Integrated Analysis Plan

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Title:	Safety Study of Bintrafusp alfa in Combination with Other Anti-cancer Therapies in Participants with Locally Advanced or Advanced Cervical Cancer
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Approval Page

Integrated Analysis Plan: MS200647_0046

Safety Study of Bintrafusp alfa in Combination with Other Anti-cancer Therapies in Participants with Locally Advanced or Advanced Cervical Cancer

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

By using eSignature, the signature will appear at the end of the document.

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2 List of Abbreviations and Definition of Terms

Abbreviation	Definition
ADA	Antidrug Antibody
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AUC_{0-t}	Area under the serum concentration-time curve from time zero to the last quantifiable concentration
$AUC_{0-\infty}$	Area under the serum concentration-time curve from time zero extrapolated to infinity
BMI	Body Mass Index
BSA	Body Surface Area
C_{EOI}	The concentration observed at the end of infusion
CI	Confidence Interval
CL	Total body clearance of drug from serum
COVID-19	Coronavirus disease 2019
C_{max}	Maximum observed concentration in serum
CR	Complete Response
CrCl	Creatinine Clearance
CSR	Clinical Study Report
C_{trough}	The concentration observed at the end of the dosing interval, before next dosing (corresponding to pre-dose or trough concentration for multiple dosing)
CV%	Coefficient of Variation (%)
DBP	Diastolic Blood Pressure
DI	Dose Intensity
DLT	Dose-limiting Toxicities
DOR	Duration of Response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	Electronic Case Report Form
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
GeoCV%	Geometric coefficient of variation
GeoMean	Geometric mean
GFR	Glomerular Filtration Rate
CCI	[redacted]
IAP	Integrated Analysis Plan

IC	Immune Cells
ICH	International Council for Harmonization
IHC	Immunohistochemistry
IPD	Important Protocol Deviations
IRR	Infusion-related Reaction
λ_Z	Terminal first order (elimination) rate constant
LLN	Lower Limit of Normal
<LLOQ	Below the lower limit of quantification
logStD	Standard deviation of log-transformed data
Max	Maximum
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MSI	Microsatellite instability
MSS	Microsatellite Stable
nAb	Neutralizing antidrug antibody
NCA	Non-Compartmental Analysis
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
nd	Not determined
OR	Objective Response
OS	Overall Survival
PD	Progressive Disease
PD-L1	Programmed Death Ligand 1
PFS	Progression-free Survival
PK	Pharmacokinetic(s)
CCI	[redacted]
PKAS	Pharmacokinetic analysis set
PR	Partial Response
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
RBC	Red Blood Cell
RDI	Relative Dose Intensity
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
SAE	Serious Adverse Event
SAF/FAS	Safety/Full Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Stable Disease
SDTM	Study Data Tabulation Model
SI	International System of Units

SMC	Safety Monitoring Committee
SMQ	Standardized MedDRA Queries
SoC	Standard of Care
SOC	System Organ Class
StD	Standard Deviation
$t_{1/2}$	Elimination half-life
T4	Thyroxine
TC	Tumor Cells
TEAE	Treatment-emergent Adverse Event
TGFβ	Transforming Growth Factor-Beta
TLF	Tables, Listings, and Figures
t_{max}	Time to reach C_{max}
TMB	Tumor Mutational Burden
TNM	Tumor, Lymph Nodes, Metastasis
TOR	Time to Objective Response
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
V_z	Volume of distribution during terminal phase
WBC	White Blood Cells

3 Modification History

Unique Identifier for IAP Version	Date of IAP Version	Author	Changes from the Previous Version
1	PPD	PPD PPD	Not Applicable
2	PPD	PPD	- Section 6: Added "Overview of Planned Analyses after Trial Discontinuation" and removed "Main Analysis" and "Final Analysis" - Section 7.1 and 10.1: added "Overview table of the impact by COVID-19" and updated listing of COVID-19 impact - Section 7.1 and 15.2.1: added "Table of treatment-emergent adverse events (TEAEs) associated to COVID-19" - Section 9.10: modification of imputation of missing data for previous and concomitant medication/procedure - Section 9.10: added details in the rules to define previous and/or concomitant medication/procedure - Section 13: specifying that for radiotherapy and brachytherapy, a dose is considered to be administered if the start date is non missing. - Section 15: considering bleeding events as AESIs - Section 15: "TGFβ-mediated skin adverse events" replaced by "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 main and final analysis of data collected for protocol MS200647_0046.

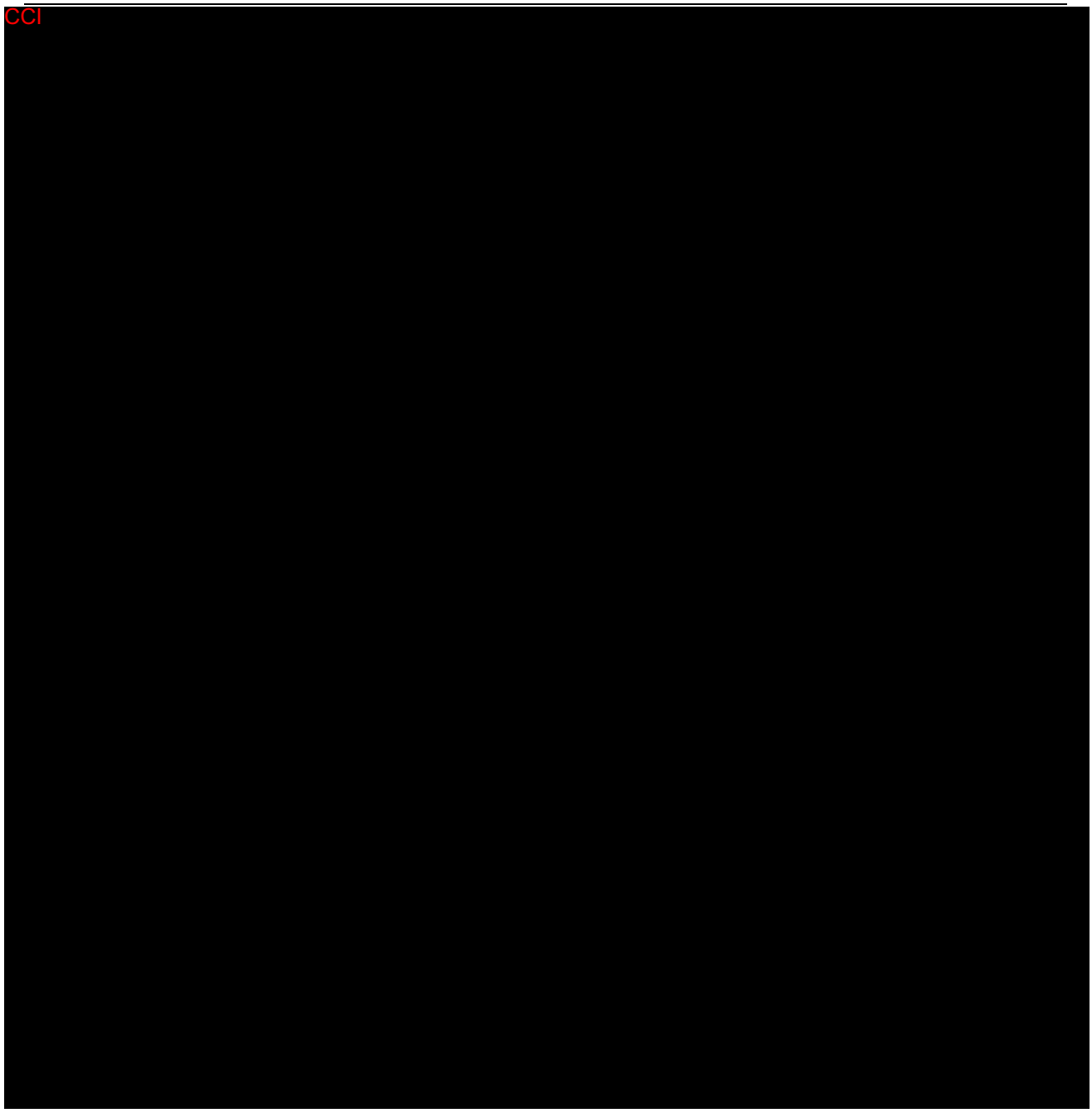
Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc or unplanned analyses performed to provide results for inclusion in 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. It describes analyses planned in the protocol apart from Safety Monitoring Committee (SMC) analyses. Details of the SMC analyses will be developed in a separate statistical analysis plan (SAP).

5 Objectives and Endpoints

Table 1 Study Objectives and Endpoints

Objectives	Endpoints	IAP Section
Primary		
To evaluate the safety and tolerability of bintrafusp alfa in combination with (1) chemotherapy with or without bevacizumab in participants with recurrent, persistent, or metastatic cervical cancer or (2) platinum therapy and definitive radiation in participants with locally advanced cervical cancer	• Occurrence of DLTs • Adverse events (AEs)	Section 15
Secondary		
To evaluate the safety and tolerability of bintrafusp alfa in combination with (1) chemotherapy with or without bevacizumab in Japanese participants with recurrent, persistent, or metastatic cervical cancer or (2) platinum therapy and definitive radiation in Japanese participants with locally advanced cervical cancer	• Occurrence of DLTs • Adverse events (AEs)	Section 15
To characterize PK profile of bintrafusp alfa	• PK profile of bintrafusp alfa in terms of C_{EOI} and C_{trough} for all participants throughout the treatment period • PK profile of bintrafusp alfa in terms of AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{1/2}$ in Cycle 1	Section 16.1
To evaluate the immunogenicity of bintrafusp alfa	• Immunogenicity of bintrafusp alfa, as measured by ADA assay, from Day 1 pre-dose through the last Safety Follow-up Visit	Section 16.4
CCI [redacted]		



6 Overview of Planned Analyses

Statistical analyses will be performed based on CDISC SDTM data. These SDTM data contain as clean as possible eCRF data, as well as external data including biomarker and PK data.

Apart from the analyses for the SMC meetings, all data will be included up to a clinical cut-off date as described in the corresponding sections below.

In addition to analyses for SMC meetings, main analysis and final analysis, additional analyses could be conducted during the study, e.g., for publication or decision-making purposes.

6.1 Safety Monitoring Committee

A SMC will be responsible for the safety evaluation in each cohort (Cohort 1A, Cohort 1B and Cohort 2) and will make recommendations for the study. Details can be found in the SMC Charter.

The SMC will evaluate safety (including DLTs) and other available data after the 3rd as well as the 8th evaluable participant completes the respective DLT observation period. Once a trigger is met, a data snapshot will be taken for provision of SMC outputs. There will be no data cut-off applied.

