NCT04916002

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title:	**A MULTICENTER, OPEN-LABEL, PHASE 2 STUDY OF INTRATUMORAL VIDUTOLIMOD (CMP-001) IN COMBINATION WITH INTRAVENOUS CEMIPLIMAB IN SUBJECTS WITH SELECTED TYPES OF ADVANCED OR METASTATIC CANCER**
Compound:	CMP-001
Protocol Number:	CMP-001-009
Clinical Phase:	**Phase 2**
Sponsor:	Regeneron Pharmaceuticals, Inc.
Versions/Dates:	Original Statistical Analysis Plan /November 18, 2024

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP), and agreed on the planned analysis defined in this document for reporting.

See appended electronic signature page

Study Biostatistician

[redacted]

See appended electronic signature page

Study Medical Director

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Definition
BOR	best overall response
CTCAE v5.0	Common Terminology Criteria for Adverse Events Version 5.0
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
ICF	Informed Consent Form
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National cancer institute
NSCLC	Non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
pDC	plasmacytoid dendritic cell
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PR	partial response
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TL	target lesion
TLR9	Toll-like receptor 9
TTR	time to response

Abbreviation or Specialist Term	Definition
W1D1	Week 1 Day 1

1. OVERVIEW

The SAP is intended to be a comprehensive and detailed description of the statistical methods, timing of analyses and analysis presentation to be used for the study specified in protocol CMP-001-009, Amendment 5 Global.

1.1. Study Description and Objectives

This is a phase 2 study to investigate intratumoral vidutolimod in combination with intravenous cemiplimab in subjects with selected types of advanced or metastatic cancer.

1.1.1. Primary Objective

The primary objective of this study is to determine the confirmed ORR with vidutolimod in combination with cemiplimab.

1.1.2. Secondary Objective(s)

The secondary objectives of the study are to:

- Evaluate the safety and tolerability of vidutolimod administered by IT injection in combination with cemiplimab
- Evaluate the efficacy of vidutolimod in combination with cemiplimab

1.1.3. Exploratory Objectives

The exploratory objectives of this study are to:

- Evaluate the effect of vidutolimod in combination with cemiplimab on injected and noninjected target lesions
- To demonstrate treatment induced immune effects consistent with vidutolimod mechanism of action, including TLR9 signaling, increase in pDC activation, corresponding increase in CD8 T cell tumor infiltration, and activation status

1.2. Statistical Hypothesis

There is no formal statistical hypothesis for the study; the analyses of this study will be descriptive and exploratory in nature.

1.3. Interim Analysis/(es)

There is no formal interim analysis in this study.

1.4. Modifications from the Statistical Section in the Final Protocol

None.

1.5. Revision History for SAP Amendments

This is the original version of the SAP .

2. INVESTIGATION PLAN

2.1. Study Design

This is a multicenter, open-label, Phase 2 clinical study of vidutolimod administered by IT injection in combination with cemiplimab IV in subjects with selected types of advanced or metastatic cancer with or without prior PD-1–blocking antibody treatment, as follows:

