Official Title: A Phase 2 Study of INCMGA00012 in Participants With Metastatic Merkel Cell Carcinoma (POD1UM-201)

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STATISTICAL ANALYSIS PLAN

INCMGA 0012-201

A Phase 2 Study of INCMGA00012 in Participants With Metastatic Merkel Cell Carcinoma (POD1UM-201)

IND Number:	**139,181**
EudraCT Number:	**2018-001627-39**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Protocol Version:	**Protocol Amendment 6 dated 22 OCT 2020**
CRF Approval Date:	**26 AUG 2019**
SAP Version:	**Amendment 2**
SAP Author:	[redacted] [redacted] **Biostatistics**
Date of Plan:	**19 MAY 2021**

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Abbreviation	Term
[redacted]	[redacted]
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_t	area under the plasma or serum concentration-time curve from time = 0 to the last measurable concentration at time = t
BMI	body mass index
BOR	best overall response
CI	confidence interval
C_{max}	maximum observed plasma or serum concentration
C_{min}	minimum observed plasma or serum concentration over the dose interval
CR	complete response
CRF	case report form
CSR	clinical study report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
DRR	durable response rate
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
[redacted]	[redacted]
FAS	full analysis set
FDA	Food and Drug Administration
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ICR	independent central review
[redacted]	[redacted]
irAE	immune-related adverse event

Abbreviation	Term
[redacted]	[redacted]
[redacted]	[redacted]
IV	intravenously
MCC	Merkel cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NE	not evaluable
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death-ligand
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
[redacted]	[redacted]
PT	preferred term
Q4W	every 4 weeks
QTcF	QT interval corrected by Fridericia
QTcB	QT interval corrected by Bazett
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
t_{max}	time to maximum concentration
TPR	timepoint response
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This study is an open-label, single-arm, multicenter, Phase 2 study that will enroll participants with advanced/metastatic MCC. Per Protocol Amendment 5, the study will target the enrollment of approximately 60 chemotherapy-naive participants, while enrollment for participants who have had prior chemotherapy will be stopped. Five participants who have had prior chemotherapy were enrolled in the study before implementation of Protocol Amendment 5.

According to Protocol Amendment 6, the study will enroll approximately 100 chemotherapy-naive participants. The primary analysis will be performed after approximately 60 chemotherapy-naive participants have been enrolled and followed for at least 6 months after confirmed response. If the study meets the predefined efficacy threshold at the primary analysis, the final analysis will occur after all 100 participants have been enrolled and followed for survival for a minimum of 2 years.

All participants will receive INCMGA00012 (retifanlimab) at the recommended Phase 2 dose of 500 mg IV Q4W. The primary endpoint is ORR in chemotherapy-naive participants as determined by ICR using RECIST v1.1.

Participants will participate in the study for up to approximately 3 years. The study consists of 3 periods: screening, study drug treatment, and follow-up. Treatment may continue for up to 2 years in the absence of disease progression, intolerable toxicity, death, withdrawal of consent, lost to follow-up, or premature discontinuation for any other reason. Participants unable to restart study drug treatment ≤ 12 weeks from the start of the treatment delay due to toxicity will be permanently discontinued from study treatment.

The follow-up period will begin once a participant has completed or prematurely discontinued the study treatment. Participants will be evaluated for AEs and other safety parameters for up to 90 days after the last dose of study treatment or until the start of new anticancer therapy, whichever occurs first. All participants entering follow-up will be assessed for survival until study completion. Participants who enter the follow-up period without experiencing disease progression will continue tumor assessments according to the schedule of activities until they experience disease progression, the start of a new anticancer treatment, withdrawal of consent, lost to follow-up, the end of the study, or death.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the INCMGA 0012-201 Protocol. The scope of this plan includes the primary and final analyses that are planned and will be executed by the Department of Biostatistics or designee. The analyses of PK [redacted] will be executed by the Department of Clinical Pharmacokinetics [redacted], respectively.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCMGA 0012-201 Protocol Amendment 6 dated 22 OCT 2020 and CRFs approved on 26 AUG 2019. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and CRF versions.

2.2. Study Objectives and Endpoints

The study objectives and endpoints are presented in Table 1.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the efficacy of INCMGA00012 in terms of the ORR in chemotherapy-naive participants with advanced/metastatic MCC.	ORR, defined as the percentage of participants having an objective response (CR or PR), according to RECIST v1.1, as determined by ICR. The primary analysis will include approximately 60 chemotherapy-naive participants who have been enrolled and followed for at least 6 months after confirmed response. The final analysis will include all enrolled participants for confirmatory purposes.
Secondary	
To determine the DOR, DCR, PFS, and OS in the chemotherapy-naive population with advanced/metastatic MCC treated with INCMGA00012.	• DOR, defined as the time from an initial objective response (CR or PR) according to RECIST v1.1 until disease progression, or death due to any cause, as determined by ICR. • DCR, defined as the proportion of participants with either an objective response or SD lasting at least 6 months. • PFS, defined as the time from the start of therapy until disease progression, or death due to any cause, as determined by the ICR. • OS, defined as the time from the start of therapy until death due to any cause.
To evaluate the safety of INCMGA00012 in participants with advanced/metastatic MCC.	Safety, determined by the number, frequency, duration, and severity of AEs using CTCAE v5.0; laboratory tests; vital signs; and ECGs.
To determine the PK of INCMGA00012 administered to participants with advanced/metastatic MCC.	The PK of INCMGA00012 when given to participants with advanced/metastatic MCC, including C_{max}, t_{max}, C_{min}, and AUC_t, will be summarized.

Table 1: Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory	
[redacted]	
To determine the efficacy of INCMGA00012 in terms of the ORR, DOR, DCR, PFS, and OS in the full study population (chemotherapy-naive and chemotherapy-refractory) with advanced/metastatic MCC. Note: Chemotherapy-refractory participants enrolled before implementation of Amendment 5 will be included in these analyses.	• ORR, defined as the percentage of participants having an objective response (CR or PR), according to RECIST v1.1, as determined by ICR. • DOR, defined as the time from an initial objective response (CR or PR) according to RECIST v1.1 until disease progression, or death due to any cause, as determined by ICR. • DCR, defined as the proportion of participants with either an objective response or SD lasting at least 6 months. • PFS, defined as the time from the start of therapy until disease progression, or death due to any cause, as determined by the ICR. • OS, defined as the time from the start of therapy until death due to any cause.

3. STUDY DESIGN

3.1. Overall Study Design

The study is a Phase 2, open-label, single-arm, multicenter study designed to assess the clinical activity and safety of INCMGA00012 in participants with advanced/metastatic MCC. As of Protocol Amendment 5, this study will enroll participants with advanced/metastatic MCC who are chemotherapy-naive. The participants should not have received any prior therapy with PD-1/PD-L1 inhibitors. All participants must submit tissue samples (fresh or archival) for central pathology review. Participants who do not have MCC confirmed by pathology may remain on study treatment.

All participants who meet the eligibility criteria during screening will receive treatment with INCMGA00012. The primary endpoint is ORR in chemotherapy-naive participants as determined by ICR according to RECIST v1.1.

According to Protocol Amendment 6, approximately 100 chemotherapy-naive participants will be enrolled. The primary analysis is planned with approximately 60 chemotherapy-naive participants, while the additional participants will be enrolled to support confirmation of efficacy and provide additional information on safety. The primary analysis will occur after approximately 60 chemotherapy-naive participants have been enrolled and followed for at least 6 months after confirmed response. If the study meets the predefined efficacy threshold at the primary analysis (see Section 3.4), the final analysis will occur after all 100 participants have been enrolled and followed for survival for a minimum of 2 years. Study enrollment may stop if the predefined efficacy threshold is not met at the time of primary analysis.

