis for Confirmed Objective Response.....46
14.2.3 Progression-Free Survival According to RECIST 1.1 as Assessed by Investigator.....46
14.2.4 Overall Survival.....48
14.2.5 Subgroup Analysis for PFS and OS.....49
14.2.6 Sensitivity Analysis for PFS.....49
14.2.7 Duration of Response.....49
14.3 Further Endpoint Analyses.....50

14.3.1 Follow-up Time for PFS 50
14.3.2 Follow-up Time for OS 50
14.3.3 Progression-Free Survival 2 51
14.3.4 Time to Response 52
14.3.5 Tumor Shrinkage in Target Lesions 52
14.3.6 Brain Lesions 52
14.3.7 Delayed Response after Initial Progression 53
14.3.8 Tumor Response as Adjudicated by IRC 53
15 Safety Analyses 53
15.1 Adverse Events 53
15.1.1 All Adverse Events 57
15.1.2 Adverse Events Leading to Study Intervention Discontinuation 62
15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events 67
15.2.1 Deaths 67
15.2.2 Serious Adverse Events 68
15.2.3 Dose-Limiting Toxicity 68
15.2.4 Bleeding Events 69
15.2.5 Adverse Events of Special Interest 69
15.2.5.1 Infusion-Related Reactions Including Immediate Hypersensitivity 69
15.2.5.2 Immune-Related AEs 69
15.2.5.3 Skin TEAEs 70
15.2.5.4 Anemia 71
15.3 Clinical Laboratory Evaluation 71
15.4 Vital Signs 74
15.5 Other Safety or Tolerability Evaluations 75
16 Analyses of Other Endpoints 75
16.1 Pharmacokinetics 75
16.1.1 Missing/non-quantifiable PK Data Handling 76
16.1.2 Descriptive PK Analysis 76
16.1.3 Pharmacokinetic Non-Compartmental Analysis 78
CCI [redacted]

16.3 Immunogenicity 80
CCI [redacted]
17 References 84
18 Appendices 85
18.1 Appendix 1: List of Important Protocol Deviations 85
18.2 Appendix 2: Identification of Previous or Concomitant Medications 85
18.3 Appendix 3: Definition of NCI-CTCAE Grading 85

2 List of Abbreviations and Definition of Terms

ADA	Antidrug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AUC_{0-t}	Area under the concentration-time curve from time zero (= dosing time) to the last sampling time at which the concentration is at or above the lower limit of quantification
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero (dosing time) extrapolated to infinity
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
BSA	Body Surface Area
BM	Biomarker (analysis population)
C_{eoi}	The concentration observed immediately at the end of infusion
CI	Confidence Interval
CrCl	Creatinine Clearance
C_{max}	Maximum observed concentration
COVID-19	2019 Novel Coronavirus Disease
CR	Complete Response
CSR	Clinical Study Report
CT	Chemotherapy
CCI [redacted]	[redacted]
CT/MRI	Computed Tomography/Magnetic Resonance Imaging
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	The concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing)
CV%	Coefficient of variation

DBP	Diastolic Blood Pressure
DCR	Disease control rate
DLT	Dose-Limiting Toxicity
DoDR	Duration of Delayed Response
DoR	Duration of Response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EOT	End of Treatment
FAS	Full Analysis Set (analysis population)
GCP	Good Clinical Practices
GeoCV%	Geometric Coefficient of Variation
GeoMean	Geometric Mean
GFR	Glomerular Filtration Rate
IAP	Integrated Analysis Plan
ICH	International Council for Harmonization
IHC	Immunohistochemistry
IMM	Immunogenicity (analysis population)
irAE	Immune-related Adverse Event
IRC	Independent Review Committee
IRR	Infusion-related reaction
CCI	[redacted]
KA	Keratoacanthoma
λz	Terminal first order (elimination) rate constant
LLN	Lower Limits of Normal
LLOQ	Lower Limit of Quantification
Max	Maximum
Mean	Arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum

n	Number of non-missing observations
NCI	National Cancer Institute
nd	Not determined
NSCLC	Non-small cell lung cancer
NE	Not Evaluable
ORR	Objective response rate
OS	Overall Survival
PD	Progression of disease
CCI	[redacted]
PFS	Progression-Free Survival
CCI	[redacted]
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set (analysis population)
PR	Partial Response
PT	Preferred Term
QTcF	Corrected QT interval by Fridericia
RDI	Relative Dose Intensity
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
SAE	Serious Adverse Event
SAF	Safety Analysis Set (analysis population)
SBP	Systolic Blood Pressure
SCR	Screening (analysis population)
SD	Stable Disease
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
SCC	Squamous Cell Carcinoma
StD	Standard Deviation
$t_{1/2}$	Apparent terminal (elimination) half-life
TEAE	Treatment-Emergent Adverse Event
TGFβ	Transforming Growth Factor β

t_{max}	The time to reach the maximum observed concentration collected during a dosing interval
TMB	Tumor Mutational Burden
TPS	Tumor Proportion Score
TtR	Time to Response
ULN	Upper Limit of Normal
WHO-DD	World Health Organization's Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	PPD	PPD	Note: Protocol Amendment 1 is considered
2.0	PPD	PPD	1. Added description for an additional interim analysis for internal planning purposes in Section 6. 2. Added analysis of COVID-19-related protocol deviations in Section 10.2.1. 3. Added description for the overview of the impact of COVID-19 events in Section 10.1. 4. Added analysis of confirmed Objective Response for participants with 6 months of follow-up in Section 14.2.1. 5. Added analysis of Progression-free Survival for participants with 6 months of follow-up in Section 14.2.4. 6. Added analysis of Overall Survival for participants with 6 months of follow-up in Section 14.2.5. 7. Added description for a listing of COVID-19 related events in Section 15.1.1. 8. Section 9.8: added a definition of the on-treatment period for immune-related adverse events. 9. Section 15.2.5.2: added a reference to the definition of the on-treatment period for immune-related adverse events. 10. Section 15.2.5.3: added two terms to the definition of potential TGFβ-mediated skin treatment-emergent events. 11. Updated definition of anemia adverse event of interest: anemia is to be considered whether it is treatment-related or not. 12. Minor corrections or updates throughout the document.
3.0	PPD	PPD	1. Minor corrections or updates throughout the document. 2. Section 6: added subsection 6.5 Follow-up Analysis.

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
			3. Section 10.1: updated the categorization of participants potentially impacted by COVID-19 who started the treatment before the pandemic (from received at least one dose during the pandemic to on-study during the pandemic). 4. Section 14.2.4: updated reasons for overall survival censoring. 5. Section 15.1.1: - added an overview of treatment-emergent adverse events by ADA status (treatment emergent ALL versus non treatment ALL). - updated the identification of COVID-19 related adverse events (from: based on a predefined list of terms provided by MedDRA; to: preferred term contains COVID-19 or SARS-COV-2). 6. Section 16.3: - added a new categorization for ADA status (treatment emergent ALL versus non treatment emergent ALL). - added a summary of the time to ADA onset and duration of ADA immunogenicity response. - added a listing of ADA results for treatment emergent ALL participants. 7. Removed sensitivity analyses for objective response, overall survival, and progression-free survival (replicated analysis based on the chemotherapy regimen that was given mostly). 8. Section 10.1: added the number and percentage of participants who switched the chemotherapy regimen. 9. Renamed potential TGFβ-mediated skin adverse events as TGF-β inhibition mediated skin adverse events.

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the interim, main, and follow-up analyses of data collected for protocol MS200647_0024.

Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned interim, main, and follow-up analyses 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 (Statistical Considerations) of the study protocol and is prepared in compliance with International Council for Harmonization (ICH) Guideline E9.

5 Objectives and Endpoints

The objectives and endpoints are defined in Table 1.

Table 1 Study Objectives and Endpoints

	Objective	Endpoint	IAP section
Primary Objective	To evaluate the safety and tolerability of bintrafusp alfa in combination with chemotherapy	• Occurrence of dose-limiting toxicities (DLTs) during the 3-week DLT observation period • Occurrence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (AEs)	Safety Analyses 15.2.3
Secondary Objective	To evaluate objective response rate (ORR) for bintrafusp alfa in combination with chemotherapy	Confirmed objective response according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) assessed by Investigator	Efficacy Analyses 14.2.1
	To evaluate progression-free survival (PFS) for bintrafusp alfa in combination with chemotherapy	PFS according to RECIST 1.1 assessed by Investigator	Efficacy Analyses 14.2.3
	To evaluate overall survival (OS) for bintrafusp alfa in combination with chemotherapy	OS	Efficacy Analyses 14.2.4
	To evaluate duration of response (DoR) for bintrafusp alfa in combination with chemotherapy	DoR assessed from complete response (CR) or partial response (PR) until progression of disease (PD) or death	Efficacy Analyses 14.2.7
	To characterize pharmacokinetic (PK) profile of bintrafusp alfa	• PK profile of bintrafusp alfa in terms of C_{eoi} and C_{trough} for all participants • PK profile of bintrafusp alfa in terms of AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, λ_z, and $t_{1/2}$ (only for participants in the safety part of the study)	Analyses of Other Endpoints 16.1
	To evaluate the immunogenicity of bintrafusp alfa	Immunogenicity of bintrafusp alfa, as measured by antidrug antibody (ADA) assay, from Screening through the last Safety Follow-up Visit	Analyses of Other Endpoints 16.3
CCI [redacted]			

CCI [redacted]

ADA = antidrug antibody, AE = adverse event, AUC_{0-t} = The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification, $AUC_{0-\infty}$ = The AUC from time zero (dosing time) extrapolated to infinity, C_{eoi} = concentration observed immediately at the end of infusion; C_{max} = Maximum observed concentration, CR = complete response, C_{trough} = concentration immediately before next dosing, CCI [redacted], DLT = dose-limiting toxicity, DoR = duration of response IHC = immunohistochemistry, IRC = Independent Review Committee, irPFS = immune-related progression-free survival, irRECIST = immune-related Response Evaluation Criteria in Solid Tumors, ORR = objective response rate, OS = overall survival, PD = progression of disease, PDL1 = programmed death ligand 1, PFS = progression-free survival, CCI [redacted], PK = pharmacokinetics, PR = partial response, RECIST 1.1 = response response evaluation criteria in solid tumors version 1.1, TEAE = treatment-emergent adverse event, TMB = tumor mutational burden, t_{max} = The time to reach the maximum observed concentration collected during a dosing interval, $t_{1/2}$ = apparent terminal (elimination) half-life, λ_z = terminal first order (elimination) rate constant.

6 Overview of Planned Analyses

This IAP focuses on interim, main, and follow-up analyses. A separate statistical analysis plan will be provided for the Safety Monitoring Committee (SMC). Table 2 below displays an overview of the planned analyses.

Further analyses may be performed, e.g., for publication purposes. Interim analyses at time points that are not specified in the protocol may be performed for internal planning purposes.

Table 2 Overview of Planned Analyses

Analysis	Data cutoff date
DLT analysis	Safety will be cleared based on DLTs observed in each of the four cohorts during the safety run-in part of the study when the last participant completes DLT observation period in the corresponding cohort.
Early interim analysis	The data cutoff date for the early interim analysis is set to the 7th of October, 2020.

Interim analysis	If Cohort A is expanded to N = 40 participants, an interim analysis will be conducted 6 months after the treatment start of the last participant in the expanded pilot cohort (Cohort A).
Main analysis	The main analysis of safety and efficacy endpoints will be conducted 18 months after the treatment start of the last participant of Cohort A.
Follow-up anaysis	The follow-up analysis will be conducted at the end of the study. The end of study is defined as 3 years after treatment start of the last participant or until all the participants in the study experienced progressive disease to the subsequent treatment, whichever occurs first. The study could also reach an end once access to study intervention for participants still benefiting is provisioned via a roll over study, expanded access, marketed product or another mechanism of access as appropriate.

The timing of conduct of the interim, main, and follow-up analyses will be triggered by the data cutoff dates mentioned in Table 2.

6.1 Safety Monitoring Committee

A SMC will be responsible for periodic safety evaluations of the study. Details can be found in the SMC Charter.

The SMC will also clear safety based on DLTs observed in each of the four cohorts during the safety run-in part of the study when the 8th evaluable participant of each cohort completes DLT observation period.

A specific statistical analysis plan will be prepared for the SMC.

6.2 Early Interim Analysis

An early interim analysis will be performed based on data cut at 07-Oct-2020. This interim analysis is intended for internal planning purposes and will include the following efficacy endpoints:

- Confirmed objective response
- Progression-free survival
- Overall survival
- Duration of response

Participant disposition, demographics, medical history, previous anticancer medications, disease history, treatment compliance and exposure, and safety data (AEs and clinical laboratory evaluations) will also be described.

The full list of tables, listings and figures to be provided is identified in the table of content of the output shells.

6.3 Interim Analysis

Once the safety profile of the pilot cohort (Cohort A) has been cleared by the SMC, an additional 32 participants will be enrolled in the expansion part of Cohort A resulting in a total sample size of N = 40 participants. An interim analysis will be conducted 6 months after the treatment start of the last participant in the expanded pilot cohort to assess additional safety data and preliminary efficacy and will describe:

- Confirmed objective response (excluding the analysis performed on the subset of participants with 6 months of follow-up)
- Progression-free survival (excluding the analysis performed on the subset of participants with 6 months of follow-up)
- Duration of response

Participant disposition, demographics, medical history, previous anticancer medications and other baseline characteristics (disease history, Eastern Cooperative Oncology Group Performance Status [ECOG PS]), treatment compliance and exposure, and safety analyses (AEs and clinical laboratory evaluations) will also be described at the time of the interim analysis.

Immunogenicity and PK analysis will be performed when all participants in each cohort of the safety run-in have finished Cycle 2. Results will be evaluated by Clinical PK/PD group (CPK) of Translational Medicine, Merck Healthcare KGaA, Darmstadt, Germany.

6.4 Main Analysis

The main analysis of safety and efficacy endpoints considering participants of Cohort A, will be conducted 18 months after the treatment start of the last participant of the cohort. All planned analyses identified in this IAP (excluding the analysis of efficacy endpoints performed on the subset of participants with 6 months of follow-up) will be performed only after this period with all study data in-house, all data queries resolved, and the database locked. A Data Review Meeting will be held prior to database lock. In addition, no database can be locked until this IAP has been approved.

6.5 Follow-up Analysis

A follow-up analysis will be conducted at the end of the study. The end of study is defined as 3 years after treatment start of the last participant or until all the participants in the study experienced progressive disease to the subsequent treatment, whichever occurs first.The following analysis will be performed:

- Disposition of participants
- Overall survival (Sections 14.2.4, 14.2.5, 14.3.2)
- Progression-free survival (Section 14.3.3)

- Adverse events

7 Changes to the Planned Analyses in the Clinical Trial Protocol

Changes from the protocol:

- Definition of the Full and Safety Analysis Set is modified compared to the protocol.
- Safety Set (DLT) is re-named to Dose-Limiting Toxicities Analysis Set (DLT).
- CCI [redacted]

Original definitions:

1. Full Analysis Set (FAS): All participants, who were administered any dose of any study intervention. Analyses will include participants as treated (i.e., in case the chemotherapy regimen was switched the latter one is used in analysis).
2. Safety Analysis Set (SAF): All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.
3. CCI [redacted]

Updated definitions:

1. FAS: All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated. In case the chemotherapy regimen was switched, the participant will be analyzed within the first chemotherapy regimen and cohort.
2. SAF: All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated. In case the chemotherapy regimen was switched, the participant will be analyzed within the first chemotherapy regimen and cohort.