The details of the analyses for SMC are provided in a separate SAP that was approved before the first SMC meeting.

6.2 Overview of Planned Analyses

The data review outcome from the 3 randomized controlled studies in NSCLC and BTC (MS200647-0005, MS200647-0037, MS200647_0055) appears to indicate, consistently across 2 indications, either poorer observed hazard ratios for PFS and OS in the experimental arms with bintrafusp alfa or low likelihood for bintrafusp alfa to add benefits compared to standard of care.

Based on this, the decision was made to restrict the analyses on this study MS200647_0046. The analyses described in Sections 10 - 16 will not be performed as planned, instead analyses based on the primary analysis data cutoff date of PPD will be performed for an abbreviated CSR (aCSR).

The analyses considered relevant for this purpose are listed below:

- Participant disposition
- Protocol deviations
- Demographic characteristics and baseline characteristics
- Previous and concomitant medications
- Treatment compliance and exposure
- Efficacy (overall survival, progression-free survival, confirmed objective response, duration of response, tumor shrinkage)
- Safety (adverse events, clinical laboratory evaluations, vital signs).

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

7 Changes to the Planned Analyses in the Clinical Study Protocol

7.1 COVID-19 Impact

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

No changes to the analysis of the primary and efficacy endpoints will be performed due to the impact of COVID-19 outbreak.

Instead, additional outputs will be generated to assess potential impacts of COVID-19 to this study including:

- Overview table of the impact by COVID-19
- Listing of COVID-19 impact
- Listing of protocol deviations related to COVID-19
- Table of treatment-emergent adverse events (TEAEs) associated to COVID-19
- Listing of adverse events related to COVID-19.

8 Analysis Sets and Subgroups

8.1 Definition of Analysis Sets

Screening Analysis Set

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

Dose-limiting Toxicity Analysis Set

The DLT set will include all participants who received at least one dose of study intervention and meet at least one of the following criteria:

- Experienced at least one DLT during the DLT period (within 4 weeks after first administration of study intervention), regardless of the administered number of doses of study intervention/completion of the DLT period.

- Received at least 80% of the planned cumulative dose during the DLT period of each treatment and completed the DLT period.

Analyses will include participants as treated.

Safety/Full Analysis Set

The safety/full analysis set (SAF/FAS) will include all participants who were administered any dose of any study intervention. Analyses will be performed as treated.

Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PKAS) will include all participants who completed at least 1 infusion of bintrafusp alfa, and who provided at least 1 sample with a measurable concentration of bintrafusp alfa. The pharmacokinetic antidrug antibody (ADA) analysis set (PKADA) is defined as a subpopulation of the PKAS and restricted to participants who have in addition at least one valid result of ADA at any time point.

Analyses will include participants as treated. All PK analyses will be based on this analysis set (or subset). Refer to Section 16.1 for protocol deviations and handling relevant to PK.

Immunogenicity Analysis Set

All participants who were administered at least 1 infusion of bintrafusp alfa and have at least one valid ADA result. Analyses will include participants as treated.

The following table summarizes the use of the analysis sets for the different analyses.

Table 2 Overview of the Analysis Sets Used in the Analyses

	Analysis Set				
Analyses	**SCR**	**SAF/FAS**	**DLT**	**PK**	**IMM**
Disposition of Participants	✓				
Protocol Deviations		✓			
Demographics and Other Baseline Characteristics		✓			
Previous and Concomitant Therapies		✓			
Compliance and Exposure		✓			
CCI [redacted]		✓			
Safety and Tolerability: Dose Limiting Toxicities (Primary)			✓		
Other Safety and Tolerability (Secondary)		✓			
Pharmacokinetics				✓	
Immunogenicity					✓
CCI [redacted]		✓			

DLT: dose-limiting toxicity; IMM: immunogenicity; PK: pharmacokinetic; SAF/FAS: safety/full analysis set; SCR: screening analysis set.

8.2 Subgroup Definition and Parameterization

The safety profile will be specifically evaluated in the specific subpopulation of Japanese participants within each cohort.

9 General Specifications for Data Analyses

This section describes any general specifications not included in subsequent sections.

Unless otherwise specified, 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. The three cohorts will be labelled as Cohort 1A, Cohort 1B and Cohort 2, respectively. For demographics and baseline data a total column will also be presented. 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.

9.1 Data Handling After Cut-off Date

By its nature, data after cut-off may be incomplete and subject to further change and will not be used for summary statistics, statistical analyses, listings or imputations.

Stop dates are not affected by this rule, e.g., a stop date of an adverse event (AE) which starts prior to the cut-off but stops after date of cut-off, will not be changed.

9.2 Study Intervention

In this study, bintrafusp alfa, bevacizumab, chemotherapies (cisplatin, carboplatin, paclitaxel) and radiotherapy are considered as study interventions. The date of first study intervention administration will be defined as the earliest administration date of any interventions (bintrafusp alfa, bevacizumab, cisplatin, carboplatin, paclitaxel, radiation). The date of last study intervention administration will be defined as the latest administration date of any interventions.

9.3 Definition of Baseline and Change from Baseline

In general, the last non-missing measurement prior to the administration of study intervention will be used as the baseline measurement for safety and efficacy analyses. If an assessment that is planned to be performed before treatment per protocol is performed on the same day as the first study intervention administration, but the assessment time is not available, it will be assumed that it was performed prior and will be considered as baseline.

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.

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

Participants who start intervention and discontinue the treatment on the same day may have 2 different sets of data collected on study day 1 (one during study and one at end of treatment visit). Data reported at the end of treatment visit will not be eligible for baseline selection.

Absolute and percent changes from baseline are defined as follows:

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

9.4 Study Day / Study Treatment Day

Day 1 is the day of start of first study intervention, the day before is Day -1 (no Day 0 is defined).

Study day / Study treatment day are defined relative to Day 1.

9.5 Definition of Duration and 'time since' Variables

Durations in days will be calculated by the difference of start and stop date + 1 (e.g., overall 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 initial cancer diagnosis) will be calculated as reference date minus date of event.

9.6 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

9.7 Date of Last Contact

The date of last contact will be derived for participants not known to have died at the analysis cut-off using the latest complete date prior to or at the data cut-off date from the following:

- All participant assessment dates (e.g., blood draws [laboratory, PK], vital signs, ECOG performance status, electrocardiogram [ECG], tumor assessments)
- Start and end dates of anticancer therapies administered after discontinuation of study intervention
- AE start and end dates
- Last known to be alive date from "Subject Status / Survival Follow-Up" eCRF page
- Study intervention start and end dates
- Date of discontinuation taken from the "Study Termination" eCRF page (do not use if reason for discontinuation is lost to follow-up)

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.

9.8 Time Window

No time windows are defined for the study.

9.9 Definition of On-treatment Period

The on-treatment period will include the initial treatment period as well as the re-initiation of treatment period if any. Whether the 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 administration to the last study intervention administration date + 30 days, or the earliest date of subsequent anticancer therapies minus 1 day, or the cut-off date, or death, whichever occurs first.

For participants with treatment ongoing at the cut-off date, all data from the first administration of study intervention up to the cut-off date will be considered as on-treatment data.

For immune-related AEs as listed in Section 15.3.3.2, 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.

Any systemic anticancer therapy, any anticancer surgery, any anticancer radiotherapy and any anticancer brachytherapy as documented in the ”Anti-cancer treatment after discontinuation”, “Surgery after discontinuation”, ”Radiotherapy after discontinuation” and “Brachytherapy after discontinuation” eCRF pages will be considered as subsequent anticancer therapy.

9.10 Imputation of Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In all participant data listings, imputed values will be displayed and imputed information will be flagged.

Partial dates, which are not to be imputed according to the IAP, will be presented in the format like “_____YYYY”.

Missing statistics, e.g., when they cannot be calculated, will be presented as “nd” standing for not determined. For example, if n=1, the standard deviation (StD) cannot be computed and will be presented as “nd”.

Incomplete dates will be handled as specified in the following table:

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 imputed to the 1st day of the month. • 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 imputed to the 1st of January. • In all other cases, the incomplete dates will not be imputed.
Disease history	Incomplete dates for disease history (e.g. initial cancer diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of progression of disease prior to study entry) 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.
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 intervention and AE resolution date (if available after imputation). • 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 the 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.
Previous and concomitant medication/procedure	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. In case the imputation results in a date later than the date of participant's death, then the date of death will be used to impute the incomplete stop date.
Dates of study intervention	Start date of study interventions: • No imputation will be done.

	End date of study interventions: • In case the last date of study intervention is missing or incomplete the date of last administration of study intervention will be taken from the treatment termination eCRF pages. • If the last date of study intervention is completely missing and there is no End of Treatment eCRF page and no death date the participant should be considered as ongoing and use the cut-off date for the analysis as the last dosing date • If the last date of study intervention is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (before the cut-off date) then imputed last dose date is: = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date) = Last day of the month, if both Year and Month are available and Year= Year of min (EOT date, death date) and Month < the month of min (EOT date, death date) = min (EOT date, death date), for all other cases
Tumor assessments	All investigation dates (e.g., X-ray, CT scan) must be completed with day, month and year. If there are multiple scan dates associated with an evaluation, i.e., radiological assessments occur over a series of days rather than the same day, the choice of date of assessment could impact the date of progression and/or date of response. 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. If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of all investigation dates (e.g., X-ray, CT-scan). If all measurement dates for an evaluation have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both previous and following assessments are not available, this assessment will not be used for any calculations.
Subsequent Anticancer Treatment	Incomplete dates for the start date of subsequent anticancer treatment (drug therapy, radiotherapy, brachytherapy, 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 the 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 treatment 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 treatment stop dates will not be imputed.
Death	For the purposes of survival analyses only, partially missing death dates will be imputed as follows: • If only the day is missing, the death date will be imputed to the maximum of the (non-imputed) day after the date of last known alive date and the 15th day of the month. • Otherwise it will not be imputed

Table 3 Stopping rules for medication/procedure end dates

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

UNK = Unknown

Table 4 Rules to define previous and/or concomitant medication/procedure

Start date of medication/procedure			Stopping rule (see Table 3)	Medication/procedure
Day	**Month**	**Year**		
UNK	UNK	UNK	Before treatment start	Previous
UNK	UNK	UNK	After treatment start	Previous and concomitant
UNK	UNK	<= Treatment start (year)	Before treatment start	Previous
UNK	UNK	<= Treatment start (year)	After treatment start	Previous and concomitant
UNK	UNK	> Treatment start (year) and <= Treatment end + 30 days (year) OR the earliest date of subsequent anticancer drug therapies minus 1 day, whichever occurs first.	After treatment start	Concomitant
UNK	<= Treatment start (month and year)		Before treatment start	Previous
UNK	<= Treatment start (month and year)		After treatment start	Previous and concomitant
UNK	> Treatment start (month and year) and <= Treatment end + 30 days (month and year) OR the earliest date of subsequent anticancer drug therapies minus 1 day, whichever occurs first.		After treatment start	Concomitant
<= Treatment start (date)			Before treatment start	Previous
<= Treatment start (date)			After treatment start	Previous and concomitant

Start date of medication/procedure			Stopping rule (see Table 3)	Medication/procedure
Day	Month	Year		
> Treatment start (date) and <= Treatment end + 30 days (date) OR the earliest date of subsequent anticancer drug therapies minus 1 day, whichever occurs first.			After treatment start	Concomitant

UNK = Unknown

9.11 Presentation of Continuous and Qualitative Variables

Continuous (non-PK) variables will be summarized using 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, the number of participants with missing values should be set to 0.