Study treatment will consist of monotherapy INCMGA00012 administered at the recommended Phase 2 dose of 500 mg IV Q4W. Treatment with study drug may continue up to 2 years in the absence of disease progression, intolerable toxicity, death, withdrawal of consent, lost to follow-up, or premature discontinuation for any other reasons.

3.1.1. Treatment Discontinuation

Participants **must** be withdrawn from study treatment for the following reasons:

- Disease progression.
- Unacceptable toxicity as noted in Protocol Section 6.5.3.
- Consent is withdrawn.
- Further participation would be, based on the medical judgment of the investigator, injurious to the health or well-being of the participant.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, institutional review board, or independent ethics committee.
- The participant becomes pregnant.

A participant **may** be discontinued from study treatment as follows:

- If a participant is noncompliant with study procedures or treatment administration, and in the judgment of the investigator the participant is not receiving a clinical benefit. When possible, the sponsor should be informed and/or consulted.
- The participant achieves a confirmed CR after at least 6 months of treatment. Participants may continue on study treatment after confirmation of CR per the discretion of the investigator if they feel the participant may gain additional benefit.

3.1.2. Study Duration

The study begins when the first participant signs the informed consent form. Participants may receive study treatment for up to 2 years, unless prematurely discontinued. Participants discontinuing treatment will enter the follow-up period after their last dose of study treatment. The study ends once every participant receiving active treatment has been followed for at least 6 months after confirmed response or until all participants have been followed for survival for a minimum of 2 years. Participants remaining on active therapy at study conclusion may be eligible for continued treatment up to 2 years from first dose if, in the assessment of the investigator, they are tolerating therapy and receiving benefit.

3.1.3. Response Assessment

Objective assessment of disease status will be evaluated according to RECIST v1.1 (Eisenhauer et al 2009) by the ICR. Participants should be actively monitored for RECIST response up until they start new anticancer therapy or have PD. [redacted] The disease response assessments according to RECIST v1.1 [redacted] by investigators will be entered into the eCRF.

Efficacy assessments of response should be performed according to schedule. Scans should follow calendar days and remain on the 8-week schedule (± 7 days), established on Cycle 1 Day 1, and should not be delayed for treatment holds or interruptions. Disease status will be assessed every 8 weeks for the first 12 months and then every 12 weeks thereafter. For participants who discontinue study treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiographic imaging according to the follow-up schedule.

Participants who continue study participation in the follow-up period without experiencing disease progression will continue to have efficacy assessments every 12 weeks (± 7 days) from the previous scan until they complete participation in the study, start a new anticancer therapy, experience disease progression, or death.

3.2. Randomization

Not applicable.

3.3. Control of Type I Error

For analysis of response rate, 2-sided 95% confidence level will be reported.

3.4. Sample Size Considerations

A pilot study of avelumab in participants with chemotherapy-naive metastatic MCC shows a confirmed ORR of 39.7% with lower 95% CI of 30.7% (D'Angelo et al 2019). A pilot study of pembrolizumab in the same population showed an ORR of 56% with lower 95% CI of 35% (Nghiem et al 2016, Nghiem et al 2019).

Based on the results from studies of avelumab and pembrolizumab, it is reasonable to target a response rate of approximately 48%. Approximately 60 chemotherapy-naive participants will be included for the primary analysis. Based on a target ORR of 48% and a sample size of approximately 60, this study has over 80% power to exclude the lower 95% confidence limit of 30% with $\alpha = 0.025$ (1-sided) in the chemotherapy-naive population.

Approximately 100 chemotherapy-naive participants will be enrolled for the final analysis. This sample size ensures that half of the 95% CI will be approximately 10% for an ORR ranging from 40% to 60%. This sample size also ensures 99% power to detect any AE with an underlying event rate as low as 0.5%.

Note: Participants who have received prior chemotherapy for MCC were enrolled up to Protocol Amendment 4.

Table 2: Response Rates and 95% Confidence Intervals

Sample Size	Number of Responses	Response Rate (%)	95% Confidence Interval (%)
60	20	33.3	21.7-46.7
60	25	41.7	29.1-55.1
60	30	50.0	36.8-63.2
60	35	58.3	44.9-70.9
60	40	66.7	53.3-78.3

3.5. Schedule of Assessments

Refer to Protocol Amendment 6 dated 22 OCT 2020 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Study Drug

INCMGA00012 is the only study drug in this study.

4.1.2. Day 1

Day 1 is the date that the first dose (Cycle 1 Day 1) of INCMGA00012 is administered to participants.

4.1.3. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date).

A study day of −1 indicates 1 day before Day 1.

4.1.4. Analysis Grouping

For the primary CSR, all analyses will be presented by chemotherapy-naive, chemotherapy-refectory, and total population. Within chemotherapy-naive participants, participants will be presented as advanced, metastatic, and total based on tumor stage at the time of screening.

4.1.5. Baseline Value

Baseline is the last nonmissing assessment obtained before the first administration of study drug.

When scheduled assessments and unscheduled assessments occur on the same day and time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.6. Handling of Missing and Incomplete Data

In general, values for missing data will not be imputed unless methods for handling missing data are specified in this section or relevant sections.

Partial disease/cancer diagnosis date will be handled as follows:

- If only the day is missing, then the imputed day will be the first of the month.
- If both the month and day are missing, then the imputed day and month will be 01 JAN.
- No imputation will be done if the date is completely missing.

Missing or partial date of last dose will be handled as follows:

- If only the day is missing, then the imputed date of the last dose will be the earlier date of the first day of the month or the date that the participant discontinued treatment.
- Otherwise, the date that the participant discontinued treatment will be used as the date of the last dose.

For relevant efficacy endpoints, partial death date will be imputed as follows:

- If mmyyyy for the last contact date = mmyyyy for the death date, then the death date will be set to the day after the last contact date.
- If mmyyyy for the last contact date < mmyyyy for the death date, then the death date will be set to the first day of the death month.
- Otherwise, the partial death date will not be imputed.

For prior and concomitant medications:

The start/stop dates recorded in the eCRF by the investigator and his or her research staff will be used to identify when a concomitant medication was taken during the study. Any missing start date must be queried for resolution. Unresolved missing start dates will be handled as follows:

- If the date is completely missing, the medication will be considered both prior and concomitant.
- If only the day is missing, and the last day of the month is before the first dose date on Day 1, then the concomitant medication will be considered as starting before Day 1, and the incomplete date will be imputed as the last day of the month.
- If only the day is missing, and the first day of the month is on or after the first dose date on Day 1, then the concomitant medication will be considered as starting after Day 1, and the incomplete date will be imputed as the first day of the month.
- If only the day is missing, and the month is equal to the month of the first dose date on Day 1, then the incomplete date will be imputed as the first day of the month.
- If both the month and day are missing, and the last day of the year is before the first dose date on Day 1, then the concomitant medication will be considered as starting before Day 1, and the incomplete date will be imputed as if it is the last day of the year. Otherwise, if the last day of the year is on or after the first dose date Day 1, the incomplete date will be imputed as if it is the first day of the year.

- If the imputed start date through the above procedure is after the stop date recorded in the eCRF, then the imputed start date will be set equal to the stop date.

4.1.7. Cycle Length and Duration

One cycle is defined as 28 days (4 weeks) for participants in this study. Cycle 1 Day 1 is the day of first infusion of INCMGA00012. Day 1 of subsequent cycles will correspond with the infusion date of INCMGA00012 within the cycle. Tumor imaging/response assessments will have a ± 7-day window during the treatment period and ± 14-day window during the follow-up period for participants who discontinued study treatment without experiencing disease progression.

4.1.8. On-Treatment Assessment/Event

Safety summaries and selected summaries of deaths will summarize only on-treatment assessments/events. On-treatment assessment/event is defined as any assessment/event obtained in the following time interval:

> Date of first administration of study drug through the date of last administration of study drug + 90 days.

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF.

If the last date of study drug is missing, on-treatment assessments/events include any assessment/event recorded in the database that occurred after the start date of study drug.