- Cohorts A1 and A2: Subjects with metastatic or locally and/or regionally advanced unresectable cutaneous squamous cell carcinoma (CSCC):
    - Cohort A1: Subjects who had not received prior systemic therapy for CSCC and who are not eligible for curative radiation
    - Cohort A2: Subjects who have progressed while receiving a PD-1–blocking antibody or within 12 weeks of discontinuation
- Cohorts B1 and B2: Subjects with metastatic or locally and/or regionally advanced unresectable Merkel cell carcinoma (MCC):
    - Cohort B1: Subjects who had not received prior systemic therapy for MCC
    - Cohort B2: Subjects who have progressed while receiving a PD-1–blocking antibody or within 12 weeks of discontinuation
- Cohorts C1 and C2: Previously treated subjects with advanced or metastatic triple-negative breast cancer (TNBC). Subjects must have previously received treatment with sacituzumab govitecan (all TNBC patients), with trastuzumab deruxtecan (HER2-low subjects) and with PARP inhibitor (for BRCA) subjects:
    - Cohort C1: Subjects who had not received prior therapy with immune checkpoint inhibitors (iCPIs)
    - Cohort C2: Subjects who have progressed while receiving a PD-1–blocking antibody or within 12 weeks of discontinuation
- Cohort D: Subjects with metastatic or locally and/or regionally advanced unresectable basal cell carcinoma (BCC) who have not received prior hedgehog pathway inhibitor therapy or prior anti-PD-1/PD-L1 therapy and who do not wish to receive or who are not candidates for a hedgehog inhibitor.
- Cohort E (not conducted in Europe): Advanced non-small cell lung cancer (NSCLC) subjects (locally advanced who are not candidates for surgical resection or definitive chemoradiation or metastatic) whose tumors have high PD-L1 expression (Tumor Proportion Score [TPS] ≥50%) based on a prior PD-L1 result as determined by College of American Pathologists (CAP)/Clinical Laboratory Improvement Amendments (CLIA) (or equivalently licensed) lab, with no EGFR, ALK or ROS1 aberrations, and who have not received prior anti-PD-1/PD-L1 therapy and are amenable to IT therapy and do not wish to receive chemotherapy.
- Cohort F: Recurrent/metastatic (R/M) Oropharynx Squamous Cell Carcinoma (OPSCC) subjects with PD-L1 combined positive score (CPS) ≥ 1, human papillomavirus (HPV)-positive disease who have not received prior systemic therapy for R/M disease. Human papillomavirus-positive status, based on a prior result, must be established in a surgical specimen or a core biopsy specimen from any site of OPSCC (primary site, nodal site, and/or distant metastatic site, either at time of diagnosis or later) in a CAP/CLIA (or equivalently licensed) lab. PD-L1 expression (CPS ≥ 1) is based on a prior PD-L1 result as determined by CAP/CLIA (or equivalently licensed) lab. Vidutolimod 10 mg will be

administered weekly for 7 doses, after which it will be administered Q3W until the subject meets a condition for discontinuation of study treatment. The first dose of vidutolimod may be administered SC or by IT injection, at the discretion of the Investigator; all subsequent doses are planned to be administered IT. The initial 7 vidutolimod doses, administered on a weekly schedule, must be completed before moving on to the Q3W vidutolimod dosing schedule.

The PD-1–blocking antibody administered in this study is cemiplimab. Treatment with cemiplimab will be administered IV infusion over 30 minutes (±10 minutes) at Week 1 Day 1 (W1D1) and Q3W thereafter. Cemiplimab administration will occur after vidutolimod administration.

All subjects will receive vidutolimod and cemiplimab according to the treatment schedule up to 2 years or until a reason for treatment discontinuation is reached.

Disease status will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) and other appropriate measures beginning predose at Week 10 Day 1 (W10D1) and will be repeated every 9 weeks (e.g. W19D1, W28D1, etc.) while the subject is on treatment. All scans should be performed at least 2 weeks after the previous vidutolimod IT injection to prevent detection of injection-related pseudoprogression. Imaging should not be delayed for delays in treatment.