Mean, median, Q1, Q3, Min, Max have the same precision as SDTM data (number of digits) for non-derived data. Statistics on derived data will be rounded to reasonable digits, whereas maximal digits will be available in ADaM datasets. StD is to be presented with one digit more than mean.

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

Percentages will be reported to one decimal place.

Descriptive statistics by nominal visit or time point, e.g., for laboratory measurements, will include only data from scheduled visits. In case of multiple available results for a scheduled visit, the result obtained at the earliest date will be considered.

No statistical tests will be performed. If confidence intervals (CIs) are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise specified in this IAP.

9.12 Pooling of Centers

Due to the small number of participants enrolled in each cohort, data from different centers will be pooled for analysis.

9.13 Unscheduled Assessments

As per database definition, unscheduled assessments are always linked to a scheduled timepoint (each unscheduled assessment is linked to the previous scheduled timepoint).

Safety data collected at an unscheduled timepoint (vital signs and laboratory data) will be analyzed according to the following scenario:

- For shift tables, they will be taken into account in the derivation of the worst assessment during the on-treatment period.
- For description at each post-baseline timepoint, the first available result (in chronological order) per timepoint will be taken into account in the analysis in case of multiple values.
- For description at Baseline, unscheduled measurements will be considered as described in Section 9.3.

Efficacy data collected at unscheduled visits will all be considered in the analysis.

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

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

9.14 Preferred Term for analysis of World Health Organization's Drug Dictionary (WHO-DD) coded data

For data coded according to WHO Drug B3 (e.g., concomitant medications), summaries will be done on the preferred term (PT) level where the PT corresponds to codes ending in 01001. With this approach, variations of salt forms of active ingredients will be analyzed under the same term, e.g. diphenhydramine and diphenhydramine hydrochloride will be analyzed as the same PT, diphenhydramine.

9.15 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).

9.16 Data collected after reinitiated treatment

Data collected after reinitiation of treatment will be included in summary tables for all analyses. Data listings will include all data where those collected during the reinitiation of treatment will be flagged.

9.17 Categorization of Participants for COVID-19 Impact Assessment

For the assessment of COVID-19 impact on this study, participants will be categorized as being affected by COVID-19 (either due to infection or due to circumstances of social distancing affecting the capabilities of sites/hospitals etc.) based on the COVID-19 pandemic period defined as follows:

- The start of COVID-19 pandemic will be defined by country as the earliest date of either the date of the first death from COVID-19 occurred in each country according to the published

data by European Centre for Disease Prevention and Control on 26th June 2020 (https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide) or 11 March 2020 (when the WHO declared COVID-19 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.

9.18 Software

All statistical analyses will be performed using statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, Windows Version 9.4 or higher) in the SAS Grid environment.

The computer program Phoenix® WinNonlin® Version 8.0, or higher (Certara, L.P., Princeton, New Jersey, USA) will be used to derive PK parameters applying non-compartmental analysis.

10 Study Participants

The subsections below include specifications for reporting participant disposition and study treatment/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Participants and Discontinuations

All participants from the screening analysis set will be considered.

The number and percentage of participants in each of the following disposition categories will be presented by cohort and total. These statistics will also be provided for the Japanese subpopulation. Percentages will be calculated based on the number of treated participants.

- Total number of participants screened (i.e., all participants who gave informed consent)
- Number of re-screened participants
- Number of participants who did not continue beyond screening overall and grouped by the main reason (participant did not meet all eligibility criteria, withdrawn informed consent, progression of disease, adverse event, lost to follow-up, death, other)
- Number and percentage of treated participants (at least one administration of study intervention)

The end of treatment status will be summarized for each study intervention separately (bintrafusp alfa, bevacizumab, all chemotherapies and radiotherapy, as applicable) as follows:

- Number and percentage of treated participants with the study intervention ongoing
- Number and percentage of treated participants who completed or discontinued the study intervention period, overall and by primary reason (completed as per protocol, adverse event,

lost to follow-up, protocol non-compliance, death, progression of disease, withdrew consent, other)

For participants who reinitiated bintrafusp alfa, the primary reason for treatment termination before bintrafusp alfa reinitiation will be considered.

- Number and percentage of participants who reinitiated bintrafusp alfa
- Number and percentage of participants who discontinued bintrafusp alfa after reinitiation

The end of study status will be summarized by:

- Number and percentage of participants with at least one study intervention ongoing
- Number and percentage of participants off-treatment and in follow-up
- Completed/Discontinued the study period, overall and by primary reason (study completed according to the protocol, adverse event, lost to follow-up, protocol non-compliance, death, withdrew consent, other)

The number and percentage of participants included in each analysis set as defined in Section 8.1 will be provided by cohort and overall. These statistics will also be provided for the Japanese subpopulation. Percentage will not be provided for the screening analysis set.

Additionally, the number of participants in each analysis set will be provided overall, by region, by country within region, and 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, ethnicity (Japanese/Non-Japanese), date of informed consent, included in the study, reason for exclusion, dates of first/last administration for each study intervention, 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 are 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 the study intervention, participant identifier at screen failure, date of informed consent at screen failure, date of screening failure, reason of screening failure. Note if participants are screened several times, all screening attempts will be listed.

In addition, a listing of participants for which bintrafusp alfa has been reinitiated will be provided with the following information: cohort, participant identifier, ethnicity (Japanese/Non-Japanese), dates of first/last administration for each study intervention, reason for termination of each study intervention, first and last reinitiation bintrafusp alfa administration date, status at end of treatment reinitiation (completed, permanently discontinued), 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.

Assessment of COVID-19 Impact

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

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

A listing COVID-19 impact will be provided with the following information: cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), dates of first/last administration of each study intervention, date of first subsequent anticancer therapy as applicable, date of the event, visit, category, event, event description/reason.

10.2 Protocol Deviations

Protocol deviations will be analyzed on the SAF/FAS analysis set.

10.2.1 Important Protocol Deviations

Important protocol deviations (IPDs) 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.

The following summary tables and listings of important protocol deviations will be provided in the SAF/FAS by cohort and overall:

- Frequency table (number and percentage) per category of important protocol deviations
- Listing of important protocol deviations which will include participant identifier, ethnicity (Japanese/Non-Japanese), category of the deviation, and a description of the deviation.

A full list of potential protocol deviations including definition and categorization is maintained in Appendix 1.

An additional listing of COVID-19 related PDs (including non-important PDs) will be provided.

Considerations for PK:

Protocol deviations or events will be reviewed by the study pharmacokineticist and biostatistician to identify deviations or events which have the potential to affect the PK results. Deviations

resulting in no evaluable PK results for a subject, and thus exclusion from PK summaries, will be documented as reasons for exclusion from these summaries.

Changes to the procedures which may impact the quality of the PK data will be considered important protocol deviations and will be described within the CSR body text. Other events which may impact the quality of the PK data will be described within the CSR body text. These changes or events will include any circumstances that will alter the evaluation of the 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 (and actual dosing time not recorded)
- Dose change, missed dose, or incomplete/inaccurate 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. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered important protocol deviations for PK. Common examples of minor (non-important) protocol deviations are a missed sample or minor deviations from sample collection times/windows.

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

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

A listing of participants excluded from the PK and DLT analysis sets as well as the corresponding reasons will be provided.

11 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be described on the SAF/FAS analysis set by cohort and overall.

11.1 Demographics

Demographic characteristics and physical measurements will be summarized descriptively using the following information from the Screening/Baseline Visit eCRF pages. Demographics will also be separately summarized by cohort for Japanese participants.

Demographic characteristics will be summarized using the following information:

- Sex: female
- Ethnicity: Hispanic or Latino, not Hispanic or Latino; Japanese, not Japanese
- 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 the site, Other.
  - For participants reporting multiple races, all combinations will be reported under 'More than one race" category.

- Age (years): summary statistics
- Age categories: < 65 years, ≥ 65 years
- Geographic Region: North America, Europe, Asia & Pacific
- Body Surface Area (BSA) (m^2) at Baseline
- Height (cm) at Baseline
- Weight (kg) at Baseline
- Body Mass Index (BMI) (kg/m^2) at Baseline
- ECOG Performance status:
  - 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

Specifications for computation (at ADaM level):

- Age [years]: (date of given informed consent - date of birth + 1) / 365.25
- The integer part of the calculated age will be used for reporting purposes. Note for rescreened participants, their latest informed consent date will be used.
- See Section 9.10 for imputation rules.
- BSA [m^2] = $\sqrt{\frac{height[cm] \times weight[kg]}{3600}}$
- BMI [kg/m^2] = $\frac{weight\,[kg]}{height[cm]^2} \times 10000$
- Investigator site codes will be used for the determination of the participant's geographic region.

Demographic characteristics including cohort, participant identifier, race (including all reported races in case of "multiple" races, and details in case of "other" race), ethnicity, geographic region, age, body mass index, body surface area, weight and height will be presented in a listing.

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 the Medical Dictionary for Regulatory Activities (MedDRA), PT as event category and MedDRA system organ class (SOC) body term as Body System category.

Medical history will be displayed in frequency tables, ordered by primary SOC and PT in alphabetical order. Each participant will be counted only once within each PT or SOC.

Listing of medical history including cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), PT, condition (reported medical history term, HIV infection, multi-drug resistance preventing effective antiretroviral therapy, multi-drug resistance not preventing effective antiretroviral therapy, aids defining opportunistic infection and specification), start/end dates, related study condition, ongoing at screening and toxicity grade (when medical history is ongoing) will be presented.

11.3 Other Baseline Characteristics

Other baseline characteristics will be summarized by cohort, overall and for Japanese participants.