Data listings will include all assessments/events, and those which are not on-treatment assessments/events will be flagged.

4.2. Variable Definitions

The following variables will only be calculated if not reported on the eCRF.

4.2.1. Body Mass Index

Body mass index will be calculated as follows:

> BMI (kg/m^2) = [weight (kg)] / [height (m)]^2.

4.2.2. Creatinine Clearance

Creatinine clearance by Cockcroft-Gault equation (Cockcroft and Gault 1976) is estimated from serum creatinine (mg/dL) determination using the following formula:

> Creatinine clearance (mL/min) = [140 − age (years)] × weight (kg) × {0.85* for female participants} / [72 × serum creatinine (mg/dL)].

*Note: For male participants use 1.0.

4.2.3. Hepatic Impairment

The baseline hepatic impairment category can be classified into normal, mild, moderate, or severe hepatic impairment based on NCI Organ Dysfunction Working Group criteria (NCI 2017) as shown in Table 3.

Table 3: National Cancer Institute Organ Dysfunction Working Group Hepatic Impairment Criteria

Hepatic Impairment Category	Normal	Mild	Moderate	Severe
Total bilirubin	≤ ULN	B1: ≤ ULN B2: > 1.0-1.5 × ULN	> 1.5-3 × ULN	> 3 × ULN
AST	≤ ULN	B1: > ULN B2: Any	Any	Any

Note: Mild hepatic impairment can be defined according to either of 2 criteria (B1 and B2).

4.2.4. Prior and Concomitant Medication

Prior medication is defined as any non-study medication started before the first dose of INCMGA00012.

Concomitant medication is defined as any non-study medication that is started accordingly:

- Before the date of first administration of INCMGA00012 and is ongoing throughout the study or ends on/after the date of first study drug administration.
- On/after the date of first administration of INCMGA00012 and is ongoing or ends during the course of study drug administration.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of INCMGA00012. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant medication.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant, that is, if the start date and end date are all missing, then the medication is considered as concomitant medication.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9.4 or later) will be used for the generation of all tables, figures, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

Interim analyses are planned for this study as defined in Section 11.

5.2. Treatment Groups

There is only 1 treatment group in this study, that is, INCMGA00012.

5.3. Analysis Populations

5.3.1. Full Analysis Set

The FAS includes all participants enrolled in the study who received at least 1 dose of study drug and are included in the primary analysis (ie, approximately 60 chemotherapy-naive participants and chemotherapy-refractory participants). The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and efficacy. Note: This analysis population will be used in the CSR reporting the primary analyses.

5.3.2. Efficacy Evaluable Population

The efficacy evaluable population includes all participants from the FAS with a centrally confirmed diagnosis of MCC who have measurable disease at baseline according to RECIST v1.1.

5.3.3. Safety Evaluable Population

The safety evaluable population includes all enrolled participants who received at least 1 dose of study drug. The safety evaluable population will be used to support the safety analysis at the primary analysis and to support all analyses, including efficacy at the final analysis.

5.3.4. Pharmacokinetic Evaluable Population

The PK evaluable population will include all participants who received at least 1 dose of study drug and have provided a baseline and at least 1 postdose PK sample. The study pharmacokineticist will review data listings of study drug administration and sample records to identify participants to be excluded from analyses of PK data. [redacted]

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

Appendix A provides a list of planned tables, figures, and listings.

6.1. Baseline and Demographics, Physical Characteristics, and Disease History

The safety evaluable population and FAS will be used for all baseline disease characteristics and demographic summaries and data listings.

6.1.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be listed in detail. The following demographics will be summarized using the safety evaluable population and FAS: age, sex, race, ethnicity, body weight, height, BMI, creatinine clearance, and hepatic function. Qualitative data will be summarized by contingency tables while quantitative data will be summarized by descriptive summary statistics.

6.1.2. Baseline Disease Characteristics and Disease History

According to data collected in the eCRF, the following information determined at initial diagnosis will be summarized for all participants: time since initial diagnosis; tumor staging, including T, N, and M staging; site of primary tumor; Merkel cell polyomavirus status; and PD-L1 assessment. Current status will also be collected in the eCRF and summarized for all participants in the safety evaluable population including the following: stage, including T, N, and M staging; Merkel cell polyomavirus status; sites of disease; HIV status; ECOG performance status; visceral disease; and liver metastasis. Tumor tissue provided for each participant at baseline will be reviewed by a central pathologist, and information regarding PD-L1 status and Merkel cell polyomavirus will be summarized for all participants in the safety evaluable population and FAS.

6.1.3. Prior Therapy

The number and percentage of participants recording any prior systemic cancer therapy, prior radiation, and prior surgery will be presented in listings for chemotherapy-refractory and chemotherapy-naive participants wherever applicable in the safety evaluable population and FAS.

6.1.4. Medical History

Medical history will be summarized for all participants in the safety evaluable population. This summary will be presented by primary SOC and PTs. The safety evaluable population will be used to summarize medical history.

6.2. Disposition of Participants

The number and percentage of participants who are on treatment, who discontinued study treatment with a primary reason for discontinuation, who are on study, and who withdrew from the study with a primary reason for study withdrawal will be summarized for all participants in the safety evaluable population and FAS.

6.3. Protocol Deviations

Protocol deviations will be presented in the participant data listings and summarized descriptively in the safety evaluable population.

6.4. Exposure

For participants in the safety evaluable population and FAS, exposure to INCMGA00012 will be summarized descriptively as follows:

- **Total number of infusions:** Total number of infusions per participant with an infusion of INCMGA00012.
- **Total dose administered (mg):** Estimated volume delivered divided by prepared volume × 500 mg.
- **Average dose (mg):** Total dose administered (mg) / total number of infusions.
- **Duration of treatment (days):** Date of last dose of INCMGA00012 – date of first dose of INCMGA00012 + 1.

  Duration of exposure in months will be calculated based on the assumption that each month has 30.4375 days. The number and percentage of participants in each duration category (ie, 0 to < 3 months, < 3 months, < 6 months, < 9 months, < 12 months, and other timepoints as applicable) will be summarized.

Infusion information collected in the eCRF will be listed. Dose delay and temporary infusion interruption may be summarized and/or listed as needed.

6.5. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary and summarized by ATC drug class and WHO drug term. Results will be summarized as number and percentage of participants with prior and concomitant medications by ATC class and WHO drug class in the safety evaluable population. For the summary of concomitant medication, only medications starting on or after the first dose of study drug and no later than 90 days after the last dose of study drug will be included. Medications with missing start/end dates will be considered as concomitant medication in the summary. Other medications will be provided in the listing. Drugs intended to manage irAEs as well as prophylaxis/premedication used to prevent infusion reactions may be summarized separately. Procedures and nondrug therapy will also be listed per the CRF.

7. EFFICACY

A list of planned tables, figures, and listings is provided in Appendix A.

7.1. General Considerations

Efficacy endpoints of this study include ORR, DOR, DCR, and PFS, based on RECIST v1.1 as determined by ICR, and OS. [redacted] For all efficacy analyses, participants with advanced and metastatic tumor status will be presented separately and combined together in the total column for chemotherapy-naive participants. The primary CSR analysis will be performed in the FAS, which includes approximately 60 chemotherapy-naive participants, and the analysis may be repeated in the final analysis including approximately 100 chemotherapy-naive participants.

7.2. Efficacy Hypotheses

Not applicable.

7.3. Analysis of the Efficacy Parameters

7.3.1. Response Criteria

Overall response will be categorized using RECIST v1.1 [redacted]. Participants will have their overall response evaluated as CR, PR, SD, PD, or NE for RECIST v1.1 [redacted] at each postbaseline radiological assessment based on changes in target lesions, nontarget lesions, and appearance of new lesions. Photographs will be taken for skin lesions if target lesions.