CCI [redacted]

Additionally, an early interim analysis has been added (see Section 6.2) for internal planning purposes.

Finally, the COVID-19 pandemic was unforeseen at the time this protocol was finalized; therefore, analyses related to the COVID-19 pandemic were added later.

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 on this study including:

- Summary of participants in pre/during/post COVID-19 study period
- Summary of COVID-19 related protocol deviations
- Summary of COVID-19 impact (missed study intervention administrations, tumor assessments or missed visits due to COVID-19)
- Listing of AEs related to COVID-19

8 Analysis Populations and Subgroups

8.1 Definition of Analysis Populations

Screening Analysis Set (SCR)

The Screening Analysis Set includes all participants, who provided informed consent, regardless of the participant's study intervention status in the study.

Dose-limiting toxicities Analysis Set (DLT)

The dose-limiting toxicities Analysis Set includes all participants of the DLT evaluation (the first 8 participants of each cohort) who were administered with at least 90% of the bintrafusp alfa infusion during the DLT observation period of 3 weeks and did not discontinue treatment for other reasons than DLT.

Full Analysis Set (FAS)

The Full Analysis Set includes all participants, who were administered any dose of any study intervention. Analyses will consider participants as treated. In case the chemotherapy regimen was switched, the participant will be analyzed within the first chemotherapy regimen and cohort.

If more than 10% switchers occur in a cohort (i.e., two or more switchers in Cohort B to D and five or more in Cohort A), sensitivity analyses for efficacy will be performed considering the chemotherapy that was given mostly and the respective cohort.

Safety Analysis Set (SAF)

The Safety Analysis Set includes all participants, who were administered any dose of any study intervention. Analyses will consider participants as treated. In case the chemotherapy regimen was switched, the participant will be analyzed within the first chemotherapy regimen and cohort.

Pharmacokinetic Analysis Set (PKAS)

The Pharmacokinetic Analysis Set includes all participants who complete at least one infusion of bintrafusp alfa, and who provide at least one sample with a measurable concentration of bintrafusp alfa, without important protocol deviations or events deemed to affect PK evaluation.

Immunogenicity Analysis Set (IMM)

The Immunogenicity Analysis Set includes all participants who have received at least of one dose of bintrafusp alfa + chemotherapy (CT) and have at least one valid antidrug antibody (ADA) result.

CCI [redacted]

[redacted]

Table 3 displays the use of the analysis sets in the different analyses:

Table 3 Overview of the Analysis Set Used in the Analyses

Analyses	SCR	DLT	FAS	SAF	PKAS	IMM	BM
Disposition	✓						
Protocol Deviations			✓				
Demographics			✓				
Baseline Assessments			✓				
Previous and Concomitant Therapies			✓				
Compliance and Exposure				✓			
Safety and Tolerability: Dose Limiting Toxicity		✓					
Safety and Tolerability: other endpoints				✓			
Efficacy			✓				
Immunogenicity						✓	
CCI [redacted]							■
Pharmacokinetics				✓	✓		

8.2 Subgroup definition and Parameterization

The following subgroups for efficacy analyses with regards to Cohort A and combined 1L Cohort A, B, C will be defined as follows:

- Age
    - age < 65 years

  - age ≥ 65 years
- Sex
  - Male
  - Female
- Geographic Region
  - North America
  - Latin America
  - Western Europe
  - Eastern Europe
  - Australia
  - Asia
- Race
  - White
  - Black or African American
  - Asian
  - American Indian or Alaska Native
  - Native Hawaiian or Other Pacific Islander
  - Not collected at this site
  - More than one race
  - Other
- Histology
  - Squamous (i.e., squamous cell carcinoma or adenosquamous carcinoma)
  - Non-squamous (i.e., all other histologies)
- Smoking status:
  - Never smoker
  - Ever smoker
- Brain metastasis at Baseline (based on "target lesions" and "non-target" lesions eCRF pages)
  - Yes
  - No
- Liver metastasis at Baseline (based on "target lesions" and "non-target" lesions eCRF pages)
  - Yes

- No

- Chemotherapy (Cohorts A and C separately and cohorts A and C combined, based on first chemotherapy received for AE summaries; Cohort A only for efficacy subgroup analysis)
  - Cisplatin
  - Carboplatin
- ADA status (see Section 16.3 for definition)
  - Never positive
  - Ever positive

  AND
  - Treatment emergent ALL versus
  - Non-treatment emergent ALL

For variables with more than two categories, in case of low number of participants within a category (< 10 participants), categories will be pooled.

Only subgroup variables with a minimum of 10 participants per subgroup will be considered for efficacy parameters.

9 General Specifications for Data Analyses

Unless otherwise indicated, all general (i.e., disposition of participants and discontinuations, protocol deviations, demographics and other baseline characteristics, and previous or concomitant medication), safety and efficacy analyses will be performed by cohort (Cohorts A, B, C and D) and combining Cohort A, B, and C (1L Cohort A, B, C). Listings will only be provided by cohort and not combined. 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.

Pooling of centers:

Because of the high number of participating centers and the anticipated small number of participants recruited 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, the 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 and laboratory data) will be analyzed according to the following scenario:

- For shift tables, they will be taken into account in the definition of the worst assessment during the study

- For description at each time post-baseline point, the first available result (in chronological order) will be taken into account in the analysis in case of multiple values.

For antidrug antibody (ADA) analysis, unscheduled visits will also be taken into account in the analysis.

For PK analysis, 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 (see further details below).

Significance level:

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

Presentation of continuous and qualitative variables:

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

- number of participants (N), number of participants with missing values
- mean, standard deviation (StD)
- median, 25th Percentile - 75th Percentile (Q1-Q3),
- minimum (Min) and maximum (Max).

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

Pharmacokinetic variables (concentrations and parameters) will be summarized as described in Section 16.1.2.

Qualitative variables will be summarized by counts and percentages.

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

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

Study intervention:

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

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 done on the preferred term (PT) level where the preferred term is corresponding 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 be only counted once in the screening analysis set, considering the latest screening (screening with latest informed consent). If a participant is re-screened several times, then he will be counted only once in the disposition table in the number of re-screened participants.

Software:

All analyses will be performed using SAS 9.4 or higher in the SAS Grid environment. The computer program Phoenix® WinNonlin® version 6.4 or higher will be used to derive PK parameters applying non-compartmental analysis (NCA).

9.1 Data Handling after Cut-off Date

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

Stop dates are not affected by this rule, e.g., a stop date of AEs, which starts prior to the cutoff, but stopped after date of cutoff, will not be changed.

9.2 Definition of Baseline and Change from Baseline

The last available/non-missing assessment prior to the first study intervention is defined as "baseline" value or "baseline" assessment for safety and efficacy analyses. If an assessment is planned to be performed prior to the first dose of study intervention in the protocol and the assessment is performed on the same day as the first dose of study intervention, it will be assumed that it was performed prior to study intervention, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study intervention.

Participants who start intervention and discontinue from the study on the same day may have 2 different sets of data collected on study day 1 (one during study and one in the End of Treatment [EOT]) visit. Data reported at the EOT visit are not eligible for baseline selection.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed as if it was an unscheduled post-dose measurement.

If a scheduled post-dose measurement actually occurred pre-dose, then the corresponding measurement will be treated and analyzed as if it was an unscheduled pre-dose measurement.

Absolute and percent changes from baseline are defined as

absolute change = visit value – baseline value

percent change = 100 * (visit value – baseline value) / baseline value

9.3 Study Day / Study Treatment Day

Day 1 is the day of start of study treatment, the day before is Day -1 (no Day 0 is defined). Study day / Study treatment day is defined relative to Day 1.

9.4 Definition of Duration and 'time since' Variables

Duration will be calculated by taking the difference of start and stop date + 1 (e.g., survival time [days] = date of death – date of first study intervention + 1), if not otherwise specified.

The time since an event (e.g., time since first diagnosis) will be calculated by subtracting the date of event from the reference date.

9.5 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.

9.6 Date of last Contact

The following complete dates will be used to determine the last date known to be alive. Only the ones among them that are before or at data cutoff shall be used in the derivation. Dates past the data cutoff will be ignored by the derivation:

- All participant assessment dates (blood draws [laboratory, PK, vital signs, performance status, ECG, tumor assessments])
- Start and end dates of anticancer 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
- Date of discontinuation from the "Study Termination" eCRF page (do not use if reason for discontinuation is lost to follow-up or death)
- Data collected after reinitiated treatment will be considered in the derivation of the last known to be alive date.

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.

9.7 Time Window

No time window defined.

9.8 Definition of On-treatment Period

The on-treatment period will include the initial treatment period as well as the reinitiation of treatment period, as applicable. Whether a participant reinitiates treatment (following the rules as outlined in the protocol) or not, the on-treatment period is defined as the time from the first study intervention to the last study intervention + 30 days, or the earliest date of subsequent anticancer therapy minus 1 day, or death, or the data cut-off date, whichever occurs first, unless otherwise stated.

Any systemic anticancer therapy, any anticancer surgery and any anticancer radiotherapy will be considered as subsequent anticancer therapy (bone radiotherapy or brain metastasis radiotherapy is regarded as palliative treatment allowed on study treatment and therefore not considered as subsequent anticancer therapy, whereas other anticancer therapy is considered as subsequent therapy).

For immune-related AEs as listed in Section 15.2.5.2, an expanded on-treatment period will be used as a default for any analysis:

Time from the first study intervention to the last study intervention date + 90 days, death OR to the earliest date of subsequent anticancer therapy minus 1 day, whichever occurs first, unless otherwise stated.

9.9 Imputation 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 [e.g., standard deviation (StD)] cannot be computed and should be presented as "nd".

Handling of incomplete dates:

- **Missing data handling rules for age calculation**

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.

- **Missing data handling rules for disease history**

Incomplete dates for disease history (date of initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

  - 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.

- **Missing data handling rules for adverse events**

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 treatment then the onset date will be imputed by the minimum of start of study treatment and AE resolution date (if not missing).
  - In all other cases, the missing onset day or missing onset month will be imputed by 1.
  - Incomplete stop dates will be imputed 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.

- **Missing data handling rules for previous and concomitant medications (see Appendix 2)**

Incomplete dates for previous and concomitant medications 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.

- **Missing data handling rules for subsequent anticancer therapy**

Incomplete dates for start date of subsequent anticancer therapy (drug therapy, radiotherapy, 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 anticancer therapy is before that date. In that case, the incomplete anticancer therapy start date will be imputed as the end date of the anticancer therapy.
- If both day and month are missing, no imputation will be performed.
- Incomplete subsequent anticancer therapy stop dates will not be imputed.

- **Missing data handling rules for death date**

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) date after the date of last known alive date and the 15th day of the month.
- Otherwise it will not be imputed.

- **Handling rules for tumor assessments**
  - 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 like "_____YYYY". If values are imputed according to the IAP, imputed values will be presented in participant data listings and imputed information will be flagged.

9.10 Scoring of HRQOL Data

Not applicable.

9.11 Data Collected after Re-initiated Treatment

Data collected after re-initiation of treatment will be included in summary tables for all analyses. Data listings will include both, data collected during the first period of treatment and during the reinitiation of treatment and data collected during the reinitiation of treatment will be flagged.

10 Study Participants

The subsections in this section include specifications for reporting participant disposition and treatment/trial discontinuations. Additionally, procedures for reporting protocol deviations are provided. Summaries will be presented by cohort, combined 1L Cohort A, B, C and all cohorts combined.

10.1 Disposition of Participants and Discontinuations

Descriptive statistics will be used to summarize participant 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 per cohort (Cohort A, B, C, and D), 1L Cohort A, B, C and overall, including reinitiation phase:

- Total number of screened participants
- Total number of re-screened participants
- Number of participants who did not continue beyond screening overall and grouped by reason (participant did not meet all eligibility criteria, withdrew consent, progressive disease, adverse event, lost to follow-up, death, other)
- Number of treated participants
- Number and percentage of participants who completed/discontinued bintrafusp alfa treatment, grouped by main reason death or progression of disease (as reported on "M7824 termination" page of the eCRF)
- Number and percentage of participants who completed/discontinued chemotherapy, grouped by chemotherapy and main reason death or progression of disease (as reported on "Chemotherapy termination" page of the eCRF)
- Number and percentage of participants with bintrafusp alfa treatment on-going

- Number and percentage of participants with chemotherapy switch, grouped by combination (e.g., cisplatin to carboplatin)
- Number and percentage of participants who reinitiated bintrafusp alfa treatment
- Number and percentage of participants who discontinued treatment after bintrafusp alfa reinitiation
- For each chemotherapy, number and percentage of participants with treatment ongoing
- Number and percentage of participants who discontinued the study, grouped by 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. The percentage of participants with percentage based on the number of participants in the FAS population will be presented (except for numbers regarding screening). The number of participants in each analysis set will also be summarized by site.

The listing of participant disposition will include all participants (i.e., including screening failures). The listing will include the following information (if applicable): cohort, participant identifier, date of informed consent, included in the study, reason for exclusion, first/last study intervention date, reason off-treatment, date and reason off-study, population flags. When the reasons, such as the reason off-treatment is categorized as "Other, specify", "Protocol non-compliance, specify" or "Withdrawal by subject, specify", the verbatim text as entered in the eCRF will be presented in the listing.

If any re-screened participants will be observed, a listing of re-screened participants will be provided and will include the following information: cohort, participant identifier, date of informed consent, date of first administration of study intervention, participant identifier at screen failure, date of informed consent at screen failure, date of screening failure, reason of screening failure.

In addition, a listing of participants for which bintrafusp alfa has been reinitiated will be provided with the following information: cohort, participant identifier, date of first study intervention, date of last study intervention, reason for treatment termination, first and last reinitiation bintrafusp alfa administration date, status at end of treatment reinitiation, and primary reason for permanent bintrafusp alfa discontinuation. When the reason is categorized as "Other, specify", "Protocol non-compliance, specify" or "Withdrawal by subject, specify", the verbatim text as entered in the eCRF will be presented in the listing.

The indirect impact of COVID-19 will be assessed as follows:

- The number and percentage of participants in pre/during/post COVID-19 study period will be provided:
    - Number of participants who started treatment prior to the COVID-19 study period
        - On-study during the COVID-19 study period

    - Discontinued the study before start of the COVID-19 study period
  - Number of participants who started treatment during the COVID-19 study period
  - Number of participants who started treatment posterior to the COVID-19 study period

The COVID-19 study period is defined as follows:

- The start of COVID-19 study period will be defined by country as the minimum of 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) and 11 March 2020 (WHO-start of world-wide pandemic).
- Post-pandemic could be defined as date (1) vaccination is released, (2) WHO declares COVID-19 pandemic over, (3) region-specific calls are made to end social distancing measures with no relevant rise in cases thereafter.