11.3.1 Disease History

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

- Histological diagnosis (Squamous cell carcinoma, Adenocarcinoma, Adenosquamous cell carcinoma, Other)
- Time since initial cancer diagnosis (months)
- Time since documented, locally advanced, inoperable or metastatic disease diagnosis (months)
- Time since last progression of disease prior to study entry (months)
- TNM classification at initial diagnosis: each T, N, M category will be described (TX, T0, N1, etc.)
- Measurable disease in the pelvis at study entry (Yes, No)

Microsatellite instability (MSI) status (High, Low, Microsatellite stable (MSS), Unknown) will also be summarized. MSI status will be centrally determined with available tumor tissue sample collected at screening and will be provided as external data. Data related to central testing will be listed as specified in Section 16.5.

A listing will also be provided including the following information: cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), histological diagnosis, date of initial cancer

diagnosis and time since initial cancer diagnosis (months), date of documented, locally advanced, inoperable or metastatic disease and time since documented, locally advanced, inoperable or metastatic disease (months), date of last progression and time since last progression of disease prior to study entry (months), TNM classification at initial diagnosis, status regarding the measurability of the disease in the pelvis at study entry.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

11.3.4 Skin Status History

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

- 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)
- Participants having history of skin conditions (No condition, 1 condition, 2 conditions, 3 or more conditions)

  No condition: At least one of the seven items above ticked "No" and no items ticked "Yes". 1, 2, 3 or more conditions: 1, 2, 3 or more of the seven items above ticked "Yes", respectively.

A listing of skin status history will be provided including the following information: cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese) and outcome for each type of skin status history.

CCI [redacted]

[redacted]

11.4 Prior Anticancer Therapy

The prior anti-cancer therapies are collected under the "Prior Anti-Cancer Drug Therapies Details" and "Prior Anti-Cancer Surgeries Details" and "Previous Pre-cancerous Procedures of the Cervix" eCRF pages.

The number and percentages of participants in each of the following anticancer therapy categories will be tabulated:

- Participants with at least one type of prior anticancer treatment (i.e., drug therapy, radiotherapy or surgery)
- Participants with at least one prior anticancer drug therapy
- Participants with at least one radiotherapy administered as part of a prior drug therapy

- Participants with at least one prior anticancer surgery
- Participants with at least one prior pre-cancerous procedure of the cervix

Previous anticancer drug therapy will be summarized as follows based on the number and percentage of participants with the following:

- Number of prior anticancer drug therapy regimens: 0 / 1 / 2 / 3 / ≥ 4
- Number of prior lines of therapy for metastatic/locally advanced disease: 0 / 1 / 2 / 3 / ≥ 4
- Intent of therapy: Neoadjuvant / Adjuvant / Metastatic or Locally Advanced
- Best response to last treatment regimen: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Non-Complete Response/Non-Progressive Disease (non-CR/non-PD) / Not Evaluable / Unknown

Previous anticancer drug therapy (radiotherapy and drug), previous anticancer surgery and pre-cancerous procedure of the cervix will be presented in separate listings as follows:

- The previous anticancer drug therapy listing will contain cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), regimen name, intent of therapy and line number in case of metastatic/locally advanced, line number, best response, documented progression disease date, type of treatment (radiotherapy, drug), PT/medication name or location of radiotherapy, start date, end date, route for drug. This listing will be sorted by cohort, participant identifier, regimen number, type of treatment (radiotherapy, drug), start date, end date, location, PT.
- The previous anticancer surgery listing will contain cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), 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.
- The pre-cancerous procedure of the cervix listing will contain cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), name of procedure, start and end dates, reason for procedure (indication), reason for procedure. This listing will be sorted by cohort, participant identifier, date of procedure, start date and end date.

12 Previous or Concomitant Medications/Procedures

The following analyses will be performed on the SAF/FAS analysis set by cohort and overall.

12.1 Previous and Concomitant Medications

Previous medications are medications, other than study intervention and pre-medications for study intervention, which started before the first administration of any study intervention.

Concomitant medications are medications, other than study intervention and pre-medications for study intervention, which are taken by participants any time during the on-treatment period, see Section 9.9. All medications starting the same day as the first administration of the study

intervention will be considered as concomitant. Medications starting at the 30th day after the last dose of study intervention will also be considered as concomitant.

A medication may be classified as both concomitant and previous. The respective flags will be derived based on start and end date. See Section 9.10 for derivation.

Concomitant medications will be summarized by number and percentage of participants from the "Concomitant medication details" eCRF page. Anatomical Therapeutic Chemical (ATC) level 2 and PT will be tabulated as given from the WHO-DD dictionary most current version. If any concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted by decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have an ATC classification level 2 coded term, it will be summarized under "Uncoded" category. Each participant will only be counted once, even if he/she received the same medication at different times.

Previous and concomitant medications will be presented in a listing which will include: cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), PT, medication name as provided by the Investigator, start date/time, end date/time (ongoing if applicable), dose, dose units, frequency, route, reason for medication (indication), reason for medication. This listing will be sorted by cohort, participant identifier, start date and time, end date and time and PT.

12.2 Premedications

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

Premedication for bintrafusp alfa will be based on "Premedication Bintrafusp alfa" eCRF page (participants for whom the question "Has the participant received premedications before bintrafusp alfa 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 chemotherapy will be provided. This listing will include cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), 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.

12.3 Concurrent Procedures

Concurrent procedures are reported according to the "Concomitant Procedures Details" eCRF page.

Concurrent procedures will be presented in a listing which will include cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), name of procedure (as provided by the Investigator), start date, end date, indication, reason for procedure, type of specimen collected, specimen property, cytology and diagnosis further to the specimen evaluation by the local (non-study) pathologist. A flag will be displayed to identify each procedure as prior to treatment or on-treatment. This listing will be sorted by cohort, participant identifier, start date, end date and procedure name.

12.4 Subsequent Anticancer Treatment

Subsequent anticancer treatment is collected under the "Anti-cancer Treatment after Discontinuation Details", "Radiotherapy after Discontinuation Details" (Cohort 2: radiotherapy administered while participant is still receiving study intervention is not considered as subsequent anticancer treatment), "Brachytherapy after Discontinuation Details", and "Surgeries after Discontinuation Details" eCRF pages.

Subsequent anticancer treatment will be presented in a listing including cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), preferred term/medication name, treatment type (medication, radiotherapy, surgery or brachytherapy), regimen name (if medication), best response (if medication), start date, end date (if medication, radiotherapy or brachytherapy), radiotherapy site/name of surgery/location (if radiotherapy, surgery or brachytherapy), curative intent of surgery, outcome of surgery. This listing will be sorted by cohort, participant identifier, start date, end date, treatment type, preferred term and medication name.

13 Study Treatment: Compliance and Exposure

The following analyses will be performed on the SAF/FAS study population by cohort overall and for Japanese participants.

For participants enrolled in Cohorts 1A and 1B, bintrafusp alfa is administered every 3 weeks until end of treatment. Cisplatin or carboplatin, paclitaxel and bevacizumab are administered as per standard of care (SoC) practices every 3 weeks until end of treatment.

For participants enrolled in Cohort 2, bintrafusp alfa is administered every 3 weeks until end of treatment. Cisplatin is administered as indicated for SoC treatment as a radiation-sensitizing agent (e.g., every week for 5 weeks). Radiotherapy is administered as per SoC practices (e.g., 5 fractions per week over 5 weeks). Brachytherapy can also be administered per local SoC.

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

All derived variables in this section will be based on "Bintrafusp alfa Administration Details", "Cisplatin Administration Details", "Carboplatin Administration Details", "Paclitaxel Administration Details", "Bevacizumab Administration Details", "Radiotherapy Administration Details" and "Brachytherapy Administration Details" eCRF pages and will include the re-initiation phase if any.

For the analysis of compliance and exposure, a dose is regarded to be administered if the actual dose received is > 0 mg for study interventions other than radiotherapy and brachytherapy, and if the start date is non missing for radiotherapy and brachytherapy.

Imputation for incomplete start and end dates of study treatments are described in Section 9.10.

Duration of Therapy (Weeks) and Number of Administrations for each study intervention

The duration of therapy (weeks) for bintrafusp alfa (Cohort 1A, 1B and 2) and every other study intervention is defined in Cohorts 1A and 1B as:

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

The duration therapy (weeks) for cisplatin when received by participants in Cohort 2 is defined as follows:

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

The duration therapy (weeks) for radiotherapy is defined as follows:

$$\text{duration of therapy} = \left(\frac{\text{date of last administration - date of first administration + 2}}{7}\right)$$

The duration therapy (weeks) for brachytherapy is defined as follows:

$$\text{duration of therapy} = \left(\frac{\text{date of last administration - date of first administration + 1}}{7}\right)$$

For each study intervention, the total number of administrations received will be calculated as the sum of all administrations received during the study.

Cumulative Dose, Dose Intensity, and Relative Dose Intensity

The cumulative actual dose of bintrafusp alfa (mg) is defined as the sum of all actual dose (mg) received by the participant as collected in the eCRF.

The cumulative actual dose of bevacizumab (mg/kg) is defined as the sum over all visits of [actual dose (mg) received at visit *i* / weight (kg) at vist *i*].

The cumulative actual dose of cisplatin and paclitaxel (mg/m²) is defined as below:

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

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

The cumulative dose of carboplatin will be computed in mg and area under the curve (AUC) as the sum of all actual doses (mg and AUC respectively) received by the participant as collected in the eCRF.

The cumulative actual dose of carboplatin (AUC) will also be derived from the actual dose expressed in mg using the Calvert equation as follows:

$$\text{Cumulative actual dose (AUC)} = \sum_{i=1}^{n} \frac{actual\ dose\ (mg)\ received\ at\ visit\ i}{Glomerular\ Filtration\ Rate\ (GFR)\ at\ visit\ i + 25}$$

Where n is the number of visits, and GFR is estimated by calculated creatinine clearance (CrCl) using the Cockcroft-Gault equation:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age [years]}) * \text{weight [kg]} * (0.85 \text{ for females only})}{72 * \text{creatinine [mg/dL]}}$$

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 value observed at the previous visit.

The cumulative actual dose for radiotherapy (Gy) is defined as the sum of all actual doses (Gy) received by the participant as collected in the eCRF.

The cumulative actual dose for brachytherapy (Gy) is defined as the sum of all actual doses (Gy) received by the participant as collected in the eCRF.