7.3.2. Primary Analysis

7.3.2.1. Objective Response Rate

The primary endpoint of the study is ORR in chemotherapy-naive participants, defined as the percentage of participants with CR or PR at any postbaseline visit before first PD or new anticancer therapy, according to RECIST v1.1 (Eisenhauer et al 2009) as determined by an ICR. The primary analysis of ORR will be performed at least 6 months after the last participant in the FAS is enrolled in the study. Participants who do not have sufficient baseline data to ascertain response will be included in the denominators in the calculation of ORR. The primary analysis of ORR will be based on the chemotherapy-naive subset of the FAS. Objective response rate and its exact 95% CI will be presented. In addition, ORR by investigator assessment will be provided as sensitivity analysis for the primary endpoint. The analysis will be repeated using the efficacy evaluable population as supportive analysis.

For participants with measurable disease at baseline, the RECIST v1.1 assessment criteria presented in Table 4 can be used to determine the overall response at a given timepoint based on the target lesion, nontarget lesion, and new lesion assessment.

Table 4: RECIST Evaluation Criteria for Overall Response

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

7.3.2.2. Handling of Missing Data in Primary Analysis

The study requires measurable disease at baseline per RECIST v1.1 as part of the inclusion criteria. However, if a participant did not have measurable disease and was administered study drug, the participant will be counted as a denominator in the calculation of ORR. Participants with subsequent missing assessments that prevent the evaluation of the primary endpoint will be considered nonresponders. No data imputation will be applied.

A response assessment of CR or PR reported before any additional anticancer therapy will be considered as a response in the calculation of ORR irrespective of the number of missed assessments before response.

7.3.2.3. Best Overall Response

The best overall response is the best response recorded from the start of the treatment until the first PD, in the order of CR, PR, SD, PD, and NE. Responses of CR, PR, or SD after a response of PD will not be considered in determining best response. The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria. The best overall response will be determined from response assessments before or on the same day as new anticancer therapy. If any alternative cancer therapy is taken while on study, any subsequent assessments will be excluded from the best overall response determination.

The best overall response for each participant is determined from the sequence of overall responses according to the following rules:

- CR = at least 2 consecutive determinations of CR at least 4 weeks apart before progression.
- PR = at least 2 consecutive determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD = at least 1 SD assessment (or better) ≥ 7 weeks after start of treatment (and not qualifying for CR or PR).
- PD = meets progression criteria comparing with nadir (and not qualifying for CR, PR, or SD).
- NE = all other cases (ie, not qualifying for confirmed CR or PR and without SD after more than 7 weeks or PD)

In the case of SD, measurements must meet the SD criteria at least after the date of first dose at a minimum of 7 weeks (49 days). Participants who fail to meet this criterion will have a best overall response of PD if the next available assessment indicates PD, or NE if there is no additional assessment available. Table 5 lists some scenarios of responses that can occur after an unconfirmed CR or PR in the 4-week follow-up time and provides a rule for determining the best overall response in these scenarios. Further detail of confirmed BOR can be found in confirmed BOR documentation.

Table 5: Confirmed Response Based on Subsequent Assessments

First Timepoint Response[a]	Second Timepoint Response	Confirmed Response[b]
CR	PR	SD or PD[c]
CR	SD	SD or PD[c]
CR	PD	SD or PD[c]
CR	CR	CR
CR	NE[a]	SD or NE[d]
CR	No further evaluation	SD or NE[d,e]
PR	CR	PR
PR	PR	PR
PR	SD[a,e]	SD
PR	NE[a]	SD or NE[d]
PR	PD	SD or PD[c]
PR	No further evaluation	SD or NE[d,e]
SD	PD	SD or PD[c]
SD	CR	SD
SD	PR	SD
SD	SD	SD
SD	NE	SD or NE[d]
SD	No further evaluation	SD or NE[d,e]
NE	CR	SD
NE	PR	SD
NE	SD	SD
NE	NE	NE
NE	PD	PD
NE	No further evaluation	NE
PD	No further evaluation	PD

[a] Subsequent documentation of CR may provide confirmation of a previously identified CR for participants where the second integrated response was NE. Subsequent documentation of PR may provide confirmation of a previously identified PR for participants where the second integrated response was NE or SD. If the third TPR confirms the CR (or PR,) then the confirmed response will be CR (or PR). Only 1 intervening NE is allowed between CRs/PRs. For example: CR NE CR = CR; PR NE PR/CR = PR. Additionally, 1 SD (≥ 25% reduction in target lesions comparing with baseline) is allowed between PRs (eg, PR SD PR/CR = PR). Note: In the following scenario, PR SD NE PR, the second PR is not a confirmed PR.

[b] A best response of SD can only be made after the participant is on study for a minimum of 49 days. If the participant is on study less than 49 days, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

[c] Best response will be SD if the first TPR is at least 49 days on study. Otherwise, the best response will be PD.

[d] Best response will be SD if the first TPR is at least 49 days on study. Otherwise, the best response will be NE.

[e] TPR is SD if the increase from the first to the second assessment does not qualify for PD.

7.3.3. Secondary Analysis

7.3.3.1. Duration of Response

Duration of response is defined as the time from first documented response (CR or PR, which is confirmed subsequently) to the time of first documented disease progression or death due to any cause. If a participant does not have an event before data cutoff or new anticancer therapy, DOR will be censored at the date of the last adequate tumor assessment before data cutoff or new anticancer therapy following the same algorithm as censoring of PFS (see Table 6). Duration of response will be analyzed in chemotherapy-naive participants at least 6 months after the last participant in the FAS is enrolled in the study. The Kaplan-Meier estimate of the distribution function will be constructed for DOR. The estimated median along with 95% CIs will be reported. A swimmer plot for DOR may be generated. Analysis of DOR will be according to RECIST v1.1 as determined by ICR in the FAS. In addition, DOR assessed by investigator may be provided. Participants with confirmed response that lasts for 6 months from Kaplan-Meier estimate (6-month DOR estimate) will be provided as DRR. The 95% CI of the DRR is derived by asymptotic CI using the standard formula for the variance of a product of independent random variables as follows:

$$Var(ORR * DOR_6) = (\sigma^2_{ORR} + \mu^2_{ORR})(\sigma^2_{DOR_6} + \mu^2_{DOR_6}) - \mu^2_{ORR}\mu^2_{DOR_6},$$

where σ^2 is the variance and μ is the mean. The percentage of participants with DOR longer than 6 months from landmark analysis will also be provided.

7.3.3.2. Disease Control Rate

Disease control rate is defined as the proportion of participants with an overall response (CR and PR) or SD lasting at least 6 months per RECIST v1.1, according to the ICR. The DCR will be assessed in chemotherapy-naive participants using the FAS, and the exact 95% CI will be reported.

7.3.3.3. Progression-Free Survival

Progression-free survival is defined as the time from the first dose of study treatment to the date of the first documented progression per RECIST v1.1 according to ICR or death due to any cause. Progression-free survival will be analyzed by the Kaplan-Meier method, including estimated median with 95% CIs and Kaplan-Meier estimated probabilities at several timepoints. If participants have no observed death or disease progression before data cutoff or new anticancer therapy, the participants will be treated as censored at their last adequate tumor assessment before cutoff or new anticancer therapy according to Table 6, which is based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007). Date of death will be determined using the Death Report, Survival Follow-Up, Subject Status, and other datasets collected in the eCRFs. Progression-free survival will be assessed for chemotherapy-naive participants in the FAS.