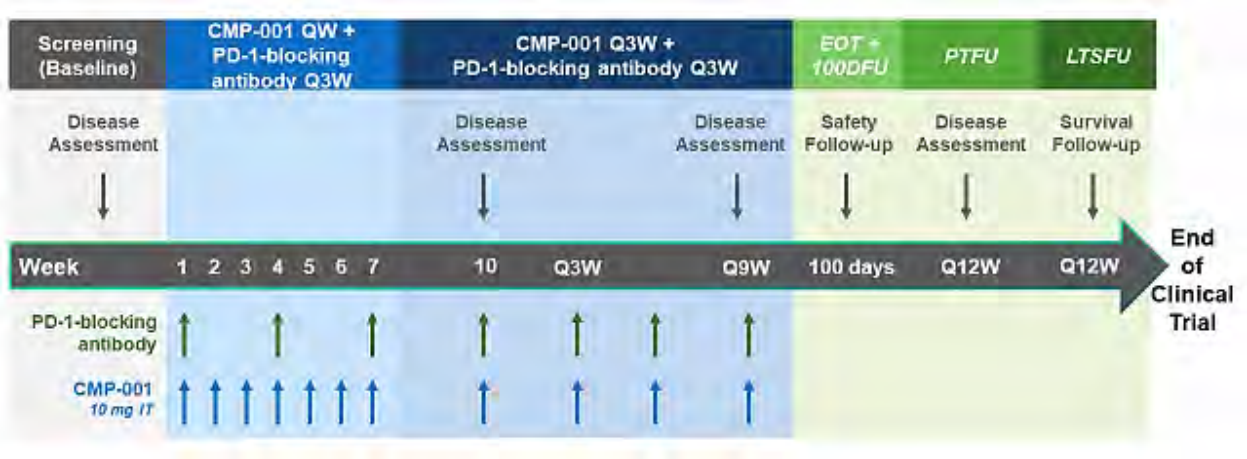
Objective responses will be assessed by the Investigator according to RECIST v1.1.

Subjects who discontinue study treatment should complete the end of treatment (EOT) visit. AEs and concomitant medications data will be collected until 100 days after the last dose of study drug (vidutolimod or cemiplimab) or until an alternative anticancer treatment is initiated, whichever occurs first, including at a 100-day safety follow-up visit.

Subjects who are posttreatment but have not met criteria for study discontinuation should remain on study for posttreatment follow-up (PTFU), which includes disease assessments every 3 months until discontinuation. Long-term survival follow-up (LTSFU) will be conducted every 3 months after the EOT visit or the last disease assessment date in PTFU.

At the end of the treatment period (2 years), the Sponsor will not continue to provide supplied study treatment to subjects/investigators unless the Sponsor chooses to extend the study. The investigator should ensure that the subjects receive appropriate standard of care to treat the condition under study.

Figure 1: Vidutolimod Study Schema



Abbreviations: 100DFU = 100-Day Follow-up; EOT = end of treatment; LTSFU = long-term survival follow-up; IT = intratumoral; PD-1 = programmed cell death protein 1; PTFU = posttreatment follow-up; Q3W = every 3 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; QW = every week; SC = subcutaneous.
Note: The first dose of vidutolimod may be administered by SC or IT injection, per Investigator discretion. All subsequent doses of vidutolimod are planned to be administered IT.

2.2. Sample Size and Power Considerations

This study is conducted as an exploratory trial. Each cohort of A1, A2, B1, B2, C1, C2D, E and F, will enroll approximately 25 subjects. The total number of subjects to be enrolled into this study is approximately 225. Based on historical data, the ORR of available treatment for each disease in Cohort is listed in Table 1. If the observed ORRs in these Cohorts A1, A2, B1, B2, C1, C2, D, E and F are at least as listed in Table 1, then the lower bound of 90% confidence interval of ORR is listed in the table below.

Table 1: ORR of Available Treatment by Cohort

Cohort	ORR of Available Treatment	Observed ORR ≥	Lower Bound of 90% Confidence Interval
A1	50%	72%	>50%
A2	<10%	24%	>10%
B1	50%	72%	>50%
B2	<10%	24%	>10%
C1	21%	40%	>21%
C2	<10%	24%	>10%
D	50%	72%	>50%
E	39%	60%	>39%
F	19%	40%	>21%

3. ANALYSIS SETS

The following defines the set(s) of subjects whose data will be used for statistical analysis.

3.1. Full Analysis Set (FAS)

The full analysis set (FAS) includes all enrolled patients who received any study drug. Efficacy endpoints will be analyzed using the FAS.

3.2. Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all enrolled patients who received any study drug. Treatment administration and all clinical safety variables will be analyzed using the SAF. The FAS and SAF are the same.

4. GENERAL STATISTICAL ANALYSIS CONSIDERATIONS

Unless otherwise stated, the following conventions will be applied when presenting summary level statistics for data.

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

All analyses will be done using SAS Version 9.4 or above.