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

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

(Cohorts 1A and 1B) The DI of chemotherapy (mg/m²/cycle) (excluding carboplatin) per 3-week period is defined as:

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

(Cohorts 1A and 1B) The DI of carboplatin (mg.min/mL/cycle) per 3-week period is defined as:

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

It will be presented both from the cumulative dose (AUC) as directly provided by the Investigator and from the cumulative dose (AUC) as derived from the actual dose (mg) provided by the Investigator using the Calvert equation.

(Cohorts 1A) The dose intensity (DI) of bevacizumab (mg/kg/cycle) per 3-week period is defined as:

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

(Cohort 2) The dose intensity (DI) of cisplatin (mg/m²/week) per 1-week period is defined as:

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

For participants who reinitiated bintrafusp alfa during the study, the 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 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, mg/kg/cycle or AUC mg.min/mL/cycle) is the planned dose at week 1 day 1 (mg/m², mg/kg or AUC).

As specified for the DI, the RDI of carboplatin will be presented using the actual doses (AUC) as provided by the Investigator in the eCRF and using the actual doses (AUC) as converted from mg to AUC using the Calvert equation.

The following summary table will be provided for each study intervention by cohort:

- Duration of therapy
- Total number of administrations received
- Cumulative actual dose
- DI (not defined for radiotherapy)
- RDI as continuous variable (not defined for radiotherapy), and categorized (< 80%, 80%-90%, > 90%)

Dose Modification

As per protocol, no dose modification is allowed for bintrafusp alfa. No summaries will be provided.

For all other study interventions, a dose reduction is observed when the answer to the question "Is there a change in dose?" = "Dose adjusted" and the planned dose collected at the respective visit is lower than that observed at the previous visit.

The number of participants with at least one dose reduction, reasons for dose reduction (Adverse event / Other), as well as a categorization of the number of administrations with reduced dose (1, 2, ≥ 3) will be summarized for each chemotherapy and bevacizumab by cohort.

Therapy Delays

Therapy delays will be derived for each administration of bintrafusp alfa, chemotherapy and bevacizumab as follows:

- Therapy delay for bintrafusp alfa = start date of current infusion – start date of the previous infusion – 21
- (Cohorts 1A and 1B) Therapy delay for chemotherapies and bevacizumab = start date of current infusion – start date of the previous infusion – 21
- (Cohort 2) Therapy delay for cisplatin = start date of current infusion – start date of the previous infusion – 7

If the result is > 0 day, this will be categorized as a delay. A participant may have more than one treatment delay throughout the study.

The following will be summarized for each study intervention (radiotherapy and brachytherapy excluded) by cohort:

- Number of participants with at least one delay, with no delay
- The maximum length of delay per participant (no delay, 1-3 days, 4-8 days, 9-15 days, ≥ 16 days)

Temporary Interruptions of Infusion

Study drug infusion temporarily interrupted as recorded on each study intervention administration details page of the eCRF will be used for analysis.

For each study intervention (excluding radiotherapy and brachytherapy), the number and percentage of participants with at least one temporary interruption and a summary of the reason(s) for temporary interruption (Adverse event, Other) will be provided.

Individual Data Listings

A listing of treatment exposure data will be provided for each study intervention. For bintrafusp alfa, chemotherapies and bevacizumab, it will include: cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), visit, infusion start date and time, infusion end date and time, change in dose and reason for change, infusion rate, planned dose (as applicable), actual dose, route, administration modification and reason for modification, treatment delay (days).

For radiotherapy, the listings will include: cohort, participant identifier, age, race, ethnicity, visit, start date, end date, number of fractions and total dose.

For brachytherapy, the listings will include: cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), visit, start date, end date, therapy type and total dose.

Administrations received during the reinitiation phase will be flagged in the listings. These listings will be sorted by cohort, participant identifier, administration start date and administration end date.

An additional listing of individual treatment exposure summary measures will be provided including cohort, participant identifier, age, race, ethnicity, study intervention, duration of therapy (weeks), total number of administrations received, cumulative dose of therapy (unit), dose intensity (unit), and relative dose intensity (%).

Chemotherapy Switch

A listing of chemotherapy switches will be provided based on the “Chemotherapy Switch” eCRF page. This listing will include cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), initial and new chemotherapy regimens and reason for switch.

14 Efficacy Analyses

CCI [redacted] They will be conducted on the SAF/FAS analysis set for each cohort independently.

CCI [redacted]

CCI

[redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

Kaplan-Meier Analysis

Kaplan-Meier estimates (product-limit estimates) will be presented by cohort together with a summary of associated statistics including the median PFS time with two-sided 95% CIs. In

CCI

[redacted]

CCI [redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

15 Safety Analyses

Safety analyses will be done on the SAF/FAS analysis set by cohort and according to the as-treated principle apart from the DLT analysis described in Section 15.1 where the DLT analysis set will be used. The analyses will also be specifically provided for Japanese participants within each cohort.

15.1 Dose-limiting Toxicities (Primary Endpoint)

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

A table of the occurrence of DLT AE will be provided by cohort including:

- Number and percentage of participants who experienced a DLT during the DLT evaluation period
- Number of DLTs per participant experienced during the DLT evaluation period (1 / 2 / ≥3)
- DLT experienced during the DLT evaluation period by SOC and PT based on the latest available MedDRA version.

A listing of DLTs will also be provided with the relevant information (see Section 15.2.1 for the variables to be included).

15.2 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. AE 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.

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 Bintrafusp alfa" = "Related" on "Adverse Event Details" eCRF page) and those of unknown relationship (i.e., no answer to the question "Relationship with Bintrafusp alfa").

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

Chemotherapy Related Adverse Events are those AEs with relationship to cisplatin or carboplatin or paclitaxel 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 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").

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

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

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 paclitaxel 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 paclitaxel consider answer to the question "Action(s) taken with Paclitaxel" = "Dose reduced" on "Adverse Event Details" eCRF page).

Adverse Events Leading to Dose Reduction of Bevacizumab are defined as AEs where "Action(s) taken with Bevacizumab" = "Dose reduced" on the "Adverse Event Details" eCRF page.

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 paclitaxel 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 paclitaxel consider answer to the question "Action(s) taken with Paclitaxel" = "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 paclitaxel (definition above).

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

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

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

Adverse Events Leading to Temporary Treatment Discontinuation: AEs leading to temporary discontinuation of at least one of the study interventions.

Adverse Events Leading to Permanent Discontinuation of Bintrafusp alfa: AEs leading to permanent discontinuation of bintrafusp alfa (i.e. answer to the question "Action(s) taken with Bintrafusp alfa" = "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 paclitaxel 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 paclitaxel consider answer to the question "Action(s) taken with Paclitaxel" = "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 paclitaxel (definition above).

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

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

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

Adverse Events Leading to Permanent Treatment Discontinuation: AEs leading to permanent discontinuation of at least one of the study interventions.

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) (see Section 15.3.3.1)
- Immune-related adverse events (irAE) (see Section 15.3.3.2)

- TGF-β inhibition mediated Skin Reaction (see Section 15.3.3.3)
- Anemia (see Section 15.3.3.4)
- Bleeding events (see Section 15.3.3.5)

15.2.1 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.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same recording period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

In case a participant has same events with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

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

- TEAEs
- Bintrafusp alfa related TEAEs
- Chemotherapy related TEAEs
- Bevacizumab related TEAEs
- Radiotherapy related TEAEs
- Brachytherapy related TEAEs
- Serious TEAEs
- Bintrafusp alfa related serious TEAEs
- Chemotherapy related serious TEAEs
- Bevacizumab related serious TEAEs
- Radiotherapy related serious TEAEs
- Brachytherapy related serious TEAEs
- 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)

- Bevacizumab related TEAEs NCI-CTCAE severity grade (≥3, ≥4)
- Radiotherapy related TEAEs NCI-CTCAE severity grade (≥3, ≥4)
- Brachytherapy related TEAEs NCI-CTCAE severity grade (≥3, ≥4)
- TEAEs leading to death
- Bintrafusp alfa related TEAEs leading to death
- Chemotherapy related TEAEs leading to death
- Bevacizumab related TEAEs leading to death
- Radiotherapy related TEAEs leading to death
- Brachytherapy related TEAEs leading to death
- Adverse events of special interest (related and not related as assessed by the Investigator):
    - Infusion-related reaction (IRR)
    - Immune related AEs (irAEs)
    - TGF-β inhibition mediated skin adverse events
    - Anemia
    - Bleeding events
- Bintrafusp alfa related adverse events of special interest:
    - Infusion-related reaction (IRR)
    - Immune related AEs (irAEs)
    - TGF-β inhibition mediated skin adverse events
    - Anemia
    - Bleeding events

Tables for TEAEs frequency corresponding to each category below will be provided by MedDRA primary SOC (ordered alphabetically) and PT (ordered alphabetically).

- TEAEs
- Bintrafusp alfa related TEAEs
- Chemotherapy related TEAEs
- Bevacizumab related TEAEs
- Radiotherapy related TEAEs
- Brachytherapy related TEAEs
- TEAEs leading to death
- Bintrafusp alfa related TEAEs leading to death
- Chemotherapy related TEAEs leading to death

- Bevacizumab related TEAEs leading to death
- Radiotherapy related TEAEs leading to death
- Brachytherapy related TEAEs leading to death

The following frequency tables will be provided by worst grade (≥ 3, ≥ 4), 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
- Bevacizumab related TEAEs by worst grade, SOC, and PT
- Radiotherapy related TEAEs by worst grade, SOC, and PT
- Brachytherapy related TEAEs by worst grade, SOC, and PT

Clinicaltrials.gov and EudraCT Requirements

Summary tables for non-serious TEAEs excluding SAEs (tabulated by SOC and PT) applying frequency threshold of 5% in at least one of the cohorts will be provided.

The following listings will be provided:

- Listing of all AE (whether treatment-emergent or not): TEAEs and AE occurring during reinitiation phase will be flagged
- Listing of TEAEs (AEs occurring during reinitiation phase will be flagged)
- 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 (AEs occurring during reinitiation phase will be flagged)
- Listing of AEs with onset or worsening occurring during the reinitiation of the treatment

Each AEs listing will include the following information: cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), first and last administration dates of each study intervention, preferred term, reported term for the AE, start or change date, end date (ongoing if missing), 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 each study intervention, toxicity grade, causality factor, action(s) taken with each study intervention, other action(s) taken, seriousness (Y/N), AESI infusion-related (Y/N), AESI immune-related (Y/N), skin AESI (Y/N), rash with hyperkeratosis, KA and SCC of skin (Y/N), immune-related skin AEs possibly mediated by PD-[L]1 inhibition (Y/N), anemia AESI (Y/N), bleeding (Y/N), dose limiting toxicity AESI (Y/N). AEs occurring after COVID-19 pandemic start and participants who switched chemotherapy will be flagged. Each listing will be sorted by cohort, participant identifier, start date, end date and preferred term.