Table 6: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
Incomplete or no baseline tumor assessments	Censored	First Dose Date
No valid postbaseline response assessments in the absence of death prior to first scheduled tumor assessment	Censored	First Dose Date
Progression documented between scheduled response assessments	Progressed	Date of first overall response of PD
No progression	Censored	Date of last valid radiologic assessment (not NE or missing)
Study discontinuation for undocumented progression	Censored	Date of last valid radiologic assessment (not NE or missing)
Study discontinuation for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE or missing)
New anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE or missing) on/before starting a new anticancer treatment
Death before first progressive response assessment	Progressed	Date of death
Death between adequate response assessments	Progressed	Date of death
Death or documented progression immediately after missing 2 or more consecutive scheduled tumor assessment	Censored	Date of last valid radiologic assessment (not NE or missing) prior to missed assessments

7.3.3.4. Overall Survival

Overall survival is defined as the time from first dose of study treatment to the date of death due to any cause. Date of death will be determined using the Death Report, Survival Follow-Up, and Subject Status eCRFs. Participants who are lost to follow-up or still alive at the time of analysis will be censored at the last known alive date. The last known alive date is defined as the later of the last study visit and the date the participant was last known alive from the Survival Follow-Up, Subject Status, or other datasets collected in the eCRFs. Kaplan-Meier curves, medians, and 95% CIs of the medians will be presented for OS. Overall survival will be assessed for chemotherapy-naive participants using the FAS.

7.3.4. Tumor Size Change Over Time

Tumor size is defined as the sum of diameters of target lesions. The best percentage change from baseline, defined as the largest decrease in tumor size for each participant, will be summarized descriptively. In addition, the best percentage change may be presented by a waterfall plot. The analysis will be performed in all participants in the FAS with a baseline tumor size available. Tumor size change over time may be assessed for chemotherapy-naive participants.

Per RECIST v1.1, target lesions considered "too small to measure" will be assigned a default value of 5 mm for purposes of this analysis. Likewise, target lesions identified as "not present" at postbaseline assessments will be assigned 0 mm for this analysis. In the event a target lesion is unaccounted for in a particular postbaseline timepoint (ie, assessment missing or NE), then the overall sum of diameters for target lesions will not be evaluable for that timepoint.

7.3.5. Subgroup Analysis

Subgroup analyses will be performed on the following based on the participant's baseline status:

- Sex: Male, Female
- Baseline ECOG performance status: 0 vs 1
- Age: < 65 years vs ≥ 65 years and < 75 years vs ≥ 75 years
- Race: Caucasian, other
- Region: North America, Europe
- Ethnicity: Non-Hispanic or Latino, other
- PD-L1 status determined by central pathology review: < 1% or missing, ≥ 1%
- Merkel cell polyomavirus status determined by central pathology review: positive, negative/equivocal/missing

Subgroup analyses will only be performed if at least 5 participants are present in each subgroup. Some grouping of classes will be considered if there are too few participants in some subgroups.

[redacted]

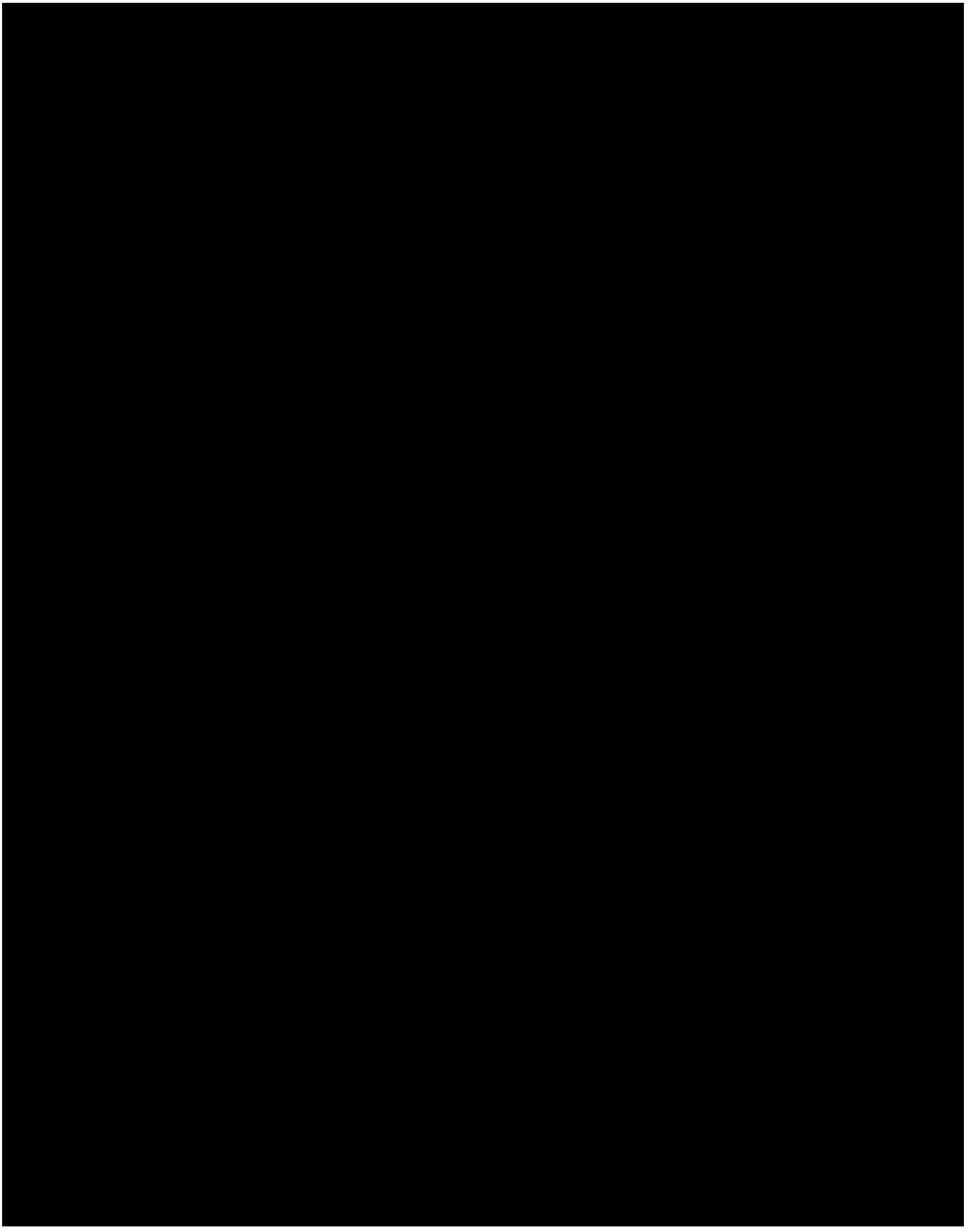
Subgroup analyses of the primary endpoint (ORR) will be performed on the FAS by presenting the point estimates in the subgroup with the exact 95% CIs. Summary tables and forest plots may be presented.

7.3.6. Exploratory Analysis

7.3.6.1. Efficacy Assessments in Full Population

Objective response rate, DOR, DCR, PFS, and OS will be analyzed in the full population following the same logic as the endpoints for the chemotherapy-naive participants.

[redacted]



[redacted]

8. SAFETY AND TOLERABILITY

A list of planned tables, figures, and listings is provided in Appendix A.

8.1. General Considerations

The clinical safety data (eg, vital signs, ECGs, routine laboratory tests, and AEs) will be summarized using descriptive statistics (eg, mean, frequency) using the safety evaluable population. The safety analyses will be performed separately for chemotherapy-naive participants and the full study population. In the chemotherapy-naive group, participants with advanced versus metastatic tumor status will be presented separately and combined together.

[redacted]

Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique PTs reported on relatively few participants.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after the first dose of study drug until 90 days after the last dose of study drug. Adverse events that occur after anticancer therapy will not be included as TEAEs. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the NCI CTCAE v5.0. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

The subset of AEs considered by the investigator to be related to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. In addition, serious TEAEs will also be tabulated.

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing causality and severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent.

Infusion-related reactions as well as irAEs (AESIs) may be summarized separately.