An overview of the COVID-19 impact on the study will also be provided. This will include the number and percentage of participants who meet the following items:

- Potentially affected by COVID-19 (Started during pandemic/Started before pandemic and on-study during pandemic)
- At least one COVID-19 impact
  - At least one adverse event related to COVID-19 (see Section 15.1.1)
  - Number of participants who died for any reason related to COVID-19
  - At least one COVID-19-related protocol deviation
  - At least one missed dose of bintrafusp alfa
  - At least one missed dose of any chemotherapy agents
  - At least one missed visit (based on protocol deviations)
  - Categorization of the total number of missed visits per participant (1, 2, 3 or > 3)
  - At least one missed tumor assessment (based on protocol deviations)
  - Categorization of the total number of missed tumor assessments per participant (1, 2, 3 or > 3)
  - At least one tele-visit replacing on-site visit (based on protocol deviations)
  - Categorization of the total number of tele-visits replacing on-site visits per participant (1, 2, 3 or > 3)
  - Number of participants who permanently discontinued bintrafusp alfa for any reason related to COVID-19
  - Number of participants who permanently discontinued at least one chemotherapy agent for any reason related to COVID-19

- Number of participants who discontinued the study for any reason related to COVID-19

A listing of all participants affected by COVID-19 including the outcome to each category of the overview table, the PT and AE number of AEs attributed to COVID-19, and the COVID-19 related protocol deviations will also be provided.

10.2 Protocol Deviations / Exclusion from Analysis Populations

10.2.1 Important Protocol Deviations

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;
- Deviation from Good Clinical Practices (GCP).

Important protocol deviations will be identified and confirmed prior to or at the Data Review Meeting at the latest and will be classified in the following categories: informed consent, eligibility and entry criteria, concomitant medication, laboratory assessment, study procedure, serious adverse event, randomization, visit schedule, IP compliance, efficacy, administrative, source document, regulatory or ethics approvals, other.

All important protocol deviations will be documented in Study Data Tabulation Model (SDTM) datasets whether identified through site monitoring, medical review or programming.

Important protocol deviations will be defined in a specific document (see Appendix 1), 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 in terms of this study may include, but may not be limited to, the following:

- Dose delayed outside the allowed window
- 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 important protocol deviations or important events for PK, the relevant PK data will be excluded from summaries based on the PK analysis set.

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. Summaries will be provided for the FAS by cohort and combined 1L Cohort A, B, C.

The following summary tables and listings of important protocol deviations will be provided:

- Frequency table per category of important protocol deviations
- Listing of important protocol deviations which will include participant identifier, category of the deviation, and a description of the deviation.

Additionally, the COVID-19 related protocol deviations will be described as follows:

- Frequency table per category of important COVID-19 related protocol deviations
- Frequency table per category of non-important COVID-19 related protocol deviations
    - Listing of COVID-19 related protocol deviations

11 Demographics and Other Baseline Characteristics

Summaries will be presented for the FAS by cohort, combined 1L Cohort A, B, C and all cohorts combined.

11.1 Demographics

Demographic characteristics will be summarized using the following information from the Screening/Baseline Visit eCRF pages.

- Sex: male, female
- Ethnicity: Hispanic or Latino, not Hispanic or Latino
- Race:
    - For participants reporting one race only: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not collected at this site, More than one race, and Other
    - For participants reporting several races, all combinations will be reported
- Age (years): summary statistics

- Age categories: < 65 years, ≥ 65 years (65-74 years, 75-84 years, ≥ 85 years)
- Geographic Region: North America, Latin America, Western Europe, Eastern Europe, Australia, Asia

Specifications for computation:

- Age [years]: (date of given informed consent - date of birth + 1) / 365.25
- Investigator site codes will be used for the determination of the participant's geographic region.

The related listing will also be provided with the following information: cohort, participant identifier, sex, race (including all reported races in case of "multiple" races, and details in case of "other" race), ethnicity, geographic region, age, age category.

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), preferred term 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 alphabetically ordered by SOC and PT. Each participant will be counted only once within each PT or SOC.

The related listing will also be provided with the following information: cohort, participant identifier, age, sex, race, preferred term, reported medical history term, start date, end date, related to study condition, ongoing, grade. This listing will be sorted by cohort, participant identifier, start date, end date, preferred term.

11.3 Other Baseline Characteristics

Other baseline characteristics include disease history, ECOG Performance Status, ECG values and results, vital signs and skin status history. Laboratory results at Baseline will be presented together with the results of all other laboratory assessments.

11.3.1 Disease History

Information on disease characteristics collected on the "Disease History" eCRF page will be summarized as follows:

- Tumor histology: adenocarcinoma, squamous cell carcinoma (SCC), large cell carcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, neuroendocrine carcinoma, diffuse idiopatic carcinoma, other
- Time since initial cancer diagnosis (months)
- Time since documented, locally advanced, inoperable or metastatic disease diagnosis (months)

- TNM classification at initial diagnosis and at study entry: each T, N, M category will be described (TX, T0, N1, etc.)
- Molecular abnormalities:
    - Epidermal Growth Factor Receptor (EGFR) (mutated, wild type)
    - Anaplastic lymphoma kinase (ALK) positive (yes, no, not applicable)
    - ROS1 rearrangement (yes, no, not applicable)
    - BRAF V600E mutation (yes, no, not applicable)

CCI [redacted]

CCI [redacted]

11.3.2 ECOG Performance Status at Baseline

The ECOG Performance Status will be described from the data collected on the "ECOG Performance Status" eCRF page. It will be described at Baseline by the frequency and percentage of participants in each category:

0: Fully active, able to carry on all pre-disease performance without restriction.

1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.

2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.

3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.

4: Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

5: Dead.

11.3.3 ECG at Baseline

ECG values and results (heart rate, PQ/PR duration, QRS duration, QT duration, Corrected QT interval by Fridericia (QTcF), rhythm, result of ECG) will be presented in a listing described in Section 15.5.

11.3.4 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 (kg)
- Body mass index (BMI) (kg/m2)
- Body Surface Area (m^2).

BMI (kg/m2) will be computed as weight(kg)/[height(m)]^2

BSA (m^2) = ([height (cm) x weight (kg)] / 3600) ½

11.3.5 Skin Status History

Skin status history is collected on the "Skin Status History" eCRF page with the following data:

- 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 UV exposure (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)

A listing of skin status history will be provided.

11.3.6 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 user, Ever user (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: never smoker, current smoker, <5, 5-<10, ≥10 and summary statistics

  Years since quitting is computed for former smokers only as (year of first study intervention - end year of smoking).

The related listing will also be provided with the following information: cohort, participant identifier, age, sex, race, nicotine use status (never used/former/current), number of smocking pack year, start and end date of nicotine consumption, duration of consumption in years. This listing will be sorted by cohort and participant identifier.

12 Previous or Concomitant Medications/Procedures

Summaries will be performed on the FAS by cohort and combined 1L Cohort A, B, C.

12.1 Previous Anticancer Medications

Previous anticancer medications for Non-small cell lung cancer (NSCLC) are collected under the "Prior Anticancer Drug Therapies for NSCLC Details", "Prior Anticancer Radiotherapy for NSCLC Details", and the "Prior Anticancer Surgeries for NSCLC Details" eCRF pages.

The number of participants in each of the following anticancer treatment categories will be tabulated:

- Participants with at least one previous anticancer treatment or procedure (i.e., drug therapy, radiotherapy or surgery)
- Participants with at least one previous anticancer drug therapy
- Participants with at least one previous anticancer radiotherapy
- Participants with at least one previous anticancer surgery.

Previous anticancer drug therapy will be summarized as follows:

- Number of any previous anticancer therapy regimens: 0 / 1 / 2 / 3 / ≥ 4
- Number of previous lines of therapy for metastatic/locally advanced disease: 0 / 1 / 2
- Intent of therapy: Neoadjuvant/ Adjuvant/ Metastatic or locally advanced/ Chemoradiation
- Best response to last treatment regimen: complete response (CR)/partial response (PR)/stable disease (SD)/progression of disease (PD)/non-complete response or non-progression of disease (Non CR/Non PD) /not evaluable (NE)/unknown.

Previous anticancer drug therapy, previous radiotherapy, and previous anticancer surgery will be presented in separate listings as follows:

- The previous anticancer drug listing will contain cohort, participant identifier, age, sex, race, preferred term, 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 cohort, participant identifier, anticancer drug start date, end date and preferred term.
- The previous radiotherapy listing will contain cohort, participant identifier, age, sex, race, start date, end date, location of radiotherapy, side and lobe if location is lung, total dose, number of fractions and best response on the treatment regimen. This listing will be sorted by cohort, participant identifier, radiotherapy start date, radiotherapy end date and location.
- The previous anticancer surgery listing will contain cohort, participant identifier, age, sex, race, date of surgery, name and location of surgery, curative intent of surgery (Y/N), and outcome of surgery. This listing will be sorted by cohort, participant identifier, surgery date, name of surgery and location of surgery.

12.2 Previous and Concomitant Medications

Previous medications are medications, other than study intervention and premedications for study intervention, which started prior to first dose date of 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 intervention and premedications for study intervention, which are taken by participants any time on-treatment (see on-treatment definition 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.

Previous and concomitant medications will be summarized from the "Concomitant Medication Details" eCRF. Anatomical Therapeutic Chemical (ATC)-2nd level and preferred term will be tabulated as given from the WHO-DD dictionary current version. In case multiple ATC's 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 within 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 a listing including cohort, participant identifier, age, sex, race, preferred term and medication name as provided by the Investigator, start date/time, end date/time, dose, dose units, frequency, route, indication, reason for the medication. A flag will be added to identify medications as previous ones and concomitant ones. This listing will be sorted by cohort, participant identifier, start date and time, end date and time (note that missing end date are considered as ongoing and will be displayed after non-missing date in case of same start date), and preferred term.

12.3 Concomitant Procedures

Concomitant procedures undertaken any time on trial, are collected under the eCRF page "Concomitant Procedures Details".

Concomitant procedures will be presented in a listing including cohort, participant identifier, age, sex, race, name of procedure (as provided by the Investigator), start date, end date, indication, and reason for procedure. A flag will be added to identify each procedure as prior to treatment or after the on-treatment period. The listing will be sorted by cohort, participant identifier, start date, end date (note that missing end date are considered as ongoing and will be displayed after non-missing date in case of same start date) and procedure name.

12.4 Subsequent Anticancer Treatment

Subsequent anticancer treatment is collected under the "Anticancer Treatment after Discontinuation Details", "Radiotherapy after Discontinuation Details" (Note: Radiotherapy done while participant is still receiving study intervention is not considered subsequent anticancer treatment.) and "Surgeries after Discontinuation Details" eCRF pages.

Subsequent anticancer treatment will be presented in a listing including cohort, participant identifier, age, sex, race, preferred term/medication name, treatment type (medication or radiotherapy or surgery), 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 cohort, participant identifier, start date, end date, treatment type, preferred term and medication name.

12.5 Premedications

Premedications are medications administered per protocol prior to study intervention.

Premedication for bintrafusp alfa will be based on "Premedication M7824" eCRF page (participants for whom the question "Has the participant received premedications before M7824 infusion?" is answered "Yes" at the corresponding visit). Premedication for chemotherapy will be based on "Premedication chemotherapy" eCRF page (participants for whom the question "Has the participant received premedications before chemotherapy infusion?" is answered "Yes" at the corresponding visit).

A listing of premedication for bintrafusp alfa and a listing of premedication for chemotherapy will be provided. Theses listings will include cohort, participant identifier, age, sex, race, name of medication, start date/time of premedication, end date/time of premedication, study days since the first study intervention, dose, unit, route. These listings will be sorted by cohort, participant 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 SAF Analysis Set by cohort and combined 1L Cohort A, B, C.

Administration details of bintrafusp alfa and other study interventions are given in Section 6 of the protocol.

Duration of Therapy (Weeks) and Number of Infusions for Bintrafusp alfa and Chemotherapy

All duration of treatment and number of infusions summaries will be based on "M7824 Administration Details", "Cisplatin Administration Details", "Carboplatin Administration Details", "Pemetrexed Administration Details", "Paclitaxel Administration Details", "Nab-paclitaxel Administration Details", "Gemcitabine Administration Details", "Docetaxel Administration Details" eCRF page.

Bintrafusp alfa, cisplatin, carboplatin, pemetrexed, paclitaxel and docetaxel are administered every 3 weeks. The duration of therapy (in weeks) for each of these treatments is defined as:

$$\text{duration of therapy} = \left(\frac{\text{date of last dose of therapy - date of first dose of therapy} + 21}{7}\right)$$

Nab-paclitaxel is administered in a 3-week cycle on Day 1, 8, and 15, in each cycle. Whether the participant reinitiates the treatment or not, the duration of therapy (in weeks) for this treatment is defined as:

$$\text{duration of nab-paclitaxel therapy} = \left(\frac{\text{date of last dose of nab-paclitaxel-date of first dose of nab-paclitaxel}+7}{7}\right)$$

Gemcitabine is administered in a 3-week cycle on Day 1, and 8 in each cycle. Whether the participant reinitiates the treatment or not, the duration of therapy (in weeks) for this treatment is defined as:

$$\text{duration of gemcitabine therapy} = \left(\frac{\text{date of last dose of gemcitabine-date of first dose of gemcitabine}+14}{7}\right)$$

Whether the participant reinitiates the treatment or not, the duration of the chemotherapy combinations (cisplatin/pemetrexed, carboplatin/pemetrexed, carboplatin/paclitaxel, carboplatin/nab-paclitaxel, cisplatin/gemcitabine, carboplatin/gemcitabine) will also be defined as follows:

$$\text{duration of chemotherapy combination} = \left(\frac{\text{date of last dose of chemo-date of first dose of chemo}+21}{7}\right)$$

An infusion is regarded to be received, if the actual dose received is > 0 mg.

The following summary tables will be provided:

- Duration of therapy (weeks) for each treatment (bintrafusp alfa, cisplatin, carboplatin, pemetrexed, paclitaxel, nab-paclitaxel, gemcitabine, docetaxel, and chemotherapy combinations)
- Number of infusions received for each treatment (bintrafusp alfa, cisplatin, carboplatin, pemetrexed, paclitaxel, nab-paclitaxel, gemcitabine, docetaxel)

Bintrafusp alfa and Chemotherapy Cumulative Dose, Dose Intensity, Relative Dose Intensity

Bintrafusp alfa and chemotherapy dosing calculations and summaries will be based on "M7824 Administration Details", "Cisplatin Administration Details", "Carboplatin Administration Details", "Pemetrexed Administration Details", "Paclitaxel Administration Details", "Nab-paclitaxel Administration Details", "Gemcitabine Administration Details", "Docetaxel Administration Details" eCRF pages. A dose is regarded to be administered, if the actual dose received is > 0 mg.

Cumulative dose (mg/m²) = sum over all visits during the time period of [actual dose (mg) received at visit *i* / body surface area [BSA] (m²) at visit *i*], where:

$$\text{BSA at a visit } i\,(\text{m}^2) = \sqrt{\left(\frac{\text{height at Baseline (cm)}*\text{weight at visit } i\,(\text{kg})}{3600}\right)}$$

The cumulative dose of carboplatin received in a time period will be first calculated in mg as the sum of the actual dose levels (mg) that the participant received within that period (directly collected in the eCRF).