Evaluation of COVID-19 effects on AEs

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

- An overview table of treatment-emergent AEs associated to COVID-19 by MedDRA primary SOC, high level terms (HLT) and PTs (ordered alphabetically).
- A listing of COVID-19 related AEs. The following listing will be generated using the 'COVID-19 related terms MedDRA 23.0 update Spreadsheet' or later version, considering all 'search terms for COVID-19-related' ='Y'. Same information as for the listing of all AEs will be provided.

15.2.2 Adverse Events Leading to Discontinuation of Study Intervention

A table presenting the overview 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 bevacizumab
- TEAEs leading to temporary discontinuation of radiotherapy
- TEAEs leading to temporary discontinuation of brachytherapy
- Bintrafusp alfa related TEAEs leading to temporary discontinuation of bintrafusp alfa
- Chemotherapy related TEAEs leading to temporary discontinuation of chemotherapy
- Bevacizumab related TEAEs leading to temporary discontinuation of bevacizumab
- Radiotherapy related TEAEs leading to temporary discontinuation of radiotherapy
- Brachytherapy related TEAEs leading to temporary discontinuation of brachytherapy
- TEAEs leading to permanent discontinuation of at least one study intervention
- TEAEs leading to permanent discontinuation of bevacizumab
- TEAEs leading to permanent discontinuation of radiotherapy
- TEAEs leading to permanent discontinuation of brachytherapy
- Bintrafusp alfa related TEAEs leading to permanent discontinuation of bintrafusp alfa
- Chemotherapy related TEAEs leading to permanent discontinuation of chemotherapy
- Bevacizumab related TEAEs leading to permanent treatment discontinuation of bevacizumab
- Radiotherapy related TEAEs leading to permanent treatment discontinuation of radiotherapy
- Brachytherapy related TEAEs leading to permanent treatment discontinuation of brachytherapy

- TEAEs leading to dose reduction of at least one study intervention
- TEAEs leading to dose reduction of at least one chemotherapy
- TEAEs leading to dose reduction of bevacizumab
- Chemotherapy related TEAEs leading to dose reduction of chemotherapy
- Bevacizumab related TEAEs leading to dose reduction of bevacizumab

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
- Bintrafusp alfa related TEAEs leading to temporary discontinuation of bintrafusp alfa
- TEAEs leading to permanent discontinuation of bintrafusp alfa
- Bintrafusp alfa related TEAEs leading to permanent discontinuation of bintrafusp alfa

A listing of TEAEs leading to permanent treatment discontinuation and a listing of TEAEs leading to temporary discontinuation will also be provided with the relevant information (see Section 15.2.1).

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

15.3.1 Deaths

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

The following summaries will be provided:

- Number and percentage of deaths
- Number and percentage of deaths within 30 days after the last dose of study intervention
- Number and percentage of deaths within 60 days after the first dose of study intervention
- Primary reason for death
    - Progressive 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 the following information: cohort, participant identifier, analysis sets in which the participant is included, age, race, ethnicity (Japanese/Non-Japanese), dates of first/last doses of

each study intervention, number of infusions, day relative to the first and the last infusion, autopsy (yes/no/unknown), AEs with fatal outcome (list PTs of AEs with outcome=Fatal, as well as Grade 5 AEs or Serious AEs resulting in death), flag for death within 30 days of last dose of study intervention and flag for death within 60 days of first dose of study intervention.

15.3.2 Serious Adverse Events

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

- Serious TEAEs
- Bintrafusp alfa related serious TEAEs
- Chemotherapy related serious TEAEs
- Bevacizumab related serious TEAEs
- Radiotherapy related serious TEAEs
- Brachytherapy related serious TEAEs

A listing of serious TEAEs will also be provided including a flag identifying AEs occurring during the reinitiation phase (see Section 15.2.1).

15.3.3 Adverse Events of Special Interest

A listing containing all pre-specified PT search terms that will be used during the identification process of the adverse events of special interest will be provided.

15.3.3.1 Infusion-Related Reaction (IRR) including Immediate Hypersensitivity

IRRs are defined as adverse events with PTs according to a pre-specified MedDRA search list, and are divided into two subcategories: “Reactions” and “Signs and symptoms” based on the temporal relationship between the day of the infusion and onset of the event:

Reactions of IRRs: should be considered when the onset is on the day of infusion (during or after the infusion if timing related to the infusion is available) 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 the onset is on the day of infusion (during or after the infusion if timing related to the infusion is available) and resolved completely, with the end date on the same day of the infusion or the day after for any of the following: pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain and urticaria.

Note: all infusions (i.e., of bintrafusp alfa, chemotherapies and bevacizumab) are to be considered.

IRRs, overall and by subcategories, will be summarized by the following variables:

- Number of participants with at least one IRR by the worst NCI-CTCAE toxicity grade (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, missing grade)
- Number of participants with IRR leading to permanent discontinuation of at least one study intervention
- Time related to first onset (infusion 1, infusion 2, infusion 3, infusion 4 or later). The events will be assigned to the actual drug infusions that the participant received, not to the planned dates. An IRR is assigned to a drug infusion if its onset is on the same date (but not before dosing when timing related to the infusion is available) or the day following the drug infusion.

A frequency table of IRR AEs by worst grade (any grade, Grade ≥ 3, Grade ≥ 4, Grade 5), SOC, and PT will also be provided.

A listing of IRRs will be provided with the relevant information (see Section 15.2.1).

15.3.3.2 Immune-related Adverse Events

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

- The AE PT matches a PT on the list of pre-selected MedDRA terms.
- The AE onset or worsening occurs during the expanded on-treatment period for irAEs (see Section 9.9).
- On the "AE" eCRF page, the question "Were corticosteroids, Immunosuppressants, hormonal therapy (e.g., Thyroid) or Insulin applied?" has the answer "Yes" selected.
- On the "imAE SPECIFIC QUESTIONS" eCRF page, either:
- The question "Does any of the following provide a clear etiology for the event, other than immune related AE?" 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

- 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.

Where 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, other than immune related AE?" (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 (i.e., at least one (clear) etiology of the event is provided) as the answer to the

question "Does any of the following provide a clear etiology for the event, other than immune related AE?", the event will be considered as a non-irAE.

PTs will be compiled into categories (subcategories): Immune-related rash, Immune-related colitis, Immune-related pneumonitis, Immune-related hepatitis, Immune-related nephritis and renal dysfunction, Immune-related endocrinopathies (adrenal insufficiency, hypogonadism, pituitary dysfunction, Type 1 diabetes mellitus, thyroid disorders), and Other immune-related adverse events (Anemia, Encephalitis, GVHD, Guillain-Barre Syndrome, Myasthenic syndrome, Myocarditis, Myositis, Neurologic events, Pancreatitis, Uveitis, Vasculitis, Other). PTs belonging to the category "Immune related endocrinopathies – Thyroid disorders" will also be compiled into sub-subcategories: Hyperthyroidism, Hypothyroidism, Thyroiditis.

irAEs will be summarized by the following variables:

- Any irAEs
- irAEs by the worst grade (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, missing grade)
- irAEs leading to permanent discontinuation of at least one study intervention
- Serious irAEs

A frequency table of irAEs by worst grade (any grade, Grade ≥ 3, Grade ≥ 4, Grade 5), category, subcategory (for immune-related endocrinopathies and other immune-related adverse events), sub-subcategory (for immune-related endocrinopathies – thyroid disorders) and PT will also be provided.

A listing of irAEs will also be provided with the relevant information (see Section 15.2.1).

15.3.3.3 TGF-β inhibition mediated Skin Adverse Events

To identify TGFβ inhibition mediated skin adverse events, MedDRA PT queries will be used to search for skin AEs of interest in the clinical database. PTs will be compiled into two categories: Narrow definition, and Broad definition. Further details (e.g., MedDRA PT queries) are regularly updated based on the current MedDRA version.

Narrow definition:

- Keratoacanthoma
- Squamous cell carcinoma of skin

Broad definition has additional PTs:

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

The overall summary of skin TEAE will include the following categories for narrow and broad definition:

- All skin TEAEs
- All skin TEAEs by worst grade (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, missing grade)
- Skin TEAEs leading to permanent discontinuation of at least one study intervention
- Serious skin TEAEs

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

A listing of skin AEs will also be provided. This listing will specifically include, for the AEs identified from the PT list, the number of lesions, if a biopsy or an excision was done and if it confirmed the diagnosis, and the location for each lesion coming from eCRF page "TGFβ MEDIATED SKIN REACTION" if available.

15.3.3.4 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)

A frequency table of treatment-emergent anemia AEs by worst grade (any grade, Grade ≥ 3, Grade ≥ 4, Grade 5), SOC and PT will be provided.

A listing of all anemia AEs will also be provided with the relevant information (see Section 15.2.1). Bintrafusp alfa related anemia will be flagged.

15.3.3.5 Bleeding Events

Bleeding events are AEs belonging to the MedDRA SMQ Haemorrhage terms (excluding laboratory terms). Bleeding treatment-emergent events and bintrafusp alfa related bleeding events will be tabulated by SOC and PT sorted by alphabetical order. The worst grade per participant, per SOC, and per PT will be reported:

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

- Grade 4
- Grade 5

15.4 Clinical Laboratory Evaluation

Baseline and on-treatment laboratory values (including corresponding normal ranges), converted into standard units, will be used for analysis.

Laboratory results will be classified according to the NCI-CTCAE criteria version 5.0 (see Appendix 2). Some of the toxicity gradings are based on laboratory measurements in conjunction with clinical findings. Non-numerical qualifiers will not be taken into consideration in the derivation of CTCAE criteria (e.g., hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived).

Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

Values below the detection limit will be imputed by half of the detection limit. In case just a text value with an "> x" is reported it will be analyzed as +1 significant digit, e.g., "> 7.2 mmol" will be analyzed as 7.3.

The following figures will be provided:

- Boxplots of the laboratory values by timepoint (only baseline and on-treatment scheduled timepoints with at least 3 values will be presented)
- Boxplots of the changes from baseline by timepoint (only on-treatment scheduled timepoints with at least 3 values will be presented)

Boxplots for laboratory parameters where toxicity grades are defined based on the ratio of the parameter value and the upper limit of normal (ULN) will be displayed using the ratio of the measured value over ULN. This comprises alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), activated partial thromboplastin time (aPTT), bilirubin, and creatinine.