5. PATIENT DISPOSITION

5.1. Screening Dispositions

The following will be provided for all patients who signed the informed consent form:

- The number of screened patients, i.e., patients who signed the screening informed consent form.
- The number of patients who are enrolled.
- The number of patients who screen-failed.
- Screen failure reasons for patients who screen-failed.

5.2. End of Treatment and End of Study Dispositions

The following will be provided based on the FAS for each cohort:

- The number of patients in each analysis set.
- The number of patients who discontinue study treatment, and the reasons for study treatment discontinuation.
- The number of patients who discontinue study, and the reasons for study discontinuation.

5.3. Protocol Deviations

Protocol deviations will be defined in a separate protocol deviation definition document and be recorded in a separate list including the deviation reasons. The important protocol deviations, such as violation of inclusion/exclusion criteria will be determined before database lock and be summarized for each cohort.

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1. Demographics

The following demographic variables will be summarized based on the FAS for each cohort:

- Age at screening (year)
- Age categories (<65, >=65)
- Sex (Male, Female)
- Ethnicity (Hispanic/Latino, Not Hispanic or Latino, Not reported)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White, Other, Not reported)
- Baseline Luteinizing Hormone (LH) (mIU/ml)
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) (kg/m2)

6.2. Baseline Disease Characteristics

The following baseline/initial disease characteristics that are common to all cohorts will be summarized based on the FAS for each cohort.

Baseline Characteristics. ECOG Performance Status at baseline, PD-L1 Status at Baseline, Time since Initial Diagnosis of Primary Cancer to First Dose (Months), Disease Type at Enrollment, Tumor Burden at Baseline, Measurable Disease at Baseline, and other key baseline information will be summarized by cohort using descriptive statistics for the Safety Analysis Set and listed by subject.

Cancer History. Cancer history (TNM staging, i.e., tumor stage, nodal status, metastatic disease status, and other key information measured at time of diagnosis) will be summarized by cohort using descriptive statistics for the FAS and listed by subject.

Prior Cancer Treatments. The prior cnacer relaed treatments will be summarized across patients by cohort using descriptive statistics for the FAS.

6.3. Medical History

Patient medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The frequency and percentage of each medical history will be summarized by SOC and PT for each cohort using the FAS.

7. EFFICACY DATA

7.1. Description of Efficacy Data

All endpoints below will be assessed based on data reported by the investigators.

ORR is defined as the number of patients with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) divided by the total number of patients.

- Confirmation of CR or PR must occur during a subsequent evaluation at a timepoint of at least 4 weeks from the initial assessment of CR or PR.
- Best overall response of SD must have met the response SD criteria at least once ≥ 56 days (9 weeks for first tumor assessment –7 days window) from the first study treatment administration
- Patient(s) without baseline tumor assessment or with either unknown or missing BOR will be counted as non-responder(s).

DOR, defined as time from first confirmed response of CR or PR to first radiographic progression or death due to any cause for patients with confirmed CR or PR. In the absence of radiographic progression or death on or before the analysis cutoff date or the date of initiation of a further anti-cancer treatment, the DOR will be censored at the date of the last valid response assessment not showing progression performed on or prior to the analysis cutoff date or initiation of a further anti-cancer treatment, whichever is earlier.

DCR, defined as the percentage of patients with a BOR of CR, PR, or stable disease (SD).

TTR, defined as time from first study treatment administration to first confirmed response of CR or PR for patients with confirmed CR or PR.

PFS defined as time from the first study treatment administration to first radiographic progression or death due to any cause. The same censoring rule as DOR will be used.

OS defined as the time from first study treatment administration to death due to any cause. For patients who have not died, OS will be censored at the last date that patient is known to be alive.

7.2. Analysis of Efficacy Data

7.2.1. Analysis of Primary Efficacy Endpoint

For each cohort, the ORR per RECIST 1.1 will be summarized using FAS, along with 95% exact confidence interval using Clopper-Pearson method.