The cumulative dose of carboplatin will also be computed in mg.min/mL using the Calvert equation as follows:

Cumulative dose (mg.min/mL) = sum over all visits during the time period of [actual dose (mg) received at visit *i* / (Glomerular Filtration Rate [GFR] at visit *i* + 25)], where GFR is estimated by calculated creatinine clearance (CrCl) using the Cockcroft-Gault equation:

Estimated GFR (mL/min) = CrCl = ((140 - age (years)) * weight (kg) * (0.85 for females only)) / (72 * creatinine (mg/dL))

Conversion factor for creatinine: 1 mg/dL = 88.4 µmol/L.

The GFR value will be capped at 125 mL/min.

In case the weight or creatinine is not available at a visit, it will be imputed to the last observed value.

The cumulative dose of bintrafusp alfa per participant in a time period is the sum of the actual dose levels of bintrafusp alfa that the participant received within that period (i.e., total dose administered [mg]).

The dose intensity (DI) of chemotherapy (mg/m²/cycle) (excluding carboplatin) per 3-week period is defined as:

$$DI=\left(\frac{\text{cumulative dose (mg/m}^2\text{)}}{\text{(duration of therapy (in weeks))/3}}\right)$$

The DI of carboplatin (mg.min/mL/cycle) per 3-week period is defined as:

$$DI=\left(\frac{\text{cumulative dose } (mg.min/mL)}{\text{(duration of therapy (in weeks))/3}}\right)$$

The DI of bintrafusp alfa (mg/cycle) per 3-week period is defined as:

$$DI=\left(\frac{\text{cumulative dose (mg)}}{\text{(duration of therapy (in weeks))/3}}\right)$$

For participants who reinitiated bintrafusp alfa during the study, formula above will also apply.

The relative dose intensity (RDI) of bintrafusp alfa is defined as the actual dose intensity divided by the planned dose per cycle (2400 mg) and expressed in percentage.

$$\text{RDI (\%)} = 100 * \left(\frac{\text{DI}}{\text{planned dose per cycle}}\right)$$

The RDI of chemotherapy agents (%) is defined as follows: RDI (%) = 100 * (DI / planned DI), where the planned DI (mg/m²/cycle or AUC mg.min/mL/cycle) depends on each chemotherapy administration schedule and is defined as follows:

(nab-paclitaxel) planned dose at week 1 day 1 (mg/m²) * 3
(gemcitabine) planned dose at week 1 day 1 (mg/m²) * 2
(all other chemotherapies) planned dose at week 1 day 1 (mg/m² or AUC)

The following summary tables will be provided:

- Cumulative dose for bintrafusp alfa (mg) and each chemotherapy (mg/m² or AUC) (cisplatin, carboplatin, pemetrexed, paclitaxel, nab-paclitaxel, gemcitabine, docetaxel)
- Dose intensity for bintrafusp alfa (mg/cycle) and each chemotherapy (mg/m²/cycle or mg.min/mL/cycle) (cisplatin, carboplatin, pemetrexed, paclitaxel, nab-paclitaxel, gemcitabine, docetaxel)
- Relative dose intensity (%) for bintrafusp alfa and each chemotherapy (cisplatin, carboplatin, pemetrexed, paclitaxel, nab-paclitaxel, gemcitabine, docetaxel): <80% / [80%-90%] / >90%.

Chemotherapy Dose Reductions

Chemotherapy dose reductions as recorded on the "Cisplatin Administration Details", "Carboplatin Administration Details", "Pemetrexed Administration Details", "Paclitaxel Administration Details", "Nab-paclitaxel Administration Details", "Gemcitabine Administration Details", "Docetaxel 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. Number of participants with at least one dose reduction, reasons for dose reduction, as well as a categorization of the number of infusion with dose reduced (1 / 2 / ≥ 3) will be summarized.

Summary tables will be provided for each chemotherapy (cisplatin, carboplatin, pemetrexed, paclitaxel, nab-paclitaxel, gemcitabine, docetaxel). No dose reduction is allowed for bintrafusp alfa.

Bintrafusp alfa and Chemotherapy Therapy Delays

Bintrafusp alfa, cisplatin, carboplatin, pemetrexed, paclitaxel and docetaxel are administered every 3 weeks. Delays of therapy for each of these treatments will be derived by infusion as the number of days since the start of last infusion – 21.

Nab-paclitaxel is administered in a 3-week cycle on Day 1, 8, and 15, in each cycle. Delays of therapy for nab-paclitaxel will be derived by infusion as the number of days since the start of last infusion – 7.

Gemcitabine is administered in a 3-week cycle on Day 1, and 8, in each cycle. Delays of therapy for gemcitabine 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 – 14.

If the value above is >0 days, then 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 participants with at least one delay
- Longest delay per participant (no delay, 1-2 days, 3-8 days, 9-15 days, ≥16 days)
- Number of delays per participant (0 delay, 1 delay, 2 delays, 3 delays, ≥ 4 delays).

Summary tables will be provided for each treatment (bintrafusp alfa, cisplatin, carboplatin, pemetrexed, paclitaxel, nab-paclitaxel, gemcitabine, docetaxel).

A listing of treatment exposure to bintrafusp alfa will be provided. It will include cohort, participant identifier, age, sex, race, cumulative dose, dose intensity, relative dose intensity, visit, infusion start date and time, infusion end date and time, change in dose and reason for change, infusion rate (mL/hr), actual dose (mg), route, administration modification and reason for modification, change in administration detail, treatment delay (days). Infusions during the reinitiation phase will be flagged in the listing. This listing will be sorted by cohort, participant identifier, infusion start date and infusion end date.

A listing of treatment exposure to nab-paclitaxel, a listing of treatment exposure to paclitaxel, a listing of treatment exposure to carboplatin, a listing of treatment exposure to cisplatin, a listing of treatment exposure to gemcitabine, a listing of treatment exposure to pemetrexed and a listing of treatment exposure to docetaxel will be provided. They will include cohort, participant identifier, age, sex, race, cumulative dose, dose intensity, relative dose intensity, visit, infusion start date and time, infusion end date and time, change in dose and reason for change, infusion rate (mL/hr), planned dose (mg), actual dose (mg), route, administration modification and reason for modification, change in administration detail, treatment delay (days). Infusions during the reinitiation phase will be flagged in these listings. These listings will be sorted by cohort, participant identifier, infusion start date and infusion end date.

Chemotherapy Switch

A listing of chemotherapy switch will also be provided based on "Chemotherapy Switch" eCRF page. Switches within cohorts (from one chemotherapy to another) and between cohorts will be considered. These listing will include cohort, participant identifier, age, sex, race, new chemotherapy regimen, reason for switch.

14 Efficacy Analyses

If not stated otherwise, efficacy analyses will be presented for the FAS by cohort and combined 1L Cohort A, B, C

14.1 Primary Endpoint Analysis

The occurrence of treatment-emergent AEs and treatment-related AEs including AESIs as primary endpoint of this study will be described in Section 15.

14.2 Secondary Endpoint Analysis

14.2.1 Confirmed Objective Response According to RECIST 1.1 as Assessed by Investigator

A secondary endpoint of this study is the confirmed objective response.

Best overall response (BOR) will be assessed based on reported overall responses at different evaluation time points from the date of first study intervention until documented disease progression in accordance to RECIST v1.1, taking requirements for confirmation into account as detailed below. Only tumor assessments performed before the start of any subsequent anti-cancer therapies will be considered in the assessment of BOR. If a tumor assessment was performed on the same day as start of new anti-cancer therapy, it will be assumed that the tumor assessment was performed prior to the start of the new anti-cancer therapy, therefore the tumor assessment will be included in the assessment of BOR.

BOR based on confirmed responses:

- 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 the first study intervention (and not qualifying for CR or PR)
- PD = PD $\leq$ 12 weeks after the first study intervention (and not qualifying for CR, PR or SD)
- NE = all other cases

SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the minimum duration for SD definition has been met.

Objective response (OR) is defined as a confirmed BOR of CR or PR according to RECIST v1.1.

Participants who do not have an on-treatment radiographic tumor assessment due to early progression, who receive anti-tumor treatments other than the study treatments prior to reaching confirmed CR or PR, or who die, progress, or drop out for any reason prior to reaching confirmed CR or PR will be counted as non-responders in the assessment of OR. Each participant will have an objective response status (0: 'no OR'; 1: 'OR'). OR rate (ORR) is the proportion of participants with OR in the analysis set.

The **disease control rate (DCR)** is defined as the proportion of participants with a confirmed best overall response of CR or PR, or SD out of the total number of participants belonging to the analysis set of interest.

The number and percentage of participants with confirmed objective response of CR, PR, SD, PD, and NE will be tabulated.

Two separate listings of tumor assessment data will be provided.

One will include cohort, participant identifier, age, sex, race, dates of first/last administration of each study intervention, date of first subsequent anticancer therapy as applicable, date of death as applicable, visit, date(s) of imaging, description of target lesions (description, site, type of lesion, assessment method, longest diameter or short axis, split/merged), non-target lesions (description, site, type of lesion, assessment method, lesion status), and new lesions (description, site, type of lesion, assessment method). This will be sorted by cohort, participant identifier, date of imaging, lesion type (target, non-target, new lesions) and lesion identifier.

The second listing will include cohort, participant identifier, age, sex, race, dates of first/last administration of each study intervention, date of first subsequent anticancer therapy as applicable, date of death as applicable, visit, date(s) of imaging, response for target lesions, response for non-target lesions, occurrence of new lesions, sum of lesion diameters, percent change in target lesions from baseline and overall response. Note that response for target and non-target lesions is not applicable at Baseline. This will be sorted by cohort, participant identifier and date of imaging.

The confirmed ORR and two-sided 95% Confidence Intervals (CIs) using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option) will be provided.

Additionally, the number and percentage of participants with DCR with a two-sided 95% CI using the Clopper-Pearson method will be displayed.

This analysis will also be conducted on the subset of participants in the FAS who have been followed for at least 6 months, i.e., data cut-off date – date of first administration + 1 ≥ 182 days.

In addition, a summary table of the reasons for non-evaluable confirmed best overall response will be provided, the following reasons will be detailed:

- No baseline assessment
- No post-baseline assessments due to death within 6 weeks after the start of study intervention
- No post-baseline assessments due to other reasons
- All post-baseline assessments have overall response 'Non-evaluable'
- New anticancer therapy started before first evaluable post-baseline assessment
- SD of insufficient duration (<6 weeks after the start of study intervention)

Note: special cases where objective 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 >12 weeks after start of study intervention and there was no evaluable tumor assessment in between)

A listing of reasons for non-evaluable confirmed best overall response will also be created including: participant identifier, age, sex, race, cohort, date of first and last study intervention, date(s) of imaging, date of first subsequent anti-cancer therapy, date of death, overall response and the reason for non-evaluable confirmed best overall response.

14.2.2 Subgroup Analysis for Confirmed Objective Response

The ORR analysis as described in 14.2.1 will be conducted in the subgroups of participants defined in Section 8.2 considering Cohort A and combined 1L Cohort A, B, C only. Those subgroups analyses will be supported by forest plots.

14.2.3 Progression-Free Survival According to RECIST 1.1 as Assessed by Investigator

A secondary endpoint of this study is progression-free survival (PFS) according to RECIST 1.1 assessed by the Investigator. The disease progression will be documented by the Investigator in the eCRF according to RECIST version 1.1.

PFS time is defined as the time from first study intervention until date of the first documentation of objective PD or death due to any cause, whichever occurs first:

PFS = (date of PD or death/censoring – date of first study intervention + 1)/ 30.4375 (months).

The following censoring rules will be applied for the PFS computation:

- Any participant with neither assessment of tumor progression, nor death date within 12 weeks, i.e., 84 days after last tumor assessment (or 24 weeks, i.e., 168 days after 12 months of follow-up) or date of first study intervention will be censored on the date of last tumor assessment or first study intervention whatever is later
- If death without previously documented PD is observed after more than 12 weeks after last tumor assessment (or 24 weeks after 12 months of follow-up), the participant will be censored at the date of the last evaluable tumor assessment
- Participants who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored at the date of first study intervention unless death occurred on or before the time of the second planned tumor assessment (i.e., 12 weeks or 24 weeks after 12 months of follow-up) in which case the death will be considered an event
- Participants who start new anticancer treatment prior to an event will be censored on the date of the last evaluable tumor assessment before anticancer therapy is given

- Participants with an event after two or more subsequent missing response assessments (i.e., no assessments in 12 weeks or 24 weeks after 12 months of follow-up) will be censored on the date of the last evaluable tumor assessment.

Censoring rules are also summarized in Table 4.

Table 4 Censoring Rules

PFS Event Status		Censoring	Date of event / censoring
Progressed or died	Within two subsequent scheduled tumor assessments after last response assessment of CR, PR or SD	Event	Minimum (Date of PD, Date of death)
	Otherwise	Censored	Date of last tumor assessment with outcome CR, PR or SD or date of first study intervention, whatever is later
Neither progressed nor died		Censored	Date of last tumor assessment with outcome CR, PR or SD or date of first study intervention, whatever is later

The last tumor assessment date is defined as the last available and evaluable tumor assessment performed prior to the cutoff date (or prior to end of study, i.e., participants lost to follow-up or who withdraw consent) or prior to subsequent anticancer therapy. If no evaluable tumor assessment is available, this date will be the date of first study intervention.

Kaplan-Meier Analysis

Kaplan-Meier estimates (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 3, 6, 9, 12 and 24 months (if applicable, further subsequent time points will be considered) 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 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. Censoring reasons are as follows:

- Ongoing in the study without an event
- No baseline assessment
- No evaluable post-baseline assessment
- Start of new anticancer therapy
- Event after 2 or more missing or non-evaluable post-baseline assessments

- Withdrawal of consent
- Lost to follow-up

  Lost to follow-up will include the following participants:

  - Participants declared as lost to follow-up on the "M7824 Termination" or "Chemotherapy Termination" or "Study Termination" eCRF pages prior to the analysis cutoff;
  - Participants with the last alive date > 14 weeks prior to the analysis cutoff date (duration of 14 weeks is based on the assessment schedule of every 12 weeks for survival follow-up interval + 2 weeks window).
- Two missed/inadequate tumor assessments prior to data cut-off date

This analysis will also be conducted on the subset of participants in the FAS who have been followed for at least 6 months, i.e., data cut-off date – date of first administration + 1 ≥ 182 days.

A listing of PFS according to RECIST 1.1 assessed by Investigator will be provided with the following information: cohort, participant identifier, age, sex, race, date of first study intervention, date of last tumor assessment, censored (yes/no), date of event/censoring, event/censoring reason, time to event.

14.2.4 Overall Survival

A secondary endpoint of this study is overall survival (OS).

OS time is defined as the date from the first study intervention to 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 data cutoff date, who withdrew consent or who are lost to follow up, OS will be censored at the last date known to be alive (see Section 9.6).

The date of event / censoring is defined in Table 5.

Table 5 Survival Event / Censoring

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

The analysis of OS time will be performed following the same approach described for PFS in Section 14.2.3. 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, 30, 36, 42, and 48 months (if applicable, further subsequent time points will be considered).