Qualitative data based on reference ranges will be described according to the categories (i.e., Abnormal, Normal). Abnormalities classified according to NCI-CTCAE toxicity grading version will be described using the worst on-treatment grade. For those parameters which are graded with two directions of toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (e.g., hypokalemia) grades at Baseline and post-baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (e.g., hyperkalemia), and vice versa.

For WBC differential counts (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil 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)

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:
- derived absolute count does not meet Grade 2-4 criteria, and
- % value < % LLN value, and
- derived absolute count ≥ 800/mm^3
- Neutrophil count decreased
    - derived absolute count does not meet Grade 2-4 criteria, and
    - % value < % LLN value, and
    - derived absolute count ≥ 1500/mm^3

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-CTCAE grades available

The following summaries will be provided for each gradable laboratory parameter:

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

The above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE, i.e.:

- Hematology:

  Hemoglobin (HB) (anemia), Leukocytes (white blood cell decreased), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased).

- Serum Chemistry:

  Albumin (hypoalbuminemia), Alkaline Phosphatase (alkaline phosphatase increased), Alanine Aminotransferase (ALT) (ALT increased), Amylase (serum amylase increased), Aspartate Aminotransferase (AST) (AST increased), Total Bilirubin (blood bilirubin increased, Cholesterol (cholesterol high), Creatinine (creatinine increased), Creatine Kinase (CPK increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Magnesium (hypomagnesemia/hypermagnesemia), Calcium

(hypocalcemia/ hypercalcemia), Glucose (hypoglycemia), Gamma Glutamyl Transferase (GGT) (GGT increased), Lipase (lipase increased), Triglycerides (hypertriglyceridemia).

- Urinalysis:

  Protein (proteinuria)

Laboratory parameters with NCI-CTCAE grades that cannot be derived from laboratory values

For all non-gradable parameters, the following summaries will be provided:

- Number and percentage of participants by worst on-treatment value (classified as low, normal, high)

  In case the worst on-treatment value for a parameter can be either the lowest or the highest, both directions will be presented.

- Shift from baseline to highest/lowest on-treatment value (classified as normal, high, low)

This applies to the following parameters:

- Hematology:

  Hematocrit, Red Blood Cell (RBC), Reticulocytes, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC).

- Serum Chemistry:

  Chloride, C-Reactive Protein, Glucose (hyperglycemia), Lactate Dehydrogenase (LDH), Phosphates (hypophosphatemia/hyperphosphatemia), Total Protein, Total Urea, Uric Acid.

Separate listings of hematology and biochemistry will be provided. Each listing will include: cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), first/last date of study intervention, laboratory parameter (units), visit, date/time (study day), SI value, change in SI value from baseline, LLN, ULN, indicator of normal range (low, normal, high), toxicity grade(s) according to NCI-CTCAE (when applicable). Highest and lowest on-treatment value, baseline and post-baseline values after the on-treatment period as well as participants who switched chemotherapy will also be flagged.

The following coagulation parameters will also be presented in a listing: prothrombin time, prothrombin time/standard prothrombin time, aPTT, aPTT/standard thromboplastin time, INR.

Liver function tests

ALT, AST, and total bilirubin will be used to assess possible drug induced liver toxicity. The ratios of test result over ULN will be calculated and classified for these three parameters during the on-treatment period.

The number and percentage of participants within each of the following liver function categories during the on-treatment period will be provided:

- ALT <3×ULN, ALT ⩾ 3×ULN, ALT ⩾ 5×ULN, ALT ⩾ 10×ULN, ALT ⩾ 20×ULN
- AST <3×ULN, AST ⩾ 3×ULN, AST ⩾ 5×ULN, 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
- BILI < 2×ULN, BILI ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and BILI ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and BILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and BILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and BILI ≥ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and BILI ≥ 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 during the on-treatment period, 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 participants with possible Gilbert's cholestasis; the right upper quadrant are the possible Hy's Law participants; the right lower quadrant is possible Temple's Corollary (participants with ALT ≥ 3×ULN but not satisfying Hy's Law).

The same plot will be provided for AST.

In addition, a listing of all total bilirubin, ALT, AST and ALP values for participants with an on-treatment total bilirubin ≥ 2×ULN, ALT ≥ 3×ULN or AST ≥ 3×ULN will be provided.

Routine urinalysis

All test results for routine urinalysis will be presented in dedicated listings:

- Urinalysis full parameters: pH, specific gravity, protein, glucose, ketones, nitrite, leukocytes by dipstick, occult blood, urobilinogen, bilirubin, color
- Microscopic examination: erythrocytes, leukocytes, epithelial cells, bacteria, crystals, casts

Hormonal tests

All results for thyrotropin, thyroxine free (free T4) will be presented in a listing.

Pregnancy tests

All results from serum or highly sensitive urine β-hCG pregnancy tests will be presented in a listing.

Other screening tests

All other screening tests results will be presented in dedicated listings:

- Hepatitis screening: hepatitis B virus surface antigen, hepatitis B virus core antibody and hepatitis C virus antibody; hepatitis B virus DNA, hepatitis C virus RNA
- HIV test, HIV RNA viral load, CD4 lymphocyte count
- M. tuberculosis IFN gamma response by T-SPOT ELISPOT; tuberculosis skin test; M. tuberculosis IFN gamma response by QuantiFERON TB Gold ELISA

15.5 Vital Signs

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

- Summary statistics over time (only present baseline value and on-treatment scheduled visits with at least three observations for the vital sign)

The following potentially clinically significant abnormalities observed during the on-treatment period will 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

A listing of vital signs will be provided including cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), vital sign parameter, visit, timepoint, date, time, value, unit, and change from baseline. Baseline values and post-baseline values collected after the on-treatment period will be flagged.

A second listing will also be provided for participants with at least one potentially clinically significant abnormality observed during the on-treatment period. For each participant, all results for a specific vital sign parameter with at least one on-treatment potentially abnormal and clinically significant value will be displayed. This listing will include cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), vital sign parameter, visit, timepoint, date, time, value, unit, and change from baseline. Baseline values and post-baseline values collected after the on-treatment period as well as participants who switched chemotherapy will be flagged.

15.6 Other Safety or Tolerability Evaluations

ECG

Single 12-lead ECGs will be performed at screening then if clinically indicated and will be collected on the "Electrocardiogram" eCRF page.

A listing of ECG values will be provided including cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), ECG parameter and unit, visit/time (study day), ECG date, value, change from baseline. Baseline values and post-baseline values collected after the on-treatment period as well as participants who switched chemotherapy will be flagged. Qualitative ECG results will also be provided.

ECOG Performance Status

The ECOG Performance Status will be described from the data collected on the "ECOG Performance Status" eCRF page.

ECOG performance status observed at each timepoint will be presented in a listing including cohort, participant identifier, age, race, ethnicity (Japanese/Non-Japanese), visit, date of visit, ECOG performance status. Baseline value and post-baseline values collected after the on-treatment period as well as participants who switched chemotherapy will be flagged.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

The analyses described in this section will be performed by the Clinical PK/PDyn 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 SAF/FAS. Summaries and statistical analyses will be based on the PKAS. Only subgroup sample size with a minimal 3 subjects will be displayed.

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

16.1.1 Missing PK Data

Concentrations below the lower limit of assay quantification

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

Pharmacokinetic concentrations <LLOQ, which are before the last quantifiable data point, will be taken as zero for calculating the area under the serum concentration-time curve of single dose profiles. Concentrations <LLOQ which occur after the last quantifiable data point will not be considered in the calculation of the terminal first order rate constant (λ_z).

Deviations, missing concentrations, and anomalous values

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

Exclusions for concentration data descriptive statistics

- Positive pre-dose values on day 1
- Concentration observed at the end of infusion (CEOI) <LLOQ
- In case of missed dose, exclude all concentrations until intended dosing is resumed
- Concentration observed at the end of the dosing interval (Ctrough) values in case samples are taken at least 7 days late or early

Exclusions for Non-Compartmental Analysis (NCA)

- Positive pre-dose values on day 1
- CEOI <LLOQ, which will be excluded from parameter derivation
- In case of missed dose, exclude all concentrations until intended dosing is resumed

Any other PK concentrations that appear implausible to the Pharmacokineticist/PK/PDyn Data Analyst without any documentation to explain the implausible value must not be excluded from the analysis. Any implausible data will be documented in the relevant listing/table.

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

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

16.1.2 Descriptive PK Analysis

Presentation of PK Concentration Data

A by-participant listing will present PK sample times, time deviations, and concentrations based on the SAF/FAS. Concentrations will be reported with the same precision as the source data.

Tables

Pharmacokinetic concentration data will be presented in tables and descriptively summarized by treatment and cohort (as appropriate) (cohorts 1A and 1B separately, and 1A/1B pooled), day, and nominal time using: n, arithmetic mean (Mean), StD, Min, median, Max, geometric mean (GeoMean), StD of log-transformed data (logStD), coefficient of variation (CV%), and geometric coefficient of variation (GeoCV%). Summaries will be based on the PKAS.

Additional table(s) will summarize PK concentrations with further stratification by ADA subsets ever positive and never positive, based on the PKADA. Additional table(s) will summarize PK concentrations with stratification by ethnicities as applicable, based on the PKAS. Only subgroup sample size with a minimum of 3 subjects will be displayed.

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

Mean, Min, median, Max, GeoMean:	3 significant digits
StD, logStD:	4 significant digits
CV%, GeoCV%:	1 decimal place

Figures

Individual PK concentration-time profiles showing all subjects by treatment and cohort will be created using the actual time points and the numeric concentration data. Plots of individual data will be based on the SAF/FAS. Median, GeoMean, and Mean concentration-time profiles by treatment and cohort (cohorts 1A and 1B separately, and 1A/1B pooled) 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 and GeoMean PK plots will include StD or logStD error bars when plotted on a linear scale. Only Mean/GeoMean/median data points with $n \geq 3$ will be shown. Summary (Mean/median) PK plots will be based on the PKAS.

Additional figures will present Mean, GeoMean, and median PK concentration-time profiles with further stratification by ADA subsets ever positive and never positive, based on the PKADA. Additional figures will present Mean, GeoMean, and median PK concentration-time profiles with stratification by race/ethnicities as applicable, based on the PKAS. Only subgroup sample size with a minimum of 3 subjects will be displayed.

16.1.3 Pharmacokinetic Non-Compartmental Analysis

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), following the first dose only unless specified otherwise.