8.2.2. Adverse Events of Special Interest

Immune-related AEs as well as infusion reactions will be considered AESIs in this study. Predefined PTs will be grouped into AESI categories and used to identify irAEs or infusion reactions without consideration of investigator's assessment of causality. Diagnosis of infusion reactions occurring anytime during the treatment period, investigator-assessed infusion reaction, and symptoms of infusion reactions that occurred within 1 day of infusion, and resolved within 2 days from onset, are infusion reactions. Adverse events of special interest identified by investigator in the AE dataset will also be listed.

Immune-related AEs and infusion reactions will be summarized in separate tables. An overall summary of AESIs will include the number (%) of participants reporting any AESIs, any ≥ Grade 3 AESIs, any treatment-related AESIs, any fatal AESIs, and any AESIs leading to infusion interruption, delay in planned treatment, or discontinuation.

The AESI first onset time will be summarized by group term for all AESI groups. The percentage of participants who experienced the events and the median time of onset from treatment start will also be provided.

Resolution time of AESIs, defined as the time from the first onset of each AESI to the date of resolution of the last PT within the group, will be summarized by group term.

8.2.3. Adverse Event Summaries

An overall summary of AEs will include:

- Number (%) of participants reporting any TEAEs
- Number (%) of participants reporting any serious TEAEs
- Number (%) of participants reporting any Grade 3 or higher TEAEs
- Number (%) of participants reporting any TEAEs related to study drug
- Number (%) of participants reporting any serious TEAEs related to study drug
- Number (%) of participants reporting any Grade 3 or higher TEAEs related to study drug
- Number (%) of participants who temporarily interrupted study drug infusion because of TEAEs
- Number (%) of participants who the next scheduled study drug dose delayed because of TEAEs

- Number (%) of participants who permanently discontinued study drug because of TEAEs
- Number (%) of participants who had a fatal TEAE

The following summaries will be produced by MedDRA term (if 10 or fewer participants appear in a table, a listing may be appropriate):

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT in decreasing order of frequency
- Summary of TEAEs by SOC, PT, and maximum severity
- Summary of ≥ Grade 3 TEAEs by SOC and PT
- Summary of ≥ Grade 3 TEAEs by PT in decreasing order of frequency
- Summary of ≥ Grade 3 TEAEs by SOC, PT, and maximum severity
- Summary of treatment-related TEAEs by SOC and PT
- Summary of treatment-related TEAEs by PT in decreasing order of frequency
- Summary of treatment-related ≥ Grade 3 TEAEs by SOC and PT
- Summary of TEAEs with a fatal outcome by SOC and PT
- Summary of serious TEAEs by SOC and PT
- Summary of treatment-related serious TEAEs by SOC and PT
- Summary of serious TEAEs by PT in decreasing order of frequency
- Summary of TEAEs leading to delay in the next scheduled study drug dose by SOC and PT
- Summary of TEAEs leading to infusion interruption by SOC and PT
- Summary of TEAEs leading to study drug discontinuation by SOC and PT

The following summaries for AESIs will be included:

- Overall summary of TEAEs of special interest
- Summary of TEAEs of special interest by group term and PT
- Summary of TEAEs of special interest by group term, PT, and maximum severity
- Summary of TEAEs of special interest with a fatal outcome by group term and PT
- Summary of TEAEs of special interest leading to delay in the next scheduled study drug dose by group term and PT
- Summary of TEAEs of special interest leading to infusion interruption by group term and PT
- Summary of TEAEs of special interest leading to study drug discontinuation by group term and PT

- Summary of Grade 3 or higher TEAEs of special interest by group term and PT
- Summary of Grade 3 or higher TEAEs of special interest by group term, PT, and maximum severity
- Summary of time–to-first onset and time-to-resolution of identified TEAEs of special interest

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit. Baseline will be determined according to Section 4.1.5. If there are multiple values that meet the criteria for baseline, Table 8 may be referred as tiebreaker to delineate which value will be defined as baseline.

Table 8: Baseline Laboratory Identification

Priority	Laboratory Visit	Proximity to Visit Window	Tiebreaker
1	Scheduled	In-window	Use smallest laboratory sequence number
2	Unscheduled	In-window	
3	Scheduled	Out-of-window	

Laboratory test values outside the normal range will be assessed for severity based on CTCAE grade or similar criteria where clinical intervention is required for CTCAE grading. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

8.3.2. Laboratory Value Summaries

All test results and associated normal ranges from laboratories will be reported in SI units. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units. For test results that will be summarized with available normal ranges, the number and percentage of participants with the laboratory values being low (but never high), normal, high (but never low), and both low and high will be calculated for each test. This shift summary may be produced for each test for the safety evaluable population. The denominator for the percentage calculation will use the number of participants in the baseline category (ie, low, high, normal, missing) as the denominator for the percentage in each of the categories during the treatment period. For numeric laboratory values, baseline value, postbaseline value, change from baseline, and percentage change from baseline will be summarized by visit.

Shift tables will be presented showing change in CTC grade from baseline to worst postbaseline grade. Separate summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory parameter has both high and low grading criteria. The denominator for the percentage calculation will be the number of participants in the baseline category.

The following summaries will be produced for laboratory data (by laboratory parameter) reported on treatment. All laboratory assessments will be listed, and those collected later than 90 days after the last treatment/exposure date will be flagged in the listings.

- Number and percentage of participants with worst postbaseline CTC grade (regardless of the baseline status) will be summarized. Each participant will be counted only for the worst grade observed after baseline.
- Shift tables using CTC grades comparing baseline with the worst postbaseline value will be produced for hematology and chemistry laboratory parameters with CTC grades.
- For laboratory parameters where CTC grades are not defined, shift tables to the worst postbaseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.
- Number and percentage of participants meeting categorical liver function test criteria, including ALT, AST and ALT/AST (> 3 ×, 5 ×, 8 ×, 10 ×, 20 × ULN), total bilirubin (> 1 ×, 2 × ULN), ALP (> 1.5 ×, 2 ×, 3 ×, 5 ×, 8 ×, 10 × ULN), combined categories of ALT/AST and total bilirubin (eg, ALT/AST > 3 × ULN and total bilirubin > ULN), as well as Hy's Law criteria (ALT or AST > 3 × ULN and total bilirubin > 2 × ULN and ALP < 2 × ULN). The worst values observed postbaseline for each participant will be used for each of the categories.

8.4. Vital Signs

Values at each scheduled visit, change, and percentage change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, body temperature, and weight will be summarized descriptively.

Criteria for clinically notable vital sign abnormalities are defined in Table 9. The abnormal values for participants exhibiting clinically notable vital sign abnormalities will be listed. Alert vital signs are defined as an absolute value outside the defined range and percentage change from baseline greater than 25%. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 9: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Respiratory rate	> 24 breaths/min	< 8 breaths/min

8.5. Electrocardiograms

Twelve-lead ECGs including HR, RR, PR, QRS, QT, QTc, QTcF, and QTcB intervals will be obtained for each participant during the study. Values at each scheduled visit, change, and percentage change from baseline will be summarized for each ECG parameter. Baseline will be

determined as the last nonmissing ECG measurements taken on or before the first administration of study drug.

Criteria for clinically notable ECG abnormalities are defined in Table 10. Participants exhibiting clinically notable ECG abnormalities will be listed with study visit. Abnormal values for participants with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed.

Table 10: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF/QTcB	> 460 ms	< 295 ms
PR	> 220 ms	< 75 ms
QRS	> 120 ms	< 50 ms
QT	> 500 ms	< 300 ms
RR	> 1330 ms	< 600 ms
HR	≥ 100 bpm and ≥ 25% increase from baseline	≤ 50 bpm and ≥ 25% decrease from baseline

QTcB = Bazett correction; QTcF = Fridericia correction.

9. PHARMACOKINETIC [redacted] ANALYSIS

9.1. Pharmacokinetic Assessments

Serum concentrations of INCMGA00012 will be monitored using a quantitative sandwich ELISA method. Single- and multiple-dose PK parameters for INCMGA00012, C_{max}, t_{max}, AUC_t, and C_{min}, will be derived from INCMGA00012 serum concentration versus time data as a secondary endpoint. Population PK analyses may be conducted using data from this study alone or combined with data from other studies.