Frequency (number and percentage) of participants with an event (death) and censoring reasons will be presented. Censoring reasons are as follows:

- Administrative censoring (alive at the date of data cut-off)
- Non-administrative censoring

  Non-administrative censoring includes:

  - Participants who withdrew consent
  - Participants declared as lost to follow-up on the "M7824 termination" or "Chemotherapy termination" or "Study termination" eCRF pages prior to the analysis cutoff.
  - Participants with the last alive date > 14 weeks prior to the analysis cutoff date (duration of 14 weeks is based on the assessment schedule of every 12 weeks for survival follow-up interval + 2 weeks window). A Kaplan-Meier plot will also be displayed.

This analysis will also be conducted on the subset of participants in the FAS who were followed for at least 6 months, i.e., data cut-off date – date of first administration + 1 ≥ 182 days.

A listing will provide the following information: cohort, participant identifier, age, sex, race, date of first study intervention, censored (yes/no), date of event/censoring, event/censoring reason, and time to event.

14.2.5 Subgroup Analysis for PFS and OS

The PFS analysis as described in 14.2.4 will be conducted in the subgroups of participants defined in Section 8.2 considering Cohort A and combined 1L Cohort A, B, C.

The OS analysis as described in 14.2.5 will be conducted in the subgroups of participants defined in Section 8.2 considering Cohort A and combined 1L Cohort A, B, C.

Those subgroups analyses will be supported by forest plots (based on PFS and OS rates at 6-month and 12-month).

14.2.6 Sensitivity Analysis for PFS

PFS counting all events (PD and death) regardless of the start of a new anticancer therapy and ignoring the number of missing evaluable tumor assessments before progression or death will be considered and Kaplan-Meier estimates and a plot as described in Section 14.2.3 will be provided.

14.2.7 Duration of Response

A secondary endpoint of this study is duration of response (DoR).

DoR is defined as the time from first documentation of objective response (CR or PR) to the date of first documentation of objective progression of disease (PD) or death due to any cause whichever occurs first. The analysis of DoR will be performed on confirmed objective response of CR or PR according to RECIST 1.1 as assessed by Investigator. The censoring rules for DoR are as described above for PFS.

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

The analysis of DoR will be performed using the 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 Month 3, 6, 9, 12 and 24 (if applicable, further subsequent time points will be considered) 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 Kaplan-Meier plot will also be displayed.

The time and duration of response per participant will also be displayed in a swimmer graph in all participants included in the FAS. The length of the bar will display the time to progression of disease/death/last tumor assessment. The arrow at the end of the bar will indicate an ongoing response (i.e., duration of response censored and participant still at risk). The first CR, PR and PD will be displayed on the graph, as well as the first subsequent anticancer therapy and the end of study intervention. Participants with delayed response will also be shown on the figure.

A listing will provide the following information: cohort, participant identifier, age, sex, race, date of first study intervention, date of first confirmed response, time to confirmed response, date of last tumor assessment, censored (yes/no), date of event/censoring, event/censoring reason, DoR.

14.3 Further Endpoint Analyses

14.3.1 Follow-up Time for PFS

A Kaplan-Meier analysis will be performed to estimate the median time of PFS follow-up duration. Therefore, the PFS censoring indicator as described in Table 4 will be reversed.

Kaplan-Meier estimates will be presented with the median time of follow-up for PFS. In particular, the follow-up rate at 3, 6, 9, 12 and 24 months (if applicable, further subsequent time points will be considered) will be estimated with corresponding two-sided 95% CIs.

A Kaplan-Meier plot will also be displayed.

14.3.2 Follow-up Time for OS

A Kaplan-Meier analysis will be performed to estimate the median time of OS follow-up duration. Therefore, the OS censoring indicator as described in Table 5 will be reversed.

Kaplan-Meier estimates will be presented with the median time of follow-up for OS. In particular, the follow-up rate at 12, 18, 24, 30, 36, 42, and 48 months will be estimated with corresponding two-sided 95% CIs.

A Kaplan-Meier plot will also be displayed.

14.3.3 Progression-Free Survival 2

An exploratory endpoint of this study is PFS2 (disease progression classified according to RECIST 1.1) assessed by Investigator.

PFS2 time is defined as the time from first study intervention to one of the following two events, whichever occurs first:

- Assessment of PD by Investigator (radiographic and/or symptomatic) after the start of first subsequent anticancer therapy, using either the date of tumor assessment from "Progression Status on First Subsequent Anti-Cancer Treatment" eCRF form, or the date of assessment from "Assessment of Disease based on Imaging (according to RECIST 1.1) - Subsequent Anti-Cancer Treatment" eCRF form whatever comes first

or

- Death due to any cause (note that death will be considered as event also if participant did not receive subsequent anticancer therapy, or if the death occurs outside the first subsequent anticancer therapy period).

PFS2 will be defined as follows and reported in months:

PFS2 = (date of the documentation of PD after the start of first subsequent anticancer therapy or death /censoring – date of first study intervention + 1)/ 30.4375 (months).

The following censoring rules will be applied for the PFS2 computation:

- Participants alive and who did not receive a first subsequent anticancer therapy will be censored at the last evaluable PFS assessment date
- Participants who received a first subsequent anticancer therapy and who did not experience an event (PD or death) will be right-censored on the date of last evaluable tumor assessment.

The analysis of PFS2 will be performed using the same approach as described for PFS in Section 14.2.3. 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 3, 6, 9, 12, and 24 months (if applicable, further subsequent time points will be considered).

A Kaplan-Meier plot of PFS2 will also be displayed.

A listing will provide the following information: cohort, participant identifier, age, sex, race, date of first study intervention, date of first subsequent anticancer therapy administration, date of last

tumor assessment, censored (yes/no), date of event/censoring, event/censoring reason, and time to event.

14.3.4 Time to Response

The time to response (TtR) will be calculated for each participant with a confirmed response according to RECIST 1.1 as the time from first study intervention until first observation of response as determined by the investigator.

TtR = (date of CR or PR– date of first study intervention + 1)/ 30.4375 (months).

Descriptive statistics of TtR and a swimmer plot (described under section 14.2.7) showing TtR, DoR and whether the response was complete or partial will be provided.

A participant listing will provide the following information: cohort, participant identifier, age, sex, race, date of first study intervention, date of response, and time to response.

14.3.5 Tumor Shrinkage in Target Lesions

Tumor shrinkage in target lesions will be measured as the percent change in sum of diameters of target lesions according to RECIST 1.1 criteria as assessed by Investigator. The sum of diameters will include all target lesions (longest diameter for non-nodal lesions and short axis for nodal target lesions).

The shrinkage in the sum of diameters from baseline will be displayed for valid timepoint assessments, only. For the purpose of this analysis, a valid timepoint assessment is defined as a complete assessment of all target lesions reported at Baseline and at least a post-baseline assessment.

For the tumor shrinkage in target lesions evaluation, all tumor assessments performed up to start of subsequent anticancer therapy, or cutoff date (whichever comes first) will be considered.

Following plots will be provided:

- Waterfall plot with stacked bars showing the shrinkage percentage at first scan and the maximum shrinkage since baseline, i.e., the percent change in the sum of diameters between baseline and the best post-baseline assessment in the timeframe described above
- Spider plot presenting the percent change from baseline for each assessment and participant

14.3.6 Brain Lesions

A brain Computed Tomography/Magnetic Resonance Imaging (CT/MRI) scan should be performed at Baseline, and subsequently if clinically indicated by development of new specific symptoms.

Based on the "Brain Imaging" eCRF page, a listing will provide the following information: cohort, participant identifier, age, sex, race, date of first study intervention, assessment visit, date of CT/MRI scan performed, tumor lesions found (Y/N) and assessment method, sorted by cohort, participant identifier, assessment visit.

14.3.7 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.

Participants having a delayed response will be flagged in the listing of tumor assessment and overall response per RECIST assessed by investigator described under section 14.2.1.

A listing of duration of response for participants having a delayed response will be provided including: cohort, 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 cutoff date (Y/N), 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.

14.3.8 Tumor Response as Adjudicated by IRC

If deemed appropriate by the study team, the tumor response of bintrafusp alfa in combination with chemotherapy will be evaluated by IRC (Independent Review Committee). The analysis of confirmed objective response and PFS according to RECIST 1.1 assessed by IRC will be performed as described in Section 14.2.1 and 14.2.3. The immune-related confirmed objective response and irPFS according to irRECIST 1.1 assessed by IRC will also be evaluated.

15 Safety Analyses

If not stated otherwise, summaries will be presented for the SAF Analysis Set by cohort and combined 1L Cohort A, B, C.

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 on-treatment period if not otherwise specified and will be described by cohort. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings. AEs occurring during the reinitiation phase will be considered in the summary tables and will be flagged in the listings.

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

Dose Limiting Toxicities Adverse Events are those events reported on the "Adverse Event Details" eCRF page with the "Is this adverse event a dose limiting toxicity" field ticked "Yes".

Bintrafusp alfa Related Adverse Events are those AEs with relationship to bintrafusp alfa reported by the Investigator as related (i.e., answer to the question "Relationship with M7824" = "Related" on "Adverse Event Details" eCRF page) and those of unknown relationship (i.e., no answer to the question "Relationship with M7824").

Chemotherapy Related Adverse Events are those AEs with relationship to cisplatin or carboplatin or pemetrexed or paclitaxel or nab-paclitaxel or gemcitabine or docetaxel defined as follows:

- For cisplatin reported by the Investigator as related (i.e., answer to the question "Relationship with Cisplatin" = "Related" on "Adverse Event Details" eCRF page) and those of unknown relationship (i.e., no answer to the question "Relationship with Cisplatin").
- For carboplatin reported by the Investigator as related (i.e., answer to the question "Relationship with Carboplatin" = "Related" on "Adverse Event Details" eCRF page) and those of unknown relationship (i.e., no answer to the question "Relationship with Carboplatin").
- For pemetrexed reported by the Investigator as related (i.e., answer to the question "Relationship with Pemetrexed" = "Related" on "Adverse Event Details" eCRF page) and those of unknown relationship (i.e., no answer to the question "Relationship with Pemetrexed").
- For paclitaxel reported by the Investigator as related (i.e., answer to the question "Relationship with Paclitaxel" = "Related" on "Adverse Event Details" eCRF page) and those of unknown relationship (i.e., no answer to the question "Relationship with Paclitaxel").
- For nab-paclitaxel reported by the Investigator as related (i.e., answer to the question "Relationship with Nab-paclitaxel" = "Related" on "Adverse Event Details" eCRF page)

and those of unknown relationship (i.e., no answer to the question "Relationship with Nab-paclitaxel").

- For gemcitabine reported by the Investigator as related (i.e., answer to the question "Relationship with Gemcitabine" = "Related" on "Adverse Event Details" eCRF page) and those of unknown relationship (i.e., no answer to the question "Relationship with Gemcitabine").
- For docetaxel reported by the Investigator as related (i.e., answer to the question "Relationship with Docetaxel" = "Related" on "Adverse Event Details" eCRF page) and those of unknown relationship (i.e., no answer to the question "Relationship with Docetaxel").

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

Adverse Events Leading to Dose Reduction of Chemotherapy Agent(s): AEs leading to dose reduction of cisplatin or carboplatin or pemetrexed or paclitaxel or nab-paclitaxel or gemcitabine or docetaxel are defined as follows:

- For cisplatin consider answer to the question "Action(s) taken with Cisplatin" = "Dose reduced" on "Adverse Event Details" eCRF page).
- For carboplatin consider answer to the question "Action(s) taken with Carboplatin" = "Dose reduced" on "Adverse Event Details" eCRF page).
- For pemetrexed consider answer to the question "Action(s) taken with Pemetrexed" = "Dose reduced" on "Adverse Event Details" eCRF page).
- For paclitaxel consider answer to the question "Action(s) taken with Paclitaxel" = "Dose reduced" on "Adverse Event Details" eCRF page).
- For nab-paclitaxel consider answer to the question "Action(s) taken with Nab-paclitaxel" = "Dose reduced" on "Adverse Event Details" eCRF page).
- For gemcitabine consider answer to the question "Action(s) taken with Gemcitabine" = "Dose reduced" on "Adverse Event Details" eCRF page).
- For docetaxel consider answer to the question "Action(s) taken with Docetaxel" = "Dose reduced" on "Adverse Event Details" eCRF page).

Note that according to the protocol, there will not be dose reduction of bintrafusp alfa.

Adverse Events Leading to Temporary Discontinuation of Bintrafusp alfa: answer to the question "Action(s) taken with M7824" = "Drug interrupted" on "Adverse Event Details" eCRF page.

Adverse Events Leading to Temporary Discontinuation of Chemotherapy: AEs leading to temporary discontinuation of cisplatin or carboplatin or pemetrexed or paclitaxel or nab-paclitaxel or gemcitabine or docetaxel are defined as follows:

- For cisplatin consider answer to the question "Action(s) taken with Cisplatin" = "Drug interrupted" on "Adverse Event Details" eCRF page.
- For carboplatin consider answer to the question "Action(s) taken with Carboplatin" = "Drug interrupted" on "Adverse Event Details" eCRF page.

- For pemetrexed consider answer to the question "Action(s) taken with Pemetrexed" = "Drug interrupted" on "Adverse Event Details" eCRF page.
- For paclitaxel consider answer to the question "Action(s) taken with Paclitaxel" = "Drug interrupted" on "Adverse Event Details" eCRF page.
- For nab-paclitaxel consider answer to the question "Action(s) taken with Nab-paclitaxel" = "Drug interrupted" on "Adverse Event Details" eCRF page.
- For gemcitabine consider answer to the question "Action(s) taken with Gemcitabine" = "Drug interrupted" on "Adverse Event Details" eCRF page.
- For docetaxel consider answer to the question "Action(s) taken with Docetaxel" = "Drug interrupted" on "Adverse Event Details" eCRF page.

Adverse Events Leading to Temporary Discontinuation of at least one Chemotherapy: AEs leading to temporary discontinuation of cisplatin or carboplatin or pemetrexed or paclitaxel or nab-paclitaxel or gemcitabine or docetaxel (definition above).

Adverse Events Leading to Temporary Treatment Discontinuation: AEs leading to temporary discontinuation of bintrafusp alfa (definition above) or AEs leading to temporary discontinuation of at least one chemotherapy (definition above).

Adverse Events Leading to Permanent Discontinuation of Bintrafusp alfa: AEs leading to permanent discontinuation of study intervention (i.e., answer to the question "Action(s) taken with M7824" = "Drug withdrawn" on "Adverse Event Details" eCRF page).

Adverse Events Leading to Permanent Discontinuation of Chemotherapy: AEs leading to permanent discontinuation of study intervention for cisplatin or carboplatin or pemetrexed or paclitaxel or nab-paclitaxel or gemcitabine or docetaxel defined as follows:

- For cisplatin consider answer to the question "Action(s) taken with Cisplatin" = "Drug withdrawn" on "Adverse Event Details" eCRF page.
- For carboplatin consider answer to the question "Action(s) taken with Carboplatin" = "Drug withdrawn" on "Adverse Event Details" eCRF page.
- For pemetrexed consider answer to the question "Action(s) taken with Pemetrexed" = "Drug withdrawn" on "Adverse Event Details" eCRF page.
- For paclitaxel consider answer to the question "Action(s) taken with Paclitaxel" = "Drug withdrawn" on "Adverse Event Details" eCRF page.
- For nab-paclitaxel consider answer to the question "Action(s) taken with Nab-paclitaxel" = "Drug withdrawn" on "Adverse Event Details" eCRF page.
- For gemcitabine consider answer to the question "Action(s) taken with Gemcitabine" = "Drug withdrawn" on "Adverse Event Details" eCRF page.
- For docetaxel consider answer to the question "Action(s) taken with Docetaxel" = "Drug withdrawn" on "Adverse Event Details" eCRF page.