To determine the consistency of treatment effect across various demographics and baseline subgroups, the ORR (with a nominal 95% confidence interval [CI]) may be estimated within each category of the following subgroup variables: age, gender, race, ECOG, prior therapy.

7.2.2. Analyses of Secondary Efficacy Endpoints

For each cohort:

- DCR will be summarized, along with 95% exact confidence interval using Clopper Pearson method.
- TTR will be summarized descriptively and using Kaplan-Meier method.
- DOR will be summarized descriptively and using Kaplan-Meier method.
- PFS and OS will be summarized using Kaplan-Meier method. Kaplan-Meier curves will be presented.
- Response in injected and noninjected target lesions by Investigator assessment
- Waterfall plots, spider plots, and swimmer plots will also be presented.

All secondary efficacy endpoints may be analyzed per cohort per subgroups specified for the primary endpoint as appropriate.

7.2.3. Exploratory Efficacy Analyses

The following exploratory efficacy analyses will be performed for the FAS.

Baseline, and change from baseline, in tumor or blood measurements of biomarkers related to TLR9, immune checkpoints, and potential markers of resistance or response to immunotherapy

Tumor biopsy obtained at baseline and specified time points during the study may be analyzed for protein, RNA, DNA, or other biomarkers related to TLR9, immune checkpoints, and potential markers of resistance or response to immunotherapy.

- Evaluate the effect of vidutolimod in combination with cemiplimab on injected and noninjected target lesions
- To demonstrate treatment induced immune effects consistent with vidutolimod mechanism of action, including TLR9 signaling, increase in pDC activation, corresponding increase in CD8 T cell tumor infiltration, and activation status

8. HYPOTHESIS TESTING METHODS AND MULTIPLICITY CONTROL

There will be no multiplicity adjustment for this study.

9. SUMMARY OF EXPOSURE DATA

9.1. Investigation Study Drug Exposure and Compliance

Exposure to study drugs will be examined and the following variables will be summarized for each cohort based on the SAF.

The number of CMP-001 and Cemiplimab doses received by each subject will be summarized descriptively by cohort for the Safety Analysis Set. The duration of exposure, dose intensities and relative dose intensity will also be summarized separately as follows with descriptive statistics in a tabular manner and a by-subject data listing.

1. Duration of Exposure

Duration of exposure will be calculated as follows:

Duration of exposure (weeks) = (first dose date of the last cycle received + corresponding cycle duration – first dose date) / 7

- For CMP-001, the corresponding cycle duration = 7 days for Week 1 through Week 6 of Q1W schedule and 21 days for Week 7 and the following Q3W schedule
- As for Cemiplimab, the corresponding cycle duration is 21 days

2. Dosing Intensities

(1) Actual dose intensity (mg/week) will be calculated as the total actual cumulative dose received divided by duration of exposure (weeks) for CMP-001 and Cemiplimab, respectively.

(2) Planned dose intensity (mg/week) will be calculated as the total planned cumulative dose to be received divided by the planned exposure duration (weeks) based on the protocol schedule.

Planned Exposure Duration (weeks) = number of planned treatments * corresponding cycle duration (weeks)

- For CMP-001, the corresponding cycle duration = 1 week for Week 1 through Week 6 of Q1W schedule and 3 weeks for Week 7 and the following Q3W schedule
- As for Cemiplimab, the corresponding cycle duration is 3 weeks

(3) Relative dose intensity (%) will be calculated based on the actual cumulative dose received relative to the planned cumulative dose throughout the exposure duration as follows:

Relative dose intensity (%) = (actual dose intensity / planned dose intensity) * 100%

3. Dosage Modifications

The number and percentage of subjects with dose delayed, withheld, interrupted, reduced, permanently withdrawn will be tabulated with the reasons for CMP-001 and Cemiplimab, respectively.

Dosing of CMP-001 and Cemiplimab, including date and time of each dose, route of administration, dose administered, location of each injection, and the volume injected into each tumor at each dosing visit will be presented in a by-subject data listing per the information from the study drug administration eCRFs.