[redacted]

[redacted]

11. INTERIM ANALYSES

An analysis is planned after approximately 20 chemotherapy-naive participants are assessable for response according to RECIST v1.1. The primary intent of this analysis is to minimize unnecessary exposure of participants to INCMGA00012 in the event of futility. An ICR will be used for interim analysis if available; otherwise, investigator response assessment may be used. The study will be stopped for futility at the interim analysis if conditional power based on the interim result is lower than 20%, which is equivalent to fewer than 6 participants with an objective response. Since confirmed BOR will be analyzed, all participants enrolled with at least 2 postbaseline response assessments or participants who discontinued early will be included in the futility analysis. Participants enrolled in the study without 2 or more postbaseline response assessments but who are ongoing in the study will not be included in the futility analysis for calculation of conditional power. Enrollment will continue while the analysis is being conducted. This futility analysis will be reviewed by an independent DMC as specified in the DMC charter. The process by which the DMC will review data and make recommendations and decisions will be documented in the DMC charter.

At the time of this amendment, the DMC has reviewed the data for the interim analysis. The preliminary efficacy based on the ORR assessed by ICR exceeded the futility threshold, and the DMC recommended the study to proceed as planned.

12. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 11.

Table 11: Statistical Analysis Plan Versions

SAP Version	Date
Original	13 MAR 2019
Amendment 1	01 JUN 2020
Amendment 2	19 MAY 2021

12.1. Changes to Protocol-Defined Analyses

Not applicable.

12.2. Changes to the Statistical Analysis Plan

The following updates were made; some are to align with Protocol Amendment 6:

- The target population was increased to 100 in the final analysis, and approximately 60 chemotherapy-naive participants will be included in the primary analysis.
- Analysis grouping was added.
- [redacted]
- Analysis of DRR was added.
- Summary of onset and resolution time to AESI were updated to include only summary statistics.

The following updates were made to align with Protocol Amendment 5:

- The sample size was revised to approximately 60 chemotherapy-naive participants.
- The endpoints of ORR, DOR, DCR, PFS, and OS in the full study population were moved from the secondary endpoints to the exploratory endpoints.
- The FAS definition was revised and updated to include efficacy analyses.
- Creatinine clearance and hepatic function variables were added for program consistency.
- PD-L1 assessment, HIV status, ECOG performance status, and liver metastasis were added to the list of disease summaries.
- The interim analysis was updated to coincide with the confirmed BOR definition.
- The AESI definition and related analysis were updated for program consistency.

Other minor administrative changes have been incorporated throughout and are noted in the redline version of the document.

13. REFERENCES

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Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. N Engl J Med 2016;374:2542-2552.

[redacted]

APPENDIX A. PLANNED TABLES, FIGURES, AND LISTINGS

This appendix provides a list of the planned tables, figures, and listings for the Clinical Study Report. The lists of tables, figures, and listings are to be used as guidelines. Modifications of the lists that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP. The reference numbers are included here for reference purposes. The output number will follow the standard shell template.

Tables

Table No.	Title	Population
Baseline and Demographic Characteristics		
1.1 Disposition		
1.1.1	Analysis Populations	Enrolled
1.1.2	Summary of Participant Disposition	Safety
1.1.3	Summary of Number of Participants Enrolled by Country and Site	Enrolled
1.1.4	Summary of Protocol Deviations	Safety
1.2 Demography		
1.2.1	Summary of Demographics	Safety
1.3 Baseline Disease Characteristics (refine per data collection)		
1.3.1	Summary of Cancer History and Baseline Disease Characteristics	Safety
1.4 Prior Medication and Concomitant Medication (refine per data collection)		
1.4.1	Summary of Prior Medications	Safety
1.4.2	Summary of Concomitant Medications	Safety
1.4.3	Summary of Prior Systemic Therapy	Safety
1.4.4	Summary of Prior Radiotherapy	Safety
1.4.5	Summary of Prior Surgery/Procedure	Safety
1.4.7	Summary of Post Anticancer Therapy	Safety
1.5 Others		
1.5.1	Summary of General Medical History	Safety
1.6.1	Summary of Death	Safety
2 Efficacy (refine subgroup analysis as needed)		
2.1.1	Summary of Best Overall Response by ICR According to RECIST 1.1	FAS
2.2.1	Summary of Duration of Response by ICR According to RECIST 1.1	FAS
2.2.2	Summary of Disease Control Rate by ICR According to RECIST 1.1	FAS
2.2.3	Summary of Progression Free Survival by ICR According to RECIST 1.1	FAS
2.2.4	Summary of Overall Survival	FAS
2.2.5.1	Summary of Largest Percentage Reduction in Sum of Diameters of Target Lesions by Investigator	FAS
2.2.5.2	Summary of Largest Percentage Reduction in Sum of Diameters of Target Lesions by ICR	FAS
2.2.5.3	Summary of Sum of Diameters of Target Lesions by Visit by Investigator	FAS
2.2.5.4	Summary of Sum of Diameters of Target Lesions by Visit by ICR	FAS
2.3.1	Summary of Best Overall Response by ICR by Sex	FAS
2.3.2.1	Summary of Best Overall Response by ICR by Age Group 1	FAS
2.3.2.2	Summary of Best Overall Response by ICR by Age Group 2	FAS
2.3.3	Summary of Best Overall Response by ICR by Race	FAS
2.3.4	Summary of Best Overall Response by ICR by Ethnicity	FAS
2.3.5	Summary of Best Overall Response by ICR by ECOG Status at Baseline	FAS
2.3.6	Summary of Best Overall Response by ICR by PD-L1 Status at Baseline	FAS

Table No.	Title	Population
2.3.7	Summary of Best Overall Response by ICR by Merkel Cell Polyomavirus at Baseline	FAS
2.3.8	Summary of Best Overall Response by ICR by Pooled Region	FAS
[redacted]	[redacted]	[redacted]
2.5.1	Summary of Best Overall Response by Investigator	FAS
2.5.2	Summary of Duration of Response by Investigator Assessment According to RECIST 1.1	FAS
2.5.3	Summary of Progression Free Survival by Investigator According to RECIST 1.1	FAS
2.5.4	Summary of Best Overall Response by ICR According to RECIST 1.1	Efficacy
Safety		
3.1 Dose Exposure		
3.1.1	Summary of Exposure to INCMGA00012	Safety
3.1.2	Summary of Dose Delay/Interruption	Safety
3.2 Adverse Events		
3.2.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety
3.2.1.2	Overall Summary of Treatment-Emergent Adverse Events of Special Interest	Safety
3.2.2.1	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.2.2	Summary of Treatment-Emergent AESI by Group Term and Preferred Term	Safety
3.2.3.1	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.4.1	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety
3.2.4.2	Summary of Treatment-Emergent Adverse Events of Special Interest by Group Term, Preferred Term, and Maximum Severity	Safety
3.2.6.1	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.6.2	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events of Special Interest by Group Term and Preferred Term	Safety
3.2.7.1	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.8.1	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.9.1	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.10.1	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.11.1	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.14.1	Summary of Treatment-Related Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.15.1	Summary of Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.16.1	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety
3.2.16.2	Summary of Treatment-Emergent Adverse Events of Special Interest With a Fatal Outcome by Group Term and Preferred Term	Safety