Adverse Events Leading to Permanent Discontinuation of at least one Chemotherapy: AEs leading to permanent discontinuation of cisplatin or carboplatin or pemetrexed or paclitaxel or nab-paclitaxel or gemcitabine or docetaxel (definition above).

Adverse Events Leading to Permanent Treatment Discontinuation: AEs leading to permanent discontinuation of bintrafusp alfa (definition above) or AEs leading to permanent discontinuation of at least one chemotherapy (definition above).

Adverse Events Leading to Discontinuation / Dose Reduction of Treatment: AEs leading to Temporary Treatment Discontinuation (definition above) or AEs leading to Permanent Treatment Discontinuation (definition above) or AEs leading to Dose Reduction of Treatment (definition above).

Adverse Event Leading to Death: AEs leading to death (as recorded on the "Adverse Event 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): AESI will be identified according to a pre-specified search list of MedDRA Preferred Terms.

Categories of AESIs considered include:

- Infusion-related reaction (IRR)
- Immune-related adverse events (irAE)
- TGF-β inhibition mediated skin AE
- Anemia

15.1.1 All Adverse Events

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

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

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

Information of switchers (switches within cohorts [from one chemotherapy to another] and between cohorts) will be included in the AE tables.

An overall summary table of TEAEs will be presented with the following information:

- TEAEs
- Bintrafusp alfa related TEAEs

- Chemotherapy related TEAEs
- Cisplatin, or carboplatin or pemetrexed related TEAEs for cisplatin or carboplatin/pemetrexed combination (Cohort A)
- Cisplatin or pemetrexed related TEAEs for cisplatin/pemetrexed combination (Cohort A)
- Carboplatin or pemetrexed related TEAEs for carboplatin/pemetrexed combination (Cohort A)
- Carboplatin or paclitaxel or nab-paclitaxel related TEAEs for carboplatin/paclitaxel or nab-paclitaxel combination (Cohort B)
- Carboplatin or paclitaxel related TEAEs for carboplatin/paclitaxel combination (Cohort B)
- Carboplatin or nab-paclitaxel related TEAEs for carboplatin/nab-paclitaxel combination (Cohort B)
- Cisplatin, or carboplatin or gemcitabine related TEAEs for cisplatin or carboplatin/gemcitabine combination (Cohort C)
- Cisplatin or gemcitabine related TEAEs for cisplatin/gemcitabine combination (Cohort C)
- Carboplatin or gemcitabine related TEAEs for carboplatin/gemcitabine combination (Cohort C)
- Docetaxel related TEAEs (Cohort D)
- Serious TEAEs
- Bintrafusp alfa related serious TEAEs
- Chemotherapy related serious TEAEs
- Cisplatin, or carboplatin or pemetrexed related serious TEAEs for cisplatin or carboplatin/pemetrexed combination (Cohort A)
- Cisplatin or pemetrexed related serious TEAEs for cisplatin/pemetrexed combination (Cohort A)
- Carboplatin or pemetrexed related serious TEAEs for carboplatin/pemetrexed combination (Cohort A)
- Carboplatin or paclitaxel or nab-paclitaxel related serious TEAEs for carboplatin/paclitaxel or nab-paclitaxel combination (Cohort B)
- Carboplatin or paclitaxel related serious TEAEs for carboplatin/paclitaxel combination (Cohort B)
- Carboplatin or nab-paclitaxel related serious TEAEs for carboplatin/nab-paclitaxel combination (Cohort B)
- Cisplatin, or carboplatin or gemcitabine related serious TEAEs for cisplatin or carboplatin/gemcitabine combination (Cohort C)

- Cisplatin or gemcitabine related serious TEAEs for cisplatin/gemcitabine combination (Cohort C)
- Carboplatin or gemcitabine related serious TEAEs for carboplatin/gemcitabine combination (Cohort C)
- Docetaxel related serious TEAEs (Cohort D)
- TEAEs NCI-CTCAE severity grade (≥3, ≥4)
- Bintrafusp alfa related TEAEs NCI-CTCAE severity grade (≥3, ≥4)
- Chemotherapy related TEAEs NCI-CTCAE severity grade (≥3, ≥4)
- Cisplatin, or carboplatin or pemetrexed related TEAEs NCI-CTCAE severity grade (≥3, ≥4) for cisplatin or carboplatin/pemetrexed combination (Cohort A)
- Cisplatin or pemetrexed related TEAEs NCI-CTCAE severity grade (≥3, ≥4) for cisplatin/pemetrexed combination (Cohort A)
- Carboplatin or pemetrexed related TEAEs NCI-CTCAE severity grade (≥3, ≥4) for carboplatin/pemetrexed combination (Cohort A)
- Carboplatin or paclitaxel or nab-paclitaxel related TEAEs NCI-CTCAE severity grade (≥3, ≥4) for carboplatin/paclitaxel or nab-paclitaxel combination (Cohort B)
- Carboplatin or paclitaxel related TEAEs NCI-CTCAE severity grade (≥3, ≥4) for carboplatin/paclitaxel combination (Cohort B)
- Carboplatin or nab-paclitaxel related TEAEs NCI-CTCAE severity grade (≥3, ≥4) for carboplatin/nab-paclitaxel combination (Cohort B)
- Cisplatin, or carboplatin or gemcitabine related TEAEs NCI-CTCAE severity grade (≥3, ≥4) for cisplatin or carboplatin/gemcitabine combination (Cohort C)
- Cisplatin or gemcitabine related TEAEs NCI-CTCAE severity grade (≥3, ≥4) for cisplatin/gemcitabine combination (Cohort C)
- Carboplatin or gemcitabine related TEAEs NCI-CTCAE severity grade (≥3, ≥4) for carboplatin/gemcitabine combination (Cohort C)
- Docetaxel related TEAEs NCI-CTCAE severity grade (≥3, ≥4) (Cohort D)
- TEAEs leading to death
- Bintrafusp alfa related TEAEs leading to death
- Chemotherapy related TEAEs leading to death
- Cisplatin, or carboplatin or pemetrexed related TEAEs leading to death for cisplatin or carboplatin/pemetrexed combination (Cohort A)
- Cisplatin or pemetrexed related TEAEs leading to death for cisplatin/pemetrexed combination (Cohort A)

- Carboplatin or pemetrexed related TEAEs leading to death for carboplatin/pemetrexed combination (Cohort A)
- Carboplatin or paclitaxel or nab-paclitaxel related TEAEs leading to death for carboplatin/paclitaxel or nab-paclitaxel combination (Cohort B)
- Carboplatin or paclitaxel related TEAEs leading to death for carboplatin/paclitaxel combination (Cohort B)
- Carboplatin or nab-paclitaxel related TEAEs leading to death for carboplatin/nab-paclitaxel combination (Cohort B)
- Cisplatin, or carboplatin or gemcitabine related TEAEs leading to death for cisplatin or carboplatin/gemcitabine combination (Cohort C)
- Cisplatin or gemcitabine related TEAEs leading to death for cisplatin/gemcitabine combination (Cohort C)
- Carboplatin or gemcitabine related TEAEs leading to death for carboplatin/gemcitabine combination (Cohort C)
- Docetaxel related TEAEs leading to death (Cohort D)
- Adverse events of special interest (related and not related as assessed by investigator):
    - Infusion-related reaction (IRR)
    - Immune related AEs (irAEs)
    - TGF-β inhibitionmediated skin TEAEs
    - Anemia TEAEs
- Bintrafusp alfa related adverse events of special interest (relationship with bintrafusp alfa as assessed by investigator):
    - Infusion-related reaction (IRR)
    - Immune related AEs (irAEs)
    - TGF-β inhibitionmediated skin TEAEs
    - Anemia TEAEs
- Treatment-emergent bleeding events
- Treatment-emergent bintrafusp alfa-related bleeding events.

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

- TEAEs
- Bintrafusp alfa related TEAEs

- Chemotherapy related TEAEs (for each chemotherapy to which the AE is related)
- TEAEs leading to death (table repeated on cisplatin versus carboplatin (Cohorts A and C))
- Bintrafusp alfa related TEAEs leading to death
- Chemotherapy related TEAEs leading to death (for each chemotherapy to which the AE is related).

The following frequency tables will be provided by worst grade (>=3, >=4, 5), SOC, and PT:

- TEAEs by worst grade, SOC, and PT
- Bintrafusp alfa related TEAEs by worst grade, SOC, and PT
- Chemotherapy related TEAEs by worst grade, SOC, and PT (for each chemotherapy to which the AE is related).

Clinicaltrials.gov and EudraCT -Requirements

Summary tables for non-serious TEAEs excluding SAEs will be provided.

A listing of AEs will contain the following information: cohort, participant identifier, age, sex, race, first and last date of study intervention, preferred term, reported term for the AE, start or change date, end date, duration of AE (in days), day relative to the first study intervention, day relative to the most recent study intervention prior to AE onset/change, relationship with bintrafusp alfa, relationship with cisplatin, relationship with carboplatin, relationship with pemetrexed, relationship with paclitaxel, relationship with nab-paclitaxel, relationship with gemcitabine, relationship with docetaxel, toxicity grade, causality factor, action(s) taken with bintrafusp alfa, action(s) taken with cisplatin, action(s) taken with carboplatin, action(s) taken with pemetrexed, action(s) taken with paclitaxel, action(s) taken with nab-paclitaxel, action(s) taken with gemcitabine, action(s) taken with docetaxel, other action(s) taken, change in grade and outcome, seriousness (Y/N), AESI infusion-related (Y/N), AESI immune-related (Y/N), TGF-β inhibition mediated skin AESI (Y/N), anemia (Y/N), dose-limiting toxicity AESI (Y/N). Participants who switched chemotherapy will be flagged. The listing will be sorted by cohort, participant identifier, start date, end date and preferred term.

Following listings will be provided with the relevant information:

- Listing of all AE (whether treatment-emergent or not): TEAEs and AE occurring during reinitiation phase will be flagged
- Listing of TEAEs
- Listing of non-TEAE for AEs occurring after enrollment (date of first signature of informed consent/date of first signature of first informed consent) but prior to the first dose of study intervention.
- Listing of AE with onset or worsening after the on-treatment period: AE occurring during reinitiation phase will be flagged

- Listing of AEs for participants who reinitiated the treatment

Evaluation of Potential Effect of ADA on Bintrafusp alfa Safety

The overall summary table of AEs as described above will also be provided by ADA status (ever positive versus never positive, and treatment emergent ALL versus non treatment emergent ALL). Only cohorts with at least 3 participants in each subgroup will be displayed.

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.

Evaluation of COVID-19 effect on AEs

The direct effect of COVID-19 for AEs will be assessed via listings of COVID-19 related AEs. COVID-19 related AEs are all AEs for which the PT contains COVID-19 or SARS-COV-2. The following information will be provided:

- Participant ID, country, age, sex, race
- Dates of first and last administration of each study intervention
- COVID-19-associated AE start date (day), COVID-19 associated AE stop date (day)
- AE PT, verbatim
- Toxicity grade
- Seriousness
- Relationship to each study intervention
- Action taken with each study intervention
- Outcome

15.1.2 Adverse Events Leading to Study Intervention Discontinuation

A table presenting the overall summary of TEAEs leading to discontinuation (temporary or permanent) or dose reduction of treatment will be presented by cohort with the following information:

- TEAEs leading to temporary discontinuation of at least one study intervention
- TEAEs leading to temporary discontinuation of bintrafusp alfa
- TEAEs leading to temporary discontinuation of chemotherapy

- TEAEs leading to temporary discontinuation of at least one chemotherapy in cisplatin or carboplatin/pemetrexed combination (Cohort A)
- TEAEs leading to temporary discontinuation of at least one chemotherapy in cisplatin/pemetrexed combination (Cohort A)
- TEAEs leading to temporary discontinuation of at least one chemotherapy in carboplatin/pemetrexed combination (Cohort A)
- TEAEs leading to temporary discontinuation of at least one chemotherapy in carboplatin or paclitaxel/nab-paclitaxel combination (Cohort B)
- TEAEs leading to temporary discontinuation of at least one chemotherapy in carboplatin/paclitaxel combination (Cohort B)
- TEAEs leading to temporary discontinuation of at least one chemotherapy in carboplatin/nab-paclitaxel combination (Cohort B)
- TEAEs leading to temporary discontinuation of at least one chemotherapy in cisplatin or carboplatin/gemcitabine combination (Cohort C)
- TEAEs leading to temporary discontinuation of at least one chemotherapy in cisplatin/gemcitabine combination (Cohort C)
- TEAEs leading to temporary discontinuation of at least one chemotherapy in carboplatin/gemcitabine combination (Cohort C)
- TEAEs leading to temporary discontinuation of docetaxel (Cohort D)
- Bintrafusp alfa related TEAEs leading to temporary discontinuation of bintrafusp alfa
- Chemotherapy related TEAEs leading to temporary discontinuation of chemotherapy
- Cisplatin or carboplatin or pemetrexed related TEAEs leading to temporary discontinuation of at least one chemotherapy in cisplatin or carboplatin/pemetrexed combination (Cohort A)
- Cisplatin or pemetrexed related TEAEs leading to temporary discontinuation of at least one chemotherapy in cisplatin/pemetrexed combination (Cohort A)
- Carboplatin or pemetrexed related TEAEs leading to temporary discontinuation of at least one chemotherapy in carboplatin/pemetrexed combination (Cohort A)
- Carboplatin or paclitaxel or nab-paclitaxel related TEAEs leading to temporary discontinuation of at least one chemotherapy in carboplatin/paclitaxel combination (Cohort B)
- Carboplatin or paclitaxel related TEAEs leading to temporary discontinuation of at least one chemotherapy in carboplatin/paclitaxel combination (Cohort B)
- Carboplatin or nab-paclitaxel related TEAEs leading to temporary discontinuation of at least one chemotherapy in carboplatin/nab-paclitaxel combination (Cohort B)
- Cisplatin or carboplatin or gemcitabine related TEAEs leading to temporary discontinuation of at least one chemotherapy in cisplatin or carboplatin/gemcitabine combination (Cohort C)