Compliance will be calculated per cohort and by CMP-001 and Cemiplimab as follows:

Treatment Compliance = (Number of doses of study drug administered during treatment period) / (Number of doses planned to be administered during treatment period) x 100%, where temporary dose discontinuation is ignored.

The percentage of subjects who have <60%, 60-80%, 80-100%, and >100% compliance will be summarized for each cohort.

9.2. Prior and Concomitant Medications/ Procedures

Prior medications procedires are defined as those taken within 30 days prior to the first dose date of the study drug and discontinued before the first dose date of the study drug. Prior medications and procedures will be summarized for each cohort based on the FAS. The number and percentage of patients who received any prior cancer related medications, prior cancer related radiotherapy, or prior cancer related surgery will be summarized. Prior cancer related medications will be summarized by setting and ATC levels.

Concomitant medications. Concomitant medications are defined as medications which are taken at any time prior to 100 days after the last dose date of the study drug (both CMP-001 and cemiplimab) or until the initiation of an alternative anti-cancer treatment, whichever is earlier. Medications with missing or partially missing start or end dates will be handled according to the conventions described in Data Coventions section. If it cannot be determined whether a medication is a prior medication due to partial medication start or end dates, the medication will be considered concomitant. Treatment medications for study-related AEs that occur more than 100 days after the last dose of study drug will be included as concomitant medications.

Concomitant medications and procedures will be summarized for each cohort based on the SAF. Concomitant medications will be summarized by ATC level 2 and ATC level 4. Patients will be counted once in all ATC categories linked to the medication.

Post-treatment anti-cancer therapy and procedure will be summarized for each cohort based on the SAF, if applicable.

10. ANALYSIS OF SAFETY DATA

The analysis of safety and tolerance will be performed on the SAF .

The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, vital signs and 12-lead ECG, etc.).

For safety variables, 3 observation periods are defined:

- The pre-treatment period is defined as the time from signing the screening ICF to before the first dose of study drug.
- The on-treatment period is defined as the time from first dose of study drug to the last dose of study drug plus 100 days or until the start of new systemic therapy for treatment of the patient's tumor (whichever is earlier).
- The post-treatment period is defined as the time starting 1 day after the end of on-treatment period.

10.1. Adverse Events

All AEs reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and graded using the current NCI-CTCAE.

Treatment-emergent adverse events are defined as AEs that develop or worsen during the on-treatment period and any treatment-related SAEs that occur during the post-treatment period.

All AEs reported in this study will be coded using Medical Dictionary for Regulatory Activities (MedDRA®).

Summaries of TEAEs will include but not limited to:

- Overview of TEAEs
- Treatment-related TEAEs and serious TEAEs by SOC and PT
- TEAEs by SOC and PT
- TEAEs by all grades and >= grade 3, presented by SOC and PT
- Treatment-related TEAEs, presented by SOC and PT
- Treatment-emergent AESIs, presented by SOC and PT
- TEAEs leading to permanent treatment discontinuation, presented by SOC and PT
- TEAEs leading to death, presented by SOC and PT
- Serious TEAEs, presented by SOC and PT

10.2. Laboratory Parameters

The clinical laboratory data consists of serum chemistry, hematology, urinalysis.

Clinical laboratory analytes will be converted to standard international (SI) units and grouped by function in summary tables for each chort on the SAF. Clinical laboratory values and change from baseline in clinical laboratory values to all scheduled assessment times will be summarized with

descriptive statistics. Summary tables for worst laboratory values during on-treatment period with CTCAE all grade and grade ≥ 3 will be generated. Shift tables from baseline to worst post-treatment NCI CTCAE grade during on-treatment period will be generated.

10.3. Vital Signs

The following vital signs parameters will be recorded and summarized:

- Respiratory rate (bpm)
- Pulse rate (bpm)
- Sitting systolic and diastolic blood pressures (mmHg)
- Body temperature (^{o}C)

Vital sign parameters will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics for each cohort.

10.4. Electrocardiography (ECG)

ECG parameters (PR, QRS, RR, and QT) will be summarized by baseline and change from baseline to each scheduled and collected assessment time.