Table No.	Title	Population
3.2.19.1	Summary of Treatment-Emergent Adverse Events Leading to Infusion Interruption by MedDRA System Organ Class and Preferred Term	Safety
3.2.19.2	Summary of Treatment-Emergent Adverse Events of Special Interest Leading to Infusion Interruption by Group Term and Preferred Term	Safety
3.2.19.3	Summary of Treatment-Emergent Adverse Events Leading to Next Scheduled Dose Delayed by MedDRA System Organ Class and Preferred Term	Safety
3.2.19.4	Summary of Treatment-Emergent Adverse Events of Special Interest Leading to Next Scheduled Dose Delayed by Group Term and Preferred Term	Safety
3.2.20.1	Summary of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by MedDRA System Organ Class and Preferred Term	Safety
3.2.20.2	Summary of Treatment-Emergent Adverse Events of Special Interest Leading to Study Drug Discontinuation by Group Term and Preferred Term	Safety
3.2.27.1	Summary of Onset and Resolution Time of Treatment-Emergent Sponsor-Defined Adverse Events of Special Interest	Safety
3.3 Laboratory		
3.3.1.1	Summary of Laboratory Hematology Values	Safety
3.3.1.2	Summary of Laboratory Chemistry Values	Safety
3.3.1.3	Summary of Laboratory Coagulation Values	Safety
3.3.1.4	Summary of Laboratory Urinalysis Values	Safety
3.3.1.5	Summary of Laboratory Endocrine Values	Safety
3.3.2.1	Shift Summary of Hematology Laboratory Values to the Worst Abnormal Value	Safety
3.3.2.2	Shift Summary of Chemistry Laboratory Values to the Worst Abnormal Value	Safety
3.3.2.3	Shift Summary of Coagulation Laboratory Values to the Worst Abnormal Value	Safety
3.3.3.1	Shift Summary of Hematology Laboratory Values in CTC Grade to the Worst Abnormal Value	Safety
3.3.3.2	Shift Summary of Chemistry Laboratory Values in CTC Grade to the Worst Abnormal Value	Safety
3.3.3.3	Shift Summary of Coagulation Laboratory Values in CTC Grade to the Worst Abnormal Value	Safety
3.3.3.4	Treatment-Emergent Worsening of Laboratory Abnormalities - Hematology	Safety
3.3.3.5	Treatment-Emergent Worsening of Laboratory Abnormalities - Chemistry	Safety
3.3.3.6	Treatment-Emergent Worsening of Laboratory Abnormalities - Coagulation	Safety
3.3.6	Summary of Liver Chemistry	Safety
3.4 Vital Signs		
3.4.1	Summary of Systolic Blood Pressure	Safety
3.4.2	Summary of Diastolic Blood Pressure	Safety
3.4.3	Summary of Pulse	Safety
3.4.4	Summary of Respiration Rate	Safety
3.4.5	Summary of Body Temperature	Safety
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3.5 ECG		
3.5.1	Summary of PR Interval (ms) From 12-Lead ECG	Safety
3.5.2	Summary of QRS Interval (ms) From 12-Lead ECG	Safety
3.5.3	Summary of QT Interval (ms) From 12-Lead ECG	Safety
3.5.4	Summary of RR Interval (ms) From 12-Lead ECG	Safety
3.5.5	Summary of QTcF Interval (ms) From 12-Lead ECG	Safety
3.5.6	Summary of QTcB Interval (ms) From 12-Lead ECG	Safety

Table No.	Title	Population
3.5.7	Summary of Heart Rate From 12-Lead ECG	Safety
[redacted]		

Figures

Figure No.	Title
Efficacy (Lab figures may be added as needed. Kaplan-Meier plots may be added for investigator and for different analysis population)	
4.1.1	Kaplan-Meier Estimates of Duration of Response by ICR
4.1.2	Kaplan-Meier Estimates of Duration of Response by Investigator
4.2.1	Kaplan-Meier Estimates of Progression-Free Survival by ICR
4.2.2	Kaplan-Meier Estimates of Progression-Free Survival by Investigator
4.3.1	Kaplan-Meier Estimates of Overall Survival
4.3.2.1	Waterfall Plot of Best Percentage Change in Sum of Target Lesions by ICR
4.3.2.2	Waterfall Plot of Best Percentage Change in Sum of Target Lesions by Investigator
4.3.3.1	Swimmer Plot of Duration of Treatment by ICR
4.3.3.2	Swimmer Plot of Duration of Treatment by Investigator
4.3.3.3	Swimmer Plot of Duration of Treatment for Responders by ICR
4.3.4.1	Forest Plot of Overall Response and 95% CI by Investigator
4.3.4.2	Forest Plot of Overall Response and 95% CI by ICR
4.5.X	Mean and Standard Error of Lab Parameters
[redacted]	[redacted]

Listings (data dump listings may be added)

Listing No.	Title
2.1 Discontinued Participants (Participant Disposition)	
2.1.1	Participant Enrollment and Disposition Status
2.1.2	Participant Inclusion and Exclusion Criteria Violations
2.2 Protocol Deviations	
2.2	Protocol Deviations
2.3 Data Excluded From PK, Efficacy, and/or Safety Analyses	
2.3	Analysis Populations
2.4 Demography and Baseline (Including Prior and Concomitant Medications)	
2.4.1	Demographic and Baseline Disease Characteristics
2.4.2	Cancer Disease History and Baseline Disease Characteristics
2.4.3	Prior Radiotherapy
2.4.4	Prior Systemic Cancer Therapy
2.4.5	Prior Surgery or Surgical Procedure
2.4.6	Medical History
2.4.7	Prior and Concomitant Medications
2.4.8	Procedures and Nondrug Therapy

Listing No.	Title
2.4.9	Summary of Post Anticancer Therapy
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2.5	Study Drug Exposure
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2.6.2	Progression-Free Survival Events and Assessments by ICR
2.6.3	Overall Response Assessment by ICR
2.6.4	Duration of Response by ICR
2.6.5.1	Response Assessment by Investigator for Target Lesions
2.6.5.2	Response Assessment by ICR for Target Lesions
2.6.6.1	Response Assessment by Investigator for Non-Target Lesions
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2.6.7.1	Response Assessment by Investigator for New Lesions
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2.6.8.1	Largest Percentage Reduction in Sum of Diameters of Target Lesions by Investigator
2.6.8.2	Largest Percentage Reduction in Sum of Diameters of Target Lesions by ICR
[redacted]	[redacted]
2.6.11	Overall Response Assessment by Investigator Assessment
2.6.12	Duration of Response by Investigator Assessment According to RECIST
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2.7 Adverse Events	
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2.7.2	Serious Adverse Events
2.7.3	Fatal Adverse Events
2.7.4	Adverse Events Leading to Study Drug Discontinuation
2.7.5	Adverse Events Leading to Study Drug Interruptions or Delays
2.7.6	Adverse Events of Special Interest
2.7.7	Adverse Events ≥ Grade 3
2.7.8	Investigator Identified Adverse Events of Special Interest
2.8 Laboratory Data	
2.8.1	Clinical Laboratory Values – Hematology
2.8.2	Clinical Laboratory Values – Chemistry
2.8.3	Clinical Laboratory Values – Urinalysis
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2.8.5	Clinical Laboratory Values – Endocrine
2.8.6.1	Abnormal Clinical Laboratory Values – Hematology
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2.8.6.4	Abnormal Clinical Laboratory Values – Coagulation
2.8.7	Clinical Laboratory Values – Pregnancy
2.8.8	Clinical Laboratory Values With Toxicity Grade 3 or Higher – Hematology
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2.8.10	Clinical Laboratory Values – Liver Chemistry
2.8.11	PK Blood Sampling Times
[redacted]	[redacted]
2.9 Vital Signs	
2.9.1	Vital Signs
2.9.2	Abnormal Vital Sign Values

Listing No.	Title
2.9.3	Alert Vital Sign Values
2.10 Electrocardiograms	
2.10.1	ECG Values
2.10.2	Abnormal ECG Values
2.10.3	Alert ECG Values
2.11 Other	
2.11.1	Tobacco Use
2.11.2	Alcohol Assumption
2.11.3	ECOG Performance Status
[redacted]	[redacted]
[redacted]	[redacted]