- Cisplatin or gemcitabine related TEAEs leading to temporary discontinuation of at least one chemotherapy in cisplatin/gemcitabine combination (Cohort C)
- Carboplatin or gemcitabine related TEAEs leading to temporary discontinuation of at least one chemotherapy in carboplatin/gemcitabine combination (Cohort C)
- Docetaxel related TEAEs leading to temporary discontinuation of docetaxel (Cohort D)
- TEAEs leading to permanent discontinuation of at least one study intervention
- TEAEs leading to permanent discontinuation of bintrafusp alfa
- TEAEs leading to permanent discontinuation of chemotherapy
- TEAEs leading to permanent discontinuation of at least one chemotherapy in cisplatin or carboplatin/pemetrexed combination (Cohort A)
- TEAEs leading to permanent discontinuation of at least one chemotherapy in cisplatin/pemetrexed combination (Cohort A)
- TEAEs leading to permanent discontinuation of at least one chemotherapy in carboplatin/pemetrexed combination (Cohort A)
- TEAEs leading to permanent discontinuation of at least one chemotherapy in carboplatin/paclitaxel or nab-paclitaxel combination (Cohort B)
- TEAEs leading to permanent discontinuation of at least one chemotherapy in carboplatin/paclitaxel combination (Cohort B)
- TEAEs leading to permanent discontinuation of at least one chemotherapy in carboplatin/nab-paclitaxel combination (Cohort B)
- TEAEs leading to permanent discontinuation of at least one chemotherapy in cisplatin or carboplatin/gemcitabine combination (Cohort C)
- TEAEs leading to permanent discontinuation of at least one chemotherapy in cisplatin/gemcitabine combination (Cohort C)
- TEAEs leading to permanent discontinuation of at least one chemotherapy in carboplatin/gemcitabine combination (Cohort C)
- TEAEs leading to permanent discontinuation of docetaxel (Cohort D)
- Bintrafusp alfa related TEAEs leading to permanent discontinuation of bintrafusp alfa
- Chemotherapy related TEAEs leading to permanent discontinuation of chemotherapy
- Cisplatin or carboplatin or pemetrexed related TEAEs leading to permanent discontinuation of at least one chemotherapy in cisplatin or carboplatin/pemetrexed combination (Cohort A)
- Cisplatin or pemetrexed related TEAEs leading to permanent discontinuation of at least one chemotherapy in cisplatin/pemetrexed combination (Cohort A)
- Carboplatin or pemetrexed related TEAEs leading to permanent discontinuation of at least one chemotherapy in carboplatin/pemetrexed combination (Cohort A)

- Carboplatin or paclitaxel or nab-paclitaxel related TEAEs leading to permanent discontinuation of at least one chemotherapy in carboplatin/paclitaxel or nab-paclitaxel combination (Cohort B)
- Carboplatin or paclitaxel related TEAEs leading to permanent discontinuation of at least one chemotherapy in carboplatin/paclitaxel combination (Cohort B)
- Carboplatin or nab-paclitaxel related TEAEs leading to permanent discontinuation of at least one chemotherapy in carboplatin/nab-paclitaxel combination (Cohort B)
- Cisplatin or carboplatin or gemcitabine related TEAEs leading to permanent discontinuation of at least one chemotherapy in cisplatin or carboplatin/gemcitabine combination (Cohort C)
- Cisplatin or gemcitabine related TEAEs leading to permanent discontinuation of at least one chemotherapyin cisplatin/gemcitabine combination (Cohort C)
- Carboplatin or gemcitabine related TEAEs leading to permanent discontinuation of at least one chemotherapy in carboplatin/gemcitabine combination (Cohort C)
- Docetaxel related TEAEs leading to permanent discontinuation of docetaxel (Cohort D)
- TEAEs leading to dose reduction of at least one chemotherapy
- TEAEs leading to dose reduction of at least one chemotherapy in cisplatin or carboplatin/pemetrexed combination (Cohort A)
- TEAEs leading to dose reduction of at least one chemotherapy in cisplatin/pemetrexed combination (Cohort A)
- TEAEs leading to dose reduction of at least one chemotherapy in carboplatin/pemetrexed combination (Cohort A)
- TEAEs leading to dose reduction of at least one chemotherapy in carboplatin/paclitaxel or nab-paclitaxel combination (Cohort B)
- TEAEs leading to dose reduction of at least one chemotherapy in carboplatin/paclitaxel combination (Cohort B)
- TEAEs leading to dose reduction of at least one chemotherapy in carboplatin/nab-paclitaxel combination (Cohort B)
- TEAEs leading to dose reduction of at least one chemotherapy in cisplatin or carboplatin/gemcitabine combination (Cohort C)
- TEAEs leading to dose reduction of at least one chemotherapy in cisplatin/gemcitabine combination (Cohort C)
- TEAEs leading to dose reduction of at least one chemotherapy in carboplatin/gemcitabine combination (Cohort C)
- TEAEs leading to dose reduction of docetaxel (Cohort D).
- Chemotherapy related TEAEs leading to dose reduction of chemotherapy

- Cisplatin or carboplatin or pemetrexed related TEAEs leading to dose reduction of at least one chemotherapy in cisplatin or carboplatin/pemetrexed combination (Cohort A)
- Cisplatin or pemetrexed related TEAEs leading to dose reduction of at least one chemotherapy in cisplatin/pemetrexed combination (Cohort A)
- Carboplatin or pemetrexed related TEAEs leading to dose reduction of at least one chemotherapy in carboplatin/pemetrexed combination (Cohort A)
- Carboplatin or paclitaxel or nab-paclitaxel related TEAEs leading to dose reduction of at least one chemotherapy in carboplatin/paclitaxel or nab-paclitaxel combination (Cohort B)
- Carboplatin or paclitaxel related TEAEs leading to dose reduction of at least one chemotherapy in carboplatin/paclitaxel combination (Cohort B)
- Carboplatin or nab-paclitaxel related TEAEs leading to dose reduction of at least one chemotherapy in carboplatin/nab-paclitaxel combination (Cohort B)
- Cisplatin or carboplatin or gemcitabine related TEAEs leading to dose reduction of at least one chemotherapy in cisplatin or carboplatin/gemcitabine combination (Cohort C)
- Cisplatin or gemcitabine related TEAEs leading to dose reduction of at least one chemotherapy in cisplatin/gemcitabine combination (Cohort C)
- Carboplatin or gemcitabine related TEAEs leading to dose reduction of at least one chemotherapy in carboplatin/gemcitabine combination (Cohort C)
- Docetaxel related TEAEs leading to dose reduction of docetaxel (Cohort D).

Frequency tables summarizing the following actions taken in response to TEAEs will be prepared and presented by PT and primary SOC in alphabetical order:

- TEAEs leading to temporary discontinuation of bintrafusp alfa
- TEAEs leading to temporary discontinuation of chemotherapy (for each chemotherapy for which the AE led to temporary discontinuation)
- Bintrafusp alfa related TEAEs leading to temporary discontinuation of bintrafusp alfa
- Chemotherapy related TEAEs leading to temporary discontinuation of chemotherapy (for each chemotherapy to which the AE is related, and for which the AE led to temporary discontinuation)
- TEAEs leading to permanent discontinuation of bintrafusp alfa (table repeated on cisplatin versus carboplatin (Cohorts A and C))
- TEAEs leading to permanent discontinuation of chemotherapy (for each chemotherapy for which the AE led to permanent discontinuation)
- Bintrafusp alfa related TEAEs leading to permanent discontinuation of bintrafusp alfa

- Chemotherapy related TEAEs leading to permanent discontinuation of chemotherapy (for each chemotherapy to which the AE is related, and for which the AE led to permanent discontinuation).

A listing of AEs leading to permanent treatment discontinuation will also be provided with the relevant information (see description of listing in Section 15.1.1). A listing of chemotherapy switchers may also be provided.

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, deaths within 60 days after first dose as well as primary reason for death, will be tabulated based on information from the "Death" eCRF page.

The following summaries will be provided by cohort and by cisplatin versus carboplatin (Cohorts A and C):

- 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 of death
    - Progression of disease and/or disease related condition
    - Event unrelated to study treatment
    - Event related to study treatment
    - Unknown

In addition, date and cause of death will be provided in an individual participant data listing together with selected dosing information (date of first/last administration of bintrafusp alfa, number of infusions of bintrafusp alfa, day relative to first and last infusion of bintrafusp alfa, date of first/last administration of cisplatin, number of infusions of cisplatin, day relative to first and last infusion of cisplatin, date of first/last administration of carboplatin, number of infusions of carboplatin, day relative to first and last infusion of carboplatin, date of first/last administration of pemetrexed, number of infusions of pemetrexed, day relative to first and last infusion of pemetrexed, date of first/last administration of paclitaxel, number of infusions of paclitaxel, day relative to first and last infusion of paclitaxel, date of first/last administration of nab-paclitaxel, number of infusions of nab-paclitaxel, day relative to first and last infusion of nab-paclitaxel, date of first/last administration of gemcitabine, number of infusions of gemcitabine, day relative to first and last infusion of gemcitabine, date of first/last administration of docetaxel, number of infusions of docetaxel, day relative to first and last infusion of docetaxel) and will include:

- Participant identifier, analysis set, age, sex, race
- AEs with fatal outcome (list preferred terms of AEs with outcome=fatal, Grade 5 or Serious resulting in death)
- Autopsy performed (Yes/No/Unknown)
- Flag for death within 30 days after last study intervention
- Flag for death within 60 days after first study intervention.

15.2.2 Serious Adverse Events

The number of participants with serious AEs (SAEs) will be described by SOC and PT:

- Serious TEAEs (table repeated on cisplatin versus carboplatin (Cohorts A and C))
- Bintrafusp alfa related serious TEAEs
- Chemotherapy related serious TEAEs (for each chemotherapy to which the AE is related).

A listing of serious TEAEs will also be provided with the relevant information (see description of listing in Section 15.1.1).

15.2.3 Dose-Limiting Toxicity

The combination will be considered safe when DLTs (as specified in protocol section 6.9.1) are observed in ≤ 2 of the 8 evaluable participants. If DLTs are observed in ≥ 3 of the 8 participants, the SMC will give a recommendation regarding clearing the corresponding combination based on a review of all relevant parameters including AEs and SAEs and risk benefit assessment for that cohort.

A table of the occurrence of DLT adverse events (as defined in Section 15.1) will be provided including:

- Number and percentage of participants who experienced a DLT during the DLT period (3 weeks from the W1D1 visit)
- Number of DLTs per participant experienced during the DLT period (1 / 2 / $\geq$3)
- DLT experienced during the DLT period by System Organ Class and Preferred Term based on the latest available MedDRA version.

A listing of DLTs will also be provided with the relevant information (see description of listing in Section 15.1.1).

15.2.4 Bleeding Events

Bleeding events are defined as adverse events with Preferred Terms (PTs) according to the MedDRA SMQ Haemorrhage terms (excluding laboratory terms). Treatment-emergent bleeding events and treatment-emergent bintrafusp alfa related bleeding events will be summarized in a frequency table presenting SOC and PT sorted by alphabetical order, by cohort (Cohort A, B, C, and D) and combining Cohorts A, B, and C (1L Cohort A, B, C) and repeated by cisplatin versus carboplatin for Cohorts A and C. The worst grade per participant, per SOC and per PT will be reported (Any grade [including missing grade], Grade ≥ 3, Grade ≥ 4, and Grade 5).

15.2.5 Adverse Events of Special Interest

15.2.5.1 Infusion-Related Reactions Including Immediate Hypersensitivity

Infusion-related reactions (IRR) are defined as adverse events with PTs on a pre-specified list of MedDRA PTs and divided into reactions versus signs and symptoms.

Reactions of IRR: should be considered when onset is on the day of bintrafusp alfa 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 bintrafusp alfa and/or chemotherapy infusion (during or after the infusion) and resolved completely with the end date on the same day of the infusion or the day after.

The frequency table of IRR AEs by worst grade, SOC, and PT will be provided and repeated on cisplatin versus carboplatin (Cohorts A and C).

The listing of IRRs will also be provided with the relevant information (see description of listing in Section 15.1.1).

15.2.5.2 Immune-Related AEs

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 preferred term matches a preferred term on the list of pre-selected MedDRA terms.

2) The AE onset or worsening occurs during the on-treatment period for irAEs (see Section 9.8).

3) On the "AE" eCRF page, the question "Were Corticosteroids, Immunosuppresants, or hormonal therapy (e.g., 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.

The frequency table of irAEs by worst grade, categories, and PT will be provided and repeated on cisplatin versus carboplatin (Cohorts A and C).

The listing of irAEs will also be provided with the relevant information (see description of listing in Section 15.1.1).

15.2.5.3 TGF-β Inhibition Mediated Skin TEAEs

TGF-β inhibition mediated skin AEs will be selected based on MedDRA PTs according to a pre-specified MedDRA search list:

Narrow definition:

- Keratoacanthoma (KA)
- Squamous cell carcinoma of skin

Broad definition has additional PTs:

- Hyperkeratosis
- Actinic keratosis
- Basal cell carcinoma
- Lip squamous cell carcinoma
- Bowen's disease

Note that the list above may not be comprehensive as it undergoes scheduled reviews for updates.

A table for TGF-β inhibition mediated skin TEAEs frequency will be provided by MedDRA PTs (including both narrow and broad definition PTs) and repeated on cisplatin versus carboplatin (Cohorts A and C). A tabulation of PTs by worst grade (any grade, ≥ 3, ≥ 4, 5) will also be provided.

A listing of TGF-β inhibition mediated skin AEs will also be provided with the relevant information (see description of listing in Section 15.1.1), plus the number of lesions, lesion location and diagnosis confirmed by biopsy/excision (Y/N).

15.2.5.4 Anemia

To identify potential anemia AEs, MedDRA PT queries will be used to search for anemia AEs of interest in the clinical database. Further details (e.g., MedDRA PT queries) are regularly updated based on the current MedDRA version.

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

The frequency table of potential treatment-emergent anemia by worst grade, SOC, and PT will be provided.

A listing of all anemia TEAEs will be provided with the relevant information (see description of listing in Section 15.1.1). Bintrafusp alfa related anemia will be flagged.

15.3 Clinical Laboratory Evaluation

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

Laboratory results will be classified according to the NCI-CTCAE Version 5.0 and as specified in Appendix 3. 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).

Summary tables over time will present summary statistics for continuous and categorical variables by timepoint, by cohort and combining Cohorts A, B, and C (1L Cohort A, B, C).

The following figures will also be provided by cohort:

- Boxplots of the laboratory values by timepoint
- Boxplots of the change from baseline by timepoint

Boxplots for laboratory parameters where toxicity grades are defined based on the ratio of the parameter values and the upper limit of normal (ULN) will not be displayed using the unit of measurement but instead using the ratio of the measured value over ULN. This comprises alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, creatinine, amylase and activated partial thromboplastin time. Values>50*ULN and values<LLN/50 may be removed from boxplots if needed for the readability of the figure (with a footnote added providing the number of participants removed from the figure).

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 cohort and combining Cohorts A, B, and C (1L Cohort A, B, C):

- Number and percentage of participants by worst on-treatment grade (>=1, >=3, >=4)
- Shift in toxicity grading from baseline to highest on-treatment grade.

The definitions of the NCI-CTCAE toxicity grading version 5.0 for each parameter are provided in Appendix 3 of this IAP.