ECG status (i.e. normal, abnormal) will be reported. Shift tables will be provided to present the post-baseline status according to the baseline status (normal or missing / abnormal) for each cohort.

10.5. Other Safety Data

Other safety data, such as data collected from physical examination that includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, skin, a brief neurologic examination, and ECOG performance status, etc, will be analyzed when necessary.

11. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

11.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product.

11.2. Data Convention

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Patients who are deemed unevaluable (NE) per RECIST 1.1 will be considered as not reaching CR/PR/SD in calculating ORR/DCR, i.e. they are not considered as responders in the numerator of ORR/DCR, but they are counted in the denominator of ORR/DCR.

Last contact date will be derived from all assessments (e.g., tumor assessments) and actual event dates (e.g., AEs, biopsy, etc).

Incomplete Death dates

If death year is completely missing, it will be imputed as the last known alive date +1. If month and day are missing, death date will be imputed to max (1 Jan of the year of death, last known alive date +1). If only day is missing, death date will be imputed to max (1st day of month and year of death, last known alive date +1).

11.3. Data for Non-Efficacy Endpoints

Incomplete Medication dates

If medication start date is completely missing, impute it to min (first dose date of any study drug, medication end date). If medication start month is missing, and medication start year is not missing: If medication start year is less than the first dose year, use the first day of the year. If medication start year is equal to the first dose year, use the first dose day and month. Else impute the day and month using 01 January. If this leads to a date after the medication end date, use medication end date instead. If medication start day is missing, and medication start month and year are not missing: If medication start year is the same as first dose year and the medication start month is the same as the first dose month, then impute medication start day using the day of first dose. If this leads to a date after the medication end date, use medication end date instead. Otherwise impute the medication start day using the first day of the month.

If medication end date is completely missing, do not impute. It's an ongoing medication. If medication end month is missing, and medication end year is not missing: Impute end date to the earlier of (reference end date, 31DECYYYY). If concomitant medication end day is missing, and concomitant medication end month and year are not missing: Impute end date using the last day of the month.

If post treatment anti-cancer therapy start month or year is missing, do not impute the date. If post-treatment anticancer therapy start day is missing, and start month and year are not missing: impute

the start day using the 15th day of the month. If this leads to a date on or before the last dose (of original treatment) date, use last dose date+1 instead.

Adverse event

If the NCI grade of a TEAE is missing, it will not be imputed. A TEAE with missing grade will be summarized under all grades in the TEAE frequency tables. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related to the investigational product.

Date of first / last study treatment

Date of first infusion is the first non-missing start date of dosing filled in the CRF "Investigational Product" module.

If a patient's date of the last dose is totally missing or unknown, his/her last visit date will be substituted.

11.4. Assignment of Data to Visit Windows and Unscheduled Assessments

Assessments taken outside of the allowable windows will be displayed according to the case report form assessment recorded by the investigator. All scheduled assessments will be summarized by the nominal visit number and no visit windows will be defined.

Unscheduled Assessments

Unscheduled visit measurements may be used for both efficacy and safety variables to provide a measurement for a baseline or endpoint value if appropriate according to their definition

12. REFERENCES

ICH E9, Statistical Principles for Clinical Trials, February 1998.

Clopper C, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika 1934; 26(4):404-413.

13. APPENDIX

13.1. Summary of Statistical Analyses

Efficacy Analysis – phase 2

Endpoint	Analysis Populations	Statistical Method per Cohort	Supportive Analysis	Subgroup Analysis	Other Analyses
ORR per RECIST1.1	FAS	ORR, along with 95% CI by using Clopper-Pearson method	No	Yes	Maybe
DCR	FAS	DCR, along with 95% CI by using Clopper-Pearson method	No	No	Same as above
TTR	FAS	Median, range	No	No	Same as above
DOR	FAS	KM estimates, range	No	No	Same as above
PFS	FAS	KM estimates	No	No	Same as above
OS	FAS	KM estimates	No	No	Same as above

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