C_{max}	Maximum observed concentration in serum
t_{max}	Time to reach C_{max}
AUC_{0-t}	Area under the serum concentration-time curve from time zero to the last quantifiable concentration
C_{trough}	The concentration observed at the end of the dosing interval, before next dosing (serum trough concentration). This PK parameter will be taken directly from the observed bintrafusp alfa concentration-time data following first and multiple doses.
C_{EOI}	The concentration observed at the end of infusion. This PK parameter will be taken directly from the observed bintrafusp alfa concentration-time data following first and multiple doses.

When applicable the following parameters will also be calculated:

$AUC_{0-\infty}$	Area under the serum concentration-time curve from time zero extrapolated to infinity. $AUC_{0-\infty} = AUC_{0-t} + AUC_{extra}$, where $AUC_{extra} = C_{lastpred}/ \lambda_z$.
$AUC_{extra\%}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation, calculated by $(1 - [AUC_{0-t}/AUC_{0-\infty}])\times100$. If $AUC_{extra\%}$ is greater than 20.0%, $AUC_{0-\infty}$ and λ_z and parameters derived from them (e.g. $t_{1/2}$, CL, and V_z) will be included in the Phoenix® WinNonlin® parameter outputs, summaries, and inferential statistics, but will be flagged.
AUC_{0-504}	Area under the serum concentration-time curve from time zero to 504 -hours. This parameter will be calculated using nominal time at 504 -hours, by extrapolation/interpolation as necessary.
$t_{1/2}$	Elimination half-life, calculated by $\ln2/\lambda_z$
λ_z	Terminal 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
CL	Total body clearance of drug from serum. CL = Dose i.v. / $AUC_{0-\infty}$
V_z	Volume of distribution during terminal phase. V_Z = Dose/($AUC_{0-\infty}$ * λ_z)

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- The time interval (h) of the log-linear regression to determine λ_z ($t_{½}$, Interval).
- Number of data points ($t_{½}$, N) included in the log-linear regression analysis to determine λ_z.
- Goodness of fit statistic (Rsq) for calculation of λ_z. If Rsq is <0.800, λ_z and parameters derived from it (e.g. $t_{1/2}$, $AUC_{0-\infty}$, CL, and V_z) will be included in the Phoenix® WinNonlin® parameter outputs, summaries, and inferential statistics, but will be flagged.

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 twofold the resulting $t_{1/2}$ itself. If this is <2.00 * $t_{1/2}$, then λ_z and parameters derived from it (e.g. $t_{1/2}$, $AUC_{0-\infty}$, CL, and V_z) will be included in the Phoenix® WinNonlin® parameter outputs, summaries, and inferential statistics, but will be flagged. Phoenix® WinNonlin® best fit methodology will be used as standard. The last quantifiable concentration should always be included in the regression analysis, while the concentration at t_{max} and any concentrations <LLOQ which occur after the last quantifiable data point should not be used.

The calculation of the areas under the serum concentration-time curve 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. The pre-dose samples will be considered as if they had been taken simultaneously with the administration.

Presentation of PK Parameter Data

Individual PK parameters will be listed by nominal study day based on the SAF/FAS.

Pharmacokinetic parameters will be reported to 3 significant figures. In export datasets, as well as in the SDTM PP/XD 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.

Pharmacokinetic parameter data will be listed and descriptively summarized in tables by treatment (dose, e.g., 2400 mg) and cohort separately (cohorts 1A and 1B separately, and 1A/1B pooled), and day using: n, Mean, StD, CV%, Min, median, Max, GeoMean, logStD, GeoCV%, and the 95% CI for the GeoMean (LCI 95% GM, UCI 95% GM). Summaries will be based on the PKAS.

Additional table(s) will summarize NCA parameters following first infusion, C_{trough}, and C_{EOI} with further stratification by ADA subsets ever positive and never positive, based on the PKADA. Additional table(s) will summarize NCA parameters following first infusion with stratification by race/ethnicities as applicable, based on the PKAS. Additional table(s) may be added, if warranted, to summarize C_{trough} and C_{EOI} with stratification by race/ethnicities as applicable, based on the PKAS. Additional table(s) will summarize NCA parameters following first infusion with further sub-stratification by ADA subsets ever positive and never positive and, nested within,

race/ethnicities as applicable, based on the PKADA. Additional table(s) may be added, if warranted, to summarize C_{trough} and C_{EOI} with further sub-stratification by ADA subsets ever positive and never positive and, nested within, race/ethnicities as applicable, based on the PKADA. Additional table(s) will summarize C_{trough} of ADA ever positive subjects with further sub-stratification by ADA subgroups (e.g. Pre-existing, Treatment boosted, Treatment emergent, Transient positive, Persistent positive), based on the PKADA. Additional table(s) will summarize C_{trough} of ADA Treatment-emergent subjects by PK day relative to day of seroconversion, based on the PKADA. Only subgroup sample size with a minimum of 3 subjects will be displayed. All above will be summarized by treatment (dose, e.g., 2400 mg across cohorts) and cohort separately (cohorts 1A and 1B separately, and 1A/1B pooled).

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, logStD:	4 significant digits
CV%, GeoCV%:	1 decimal place

Individual C_{trough} and C_{EOI} values will be plotted against actual time points on a linear scale, for all subjects by treatment and cohort. Plots of individual data will be based on the SAF/FAS.

Arithmetic mean C_{trough} ±StD and C_{EOI} ±StD and GeoMean C_{trough} ±logStD and C_{EOI} ±logStD will be plotted versus nominal day on a linear scale. Median C_{trough} and C_{EOI} will also be plotted versus nominal day on a linear scale. Summary plots will be based on the PKAS. Additional figures will present Mean, GeoMean, and median C_{trough} and C_{EOI} with further stratification by ADA subsets ever positive and never positive, based on the PKADA. Additional figures may be added, if warranted, to present Mean, GeoMean, and median C_{trough} and C_{EOI} with stratification by ethnicities as applicable, based on the PKAS. Only subgroup sample size with a minimum 3 subjects will be displayed.

For ADA treatment-emergent subjects with at least one C_{trough} measurement before and after ADA seroconversion, individual C_{trough} will be plotted versus relative PK day for each cohort (for readability, split further into groups of 10 subjects or fewer as needed). Box plots will be prepared for C_{trough} versus relative PK day.

All above will be summarized by treatment (dose, e.g., 2400 mg across cohorts) and cohort separately (cohorts 1A and 1B separately, and 1A/1B pooled).

The Phoenix WinNonlin NCA Core Output will be provided in a separate listing.

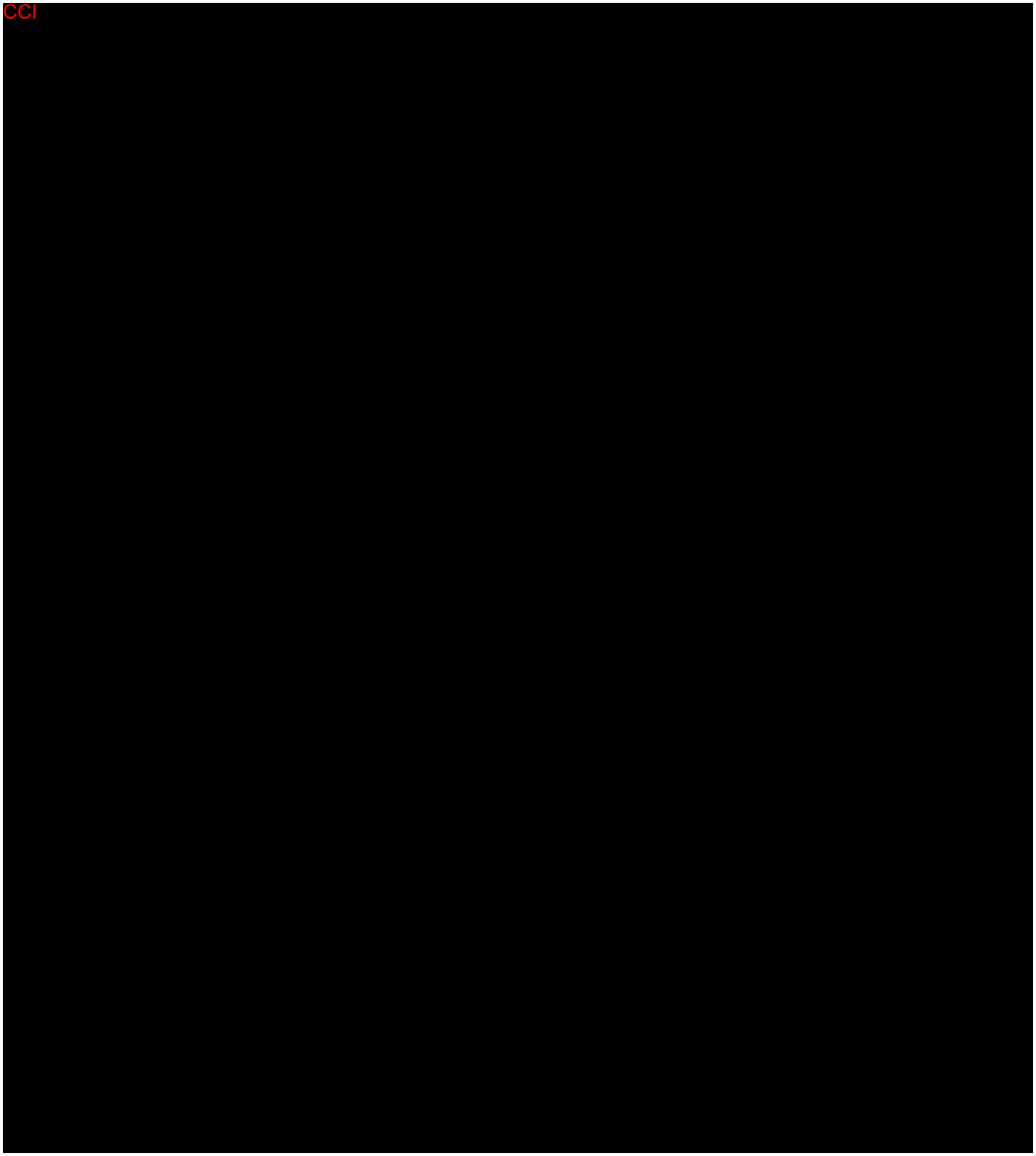
CCI [redacted]

[redacted]

16.3 Patient-reported Outcome

Not applicable.

CCI



CCI [redacted]

[redacted]

CCI [redacted]

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18 Appendices

18.1.1 Appendix 1 - List of Important Protocol Deviations

See document: *List of Protocol Deviations – Appendix 1*

18.1.2 Appendix 2 - Definition of NCI-CTCAE Grading

See document: *NCI CTCAE V5.0 guidance.xlsx.*