For WBC differential counts (neutrophil, lymphocyte counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and

lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

Derived differential absolute count = (WBC count) * (Differential %value / 100)

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 (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4], or
- Corrected calcium (mmol/L) = measured total calcium (mmol/L) + 0.02 (40 – serum albumin [g/L])

Laboratory Parameters with NCI-CTC Grades not Available

For all non-gradable parameters, the following summaries will be displayed by cohort and combining Cohorts A, B, and C (1L Cohort A, B, C):

- 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 during on-treatment period will be described per cohort and combining Cohorts A, B, and C (1L Cohort A, B, C):

- 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
- ALP ≤ 2×ULN, ALP > 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, 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 total bilirubin ≥2×ULN. The left lower quadrant is then considered normal or insignificant elevations in liver chemistries, the upper left quadrant indicates patients with possible Gilbert's cholestasis; the right upper quadrant is the possible Hy's Law patients; the right lower quadrant is possible Temple's Corollary (patients with ALT ≥ 3 x ULN but not satisfying Hy's Law). A plot of peak AST versus peak total bilirubin, both relative to the ULN will also be provided.

In addition, a listing of all TBILI, ALT, AST and ALP values for participants with a post-baseline TBILI ≥ 2×ULN, ALT≥ 3×ULN or AST ≥ 3×ULN will be provided, including values expressed as multiples of ULN. A listing to study switchers may also be provided.

Separate listings of hematology and biochemistry will be created. Each listing will include cohort, participant identifier, age, sex, race, first dose date, last dose date, laboratory parameter (units), visit, date, International System of Units (SI) value, change from baseline, lower limits of normal (LLN), upper limits of normal (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 cohort, participant identifier, laboratory measurement date, time and parameter. The baseline values and post-baseline values after the on-treatment period will be flagged.

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

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

Pregnancy Test

All test results for pregnancy test as collected on the "Pregnancy Test" eCRF page will be listed.

15.4 Vital Signs

The following summary will be prepared for vital signs: body temperature, pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and respiration rate considering only participants with post-baseline values during on-treatment period:

- Summary statistics over time

Potentially clinically significant abnormalities will also be 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 beats/min and decrease from baseline ≥ 20 beats/min in heart rate
- ≥ 100 beats/min and increase from baseline ≥ 20 beats/min in heart rate
- ≤ 20 breaths/min and decrease from baseline ≥ 5 breaths/min in respiratory rate
- ≥ 20 breaths/min and increase from baseline ≥ 5 breaths/min in respiratory rate
- ≥ 10% weight increase
- ≥ 10% weight decrease

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 cohort, participant identifier, age, sex, race, vital sign parameter, unit, visit, date/time, on-treatment flag, value, baseline value, and change from baseline. Listings will be sorted by cohort, participant identifier, vital sign parameter, vital sign measurement date and time.

15.5 Other Safety or Tolerability Evaluations

ECOG Performance Status

ECOG performance status will be presented in a listing at each time point (see details of the categories in Section 11.3.2). The baseline values and post-baseline values after the on-treatment period will be flagged.

ECG

Analyses of baseline characteristics with respect to ECGs are discussed in Section 11.3.3.

A listing of ECG values will also be provided with the following information: cohort, participant identifier, age, sex, race, ECG parameter and unit, visit, ECG date and value. The listing will be sorted by cohort, participant identifier, ECG parameter and ECG date. It will include all the ECG values collected during the study.

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 based on the Safety Analysis Set. Summaries and statistical analyses will be based on the PK Analysis Set.

Participants who switched chemotherapy will be flagged in listings. Pharmacokinetic concentrations / PK parameters mentioned herein refer to those of bintrafusp alfa.

16.1.1 Missing/non-quantifiable PK Data Handling

Concentrations Below the Lower Limit of Assay Quantification

Pharmacokinetic concentrations below the lower limit of quantification ([LLOQ] BLQ) are set to zero for calculating parameters and descriptive statistics.

Pharmacokinetic concentrations BLQ which are before the last quantifiable data point will be taken as zero for calculating the AUC of single dose profiles. Concentrations BLQ which occur after the last quantifiable data point will not be considered in the calculation of the terminal first order rate constant (λz).

Deviations, Missing Concentrations, and Anomalous Values

Pharmacokinetic parameters will be calculated using the actual elapsed time since dosing. When the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data. 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 and/or Section 8.1), documented handling error, or analytical error (as documented in the protocol deviation log, bioanalytical data, and/or 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 must be provided in the CSR. Any other PK concentrations that appear implausible to the Pharmacokineticist/PK/PD 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 (i.e., descriptive statistics), 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 based on the PKAS 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 PK Analysis

Presentation of PK Concentration Data

Listings

Individual PK sample times, time deviations, and concentration data will be listed by part, participant, cohort, study day, and nominal time. Concentration listings will be based on the SAF. Pharmacokinetic concentrations will be reported with the same precision as the source data provided by the bioanalytical laboratory. Actual elapsed sample collection times will be rounded to two decimal places with units of hours for reporting purposes in listings.

Tables

Pharmacokinetic concentration data will be presented in tables and descriptively summarized for the PKAS in safety part only/first dose by cohort, 1L Cohort A, B, C, overall (all cohorts), day, and nominal time using: number of non-missing observations (n), arithmetic mean (Mean), StD, coefficient of variation (CV%), Min, median (Median), and Max. Additional table(s) will summarize with further stratification by ADA subgroups ever positive and never positive. Only ADA subgroup sample size with a minimum of 3 participants will be displayed. Summaries of pre-dose and end-of-infusion concentrations other than first dosing interval will be covered by the parameter summaries only.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data provided by the bioanalytical laboratory and rounded for reporting purposes only. The following conventions will be applied when reporting descriptive statistics of PK concentration data:

Mean, Min, Median, Max:	3 significant digits
StD:	4 significant digits
CV%:	1 decimal place

Figures

Individual PK concentration-time profiles showing all participants by part and cohort will be created for serial sampling (i.e., safety part, first dose) using the actual time points and the numeric concentration data. Arithmetic mean and median concentration-time profiles by cohort, 1L Cohort A, B, C, and overall (all cohorts combined) for serial sampling (i.e., safety part, first dose) will be provided using scheduled (nominal) time points and the numeric concentration data. All concentration-time plots for PK data will be presented both on a linear and on a semi-logarithmic scale. Mean PK plots will include StD error bars when plotted on a linear scale. Individual data will be presented based on the SAF, and summaries will be based on the PKAS. Additional figure(s) will be presented with further stratification by ADA subgroups ever positive and never positive. Only ADA subgroup sample size with a minimum of 3 participants will be displayed. Figures of pre-dose and end-of-infusion concentrations other than first dosing interval will be covered by the parameter summaries only.

16.1.3 Pharmacokinetic Non-Compartmental Analysis

Presentation of PK Parameter Data

Listings

Individual PK parameter data will be listed by part, participant, cohort, and study day. Parameter listings will be based on the SAF. Pharmacokinetic parameters will be reported to 3 significant digits in listings.

Tables

Pharmacokinetic parameter data will be presented in tables and descriptively summarized for the PKAS by part, cohort, 1L Cohort A, B, C, overall by part (all cohorts within each part), overall (all parts/cohorts), and day using: n, Mean, StD, CV%, Min, Median, 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 subgroups ever positive and never positive. Only ADA subgroup sample size with a minimum of 3 participants will be displayed.

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

The PK parameters listed below will be calculated for bintrafusp alfa using the actual time elapsed from dosing (or using scheduled time if actual time is not available, e.g., any analyses prior to final analysis). Pharmacokinetic concentrations will be analyzed with the same precision as the source data provided by the bioanalytical laboratory. Actual elapsed sample collection times will be analyzed unrounded (maximum of 14 significant digits). The pre-dose samples will be considered as if they had been taken simultaneously with the start of infusion (i.e., time zero).

C_{eoi}	The concentration observed immediately at the end of infusion. This will be taken directly from the observed bintrafusp alfa concentration-time data.
C_{trough}	The concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing). This will be taken directly from the observed bintrafusp alfa concentration-time data.

AUC_{0-t}	Area under the concentration-time curve (AUC) from time zero (i.e., infusion start time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. (Safety part only; first dose only)
$AUC_{0-\infty}$	The AUC from time zero (infusion start time) extrapolated to infinity, based on the predicted value for the concentration at t_{last} ($C_{last\ pred}$), as estimated using the linear regression from λz determination. $AUC_{0-\infty} = AUC_{0-t}+C_{last\ pred}/\ \lambda z$. (Safety part only; first dose only)
$t_{1/2}$	Apparent terminal (elimination) half-life, calculated by ln2/ λz. (Safety part only; first dose only)
λz	Terminal first order (elimination) rate constant, determined from the terminal slope of the log-transformed concentration-time curve using linear regression on terminal data points of the curve. (Safety part only; first dose only)
C_{max}	Maximum observed concentration. (Safety part only; first dose only)
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values). (Safety part only; first dose only)
CL	Total body clearance. $CL = Dose/AUC_{0-\infty}$. (Safety part only; first dose only)
V_z	Volume of distribution during terminal phase following intravenous dosing. $V_z = Dose/(AUC_{0-\infty}*\lambda z)$. (Safety part only; first dose only)

The following PK parameters (Safety part only; first dose only) will be calculated for diagnostic purposes and listed, but will not be summarized:

- The time interval (h) of the log-linear regression to determine λz ($t_{1/2}$, Interval).
- The starting time point (h) of the time interval of the log-linear regression to determine λ_z (Lambda_z_low).
- The ending time point (h) of the time interval of the log-linear regression to determine λ_z (Lambda_z_upp).
- Number of data points ($t_{1/2}$, N) included in the log-linear regression analysis to determine λz.
- Goodness-of-fit statistic (adjusted Rsq) for calculation of λz.

- Percentage of $AUC_{0-\infty}$ obtained by extrapolation ($AUC_{extra\%}$), calculated by $(1-[AUC_{0-t}/AUC_{0-\infty}])\times 100$.

The regression analysis (determination of λ_z) should contain as many data points as possible (but excluding C_{max}) and has to include concentration data from at least 3 different time points, consistent with the assessment of a straight line (the terminal elimination phase) on the log-transformed scale. The observation period over which the regression line is estimated should be at least two-fold the resulting $t_{1/2}$ itself. If $AUC_{extra\%}$ >20.0% and/or adjusted Rsq of λ_z is <0.800 and/or $t_{1/2}$, Interval is less than twofold the resulting $t_{1/2}$, then λ_z and all derived parameters (e.g., $t_{1/2}$, $AUC_{0-\infty}$, CL, etc.) will be listed and flagged but excluded from descriptive statistics.

The calculation of the AUCs will be performed using the mixed log-linear trapezoidal method (linear up, log down). Extrapolated areas will always be computed using the predicted last concentration that is estimated using the linear regression from terminal rate constant determination.

Figures

Individual PK trough concentration (C_{trough}) and end of infusion concentration (C_{eoi}) values will be plotted against actual study day on a linear scale, for all participants by part and cohort including the combined 1L Cohort A, B, C. Individual data will be presented based on the SAF.

Arithmetic mean (±StD), geometric mean, and median C_{trough} and C_{eoi} will be plotted versus nominal study day by part, cohort, overall by part (all cohorts within each part), and overall (all parts/cohorts) on a linear scale. Summaries will be based on the PKAS. Additional figure(s) will be presented with further stratification by ADA subgroups ever positive and never positive. Only ADA subgroup sample size with a minimum of 3 participants will be displayed. Summary figures of mean or median will contain a footnote denoting n per time point.

The Phoenix WinNonlin non-compartmental Core Output will be provided in a separate listing.

CCI [redacted]

[redacted]

16.3 Immunogenicity

The IMM analysis set will be used to evaluate the immunogenicity of bintrafusp alfa. Results will be displayed by cohort and combined 1L Cohort A, B, C.

Antidrug antibody (ADA) will be assessed prior to bintrafusp alfa 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 Table 6.

Table 6 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

NR = no result, NA = not applicable, 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 the table below (Table 7).

Table 7 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 ADA 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 ADA result at any time point
Pre-existing	A positive ADA result prior to treatment with bintrafusp alfa	Number of participants with valid baseline ADA result
Treatment boosted	A positive ADA result prior to treatment with bintrafusp alfa and the titer ≥ 8*baseline titer at least one post-baseline value	Number of participants with a valid baseline ADA result and at least one valid post-baseline ADA result
Treatment emergent (induced)	Not positive prior to treatment (includes missing or NR) with bintrafusp alfa and with at least one positive post-baseline result	Number of participants with at least one valid post-baseline ADA result and without positive ADA baseline result (including missing, NR)
Treatment emergent (ALL)	Treatment emergent plus Treatment boosted	Number of participants with at least one valid post-baseline ADA result
ADA Non-Treatment-emergen	All participants at risk minus Treatment emergent (ALL)	Number of participants with at least one valid post-baseline ADA result
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 ADA result and without positive baseline ADA result (including missing, 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 ADA result and without positive baseline ADA result (including missing, NR)

Start of Immunogenicity Response

- For participants with treatment-emergent response, the date of the first assessment with positive ADA result will be considered as start date of ADA response.
- For participants with treatment-boosted response, the date of the first boosted assessment (i.e., first post-baseline date where titer ≥ 8 * baseline titer) will be considered as start date of ADA response.

Time to Onset of Response for Treatment Emergent ALL

Time to onset (weeks) of ADA response will be calculated as:

- (Date of first positive ADA assessment – start date of bintrafusp alfa treatment + 1) / 7 for treatment-emergent participants
- (Date of first boosted (titer ≥ 8 * baseline titer) ADA assessment – start date of bintrafusp alfa treatment + 1) / 7 for treatment boosted participants

Duration of ADA Response for Treatment Emergent ALL

Duration of ADA immunogenicity response (weeks) is defined as:

- (Date of last positive ADA assessment – date of first positive ADA assessment + 1) / 7 for treatment-emergent participants
- (Date of last positive ADA assessment - date of first boosted (titer ≥ 8 * baseline titer) ADA assessment + 1) / 7 for treatment boosted participants

Potential effect of ADA on safety, efficacy and PK will be evaluated on ADA positive status (ever positive versus never positive, and treatment-emergent ALL versus non-treatment emergent ALL). The following analysis will be described:

- The frequency and percentage of each ADA category will be tabulated.
- The ADA titer value by timepoint will be summarized.
- The maximum observed ADA titer per participant will be tabulated (as quantitative and categorical variable). For each discrete titer value, percentages will be calculated using the total number of participants with at least one positive result as the denominator.
- The time to onset of response for treatment-emergent ALL participants will be summarized.

- The duration of ADA immunogenicity response for treatment-emergent ALL participants will be summarized.
- Evaluation of potential effect of ADA on bintrafusp alfa safety (see Section 15.1.1).
- Evaluation of potential effect of ADA on bintrafusp alfa efficacy
    - for confirmed best overall response according to RECIST 1.1 as assessed by Investigator (see Section 14.2.2)
    - for progression-free survival according to RECIST 1.1 as assessed by Investigator (see Section 14.2.5)
    - for overall survival (see Section 14.2.5).
- Evaluation of potential effect of ADA on bintrafusp alfa Pharmacokinetic (see Section 16.1.2).

A listing of all individual ADA results from ever positive participants will be prepared by time point. An additional listing of all individual ADA results from treatment-emergent ALL participants will also be provided.

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18 Appendices

18.1 Appendix 1: List of Important Protocol Deviations

See document: ctp-emr200647-0024-iap-appendix-1.

18.2 Appendix 2: Identification of Previous or Concomitant Medications

See document: ctp-emr200647-0024-iap-appendix-2.

18.3 Appendix 3: Definition of NCI-CTCAE Grading

See document: CTC V5.0 guidance.xlsx.