BeiGene

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-900-101
Study Protocol Title:	Phase 1/2 Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-PD-L1 Monoclonal Antibody BGB-A333 Alone and in Combination with Anti-PD-1 Monoclonal Antibody Tislelizumab in Patients with Advanced Solid Tumors
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
A317	BGB-A317
A333	BGB-A333
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
CR	complete response
CSR	clinical study report
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture (system)
FDA	Food and Drug Administration
irAE	immune-related adverse event
iRECIST	immune-related Response Evaluation Criteria in Solid Tumors
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	pharmacodynamics; progressive disease
PD-1	programmed cell death protein-1
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	prothrombin time; preferred term
Q2W	every 2 weeks
Q3W	every 3 weeks
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SMC	Safety Monitoring Committee
SOC	system organ class
TEAE	treatment-emergent adverse event
UC	urothelial carcinoma; urothelial cancer

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to pre-specify the procedures and the statistical methods (before the database lock) that will be used to analyze data and report results for Study BGB-900-101: a Phase 1-2 Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-PD-L1 Monoclonal Antibody BGB-A333 Alone and in Combination with Anti-PD-1 Monoclonal Antibody Tislelizumab in Patients with Advanced Solid Tumors. This SAP is for the final analyses of the final study protocol (Protocol amendment 2.0). Supporting documents and references are included in Appendices.

The analyses to the sample data of pharmacokinetics (PK), pharmacodynamics (PD), pharmacogenomics (ADA) and biomarkers, are not covered in this document and they will be described in separate documents.

2 STUDY OVERVIEW

2.1 OVERVIEW

This is an open-label, multicenter, nonrandomized Phase 1 and Phase 2 clinical trial. This study consists of the following phases:

- Phase 1A (BGB-A333 dose escalation): approximately 4-5 dose levels or dosing regimens will be tested in patients with advanced solid tumors. Additional dose levels could be tested if needed. The modified 3+3 design will be used in the dose escalation. At least 6 evaluable patients should be enrolled at the MTD level, the RP2D level or at the highest dose level tested if MTD is not reached.
- Phase 1B (BGB-A333 and tislelizumab dose confirmation): a cohort of approximately 6 patients with solid tumors will be treated with BGB-A333 and tislelizumab (200 mg, Q3W, IV). The SMC will make a recommendation on the selection of BGB-A333 dose based on available safety, efficacy, PK and exploratory data from Phase 1A. If the initial dose combination is deemed not tolerated, additional cohorts of patients may be enrolled to evaluate lower doses or alternative dosing regimens of BGB-A333 and tislelizumab.
- Phase 2B (BGB-A333 and tislelizumab dose expansion): approximately 20 patients with UC may be enrolled.

All patients will receive study drug until 1) they are no longer considered to be achieving clinical benefit, 2) unacceptable toxicity, or 3) withdrawal of informed consent.

In Phase 1A (BGB-A333 monotherapy), if patients progress on BGB-A333 without other safety concerns, these patients may be treated with a higher dose of BGB-A333 that is deemed to be well tolerated by SMC. The decision to modify the dose of BGB-A333 must be discussed with the sponsor's medical monitor and documented in the study records.

In Phase 1A (BGB-A333 monotherapy), if patients progress on BGB-A333 monotherapy without other safety concerns, these patients may receive combination of BGB-A333 and tislelizumab at doses that are deemed to be well tolerated by SMC. The decision to add tislelizumab to patients

treated with BGB-A333 alone must be discussed with the sponsor's medical monitor and documented in the study records.

Planned dose levels for BGB-A333 and tislelizumab are provided in Table 1. All patients will be monitored continuously for AEs. Treatment modifications (eg, dose delay or discontinuation) will be based on specific AE criteria, as described in Section 5.4 of the protocol. Reasons for dose modifications or delay or treatment discontinuation will be documented in the patients' chart and recorded in the eCRF.

Table 1. Planned Dose Levels for BGB-A333 and Tislelizumab

Study Drug	Dose	Frequency of Administration	Route of Administration
BGB-A333	450 mg, 900 mg, 1350 mg, 1800 mg, 2250 mg (optional)	Every 3 weeks (additional dose levels or dosing regimens may be explored)	Intravenous
Tislelizumab	200 mg	Every 3 weeks (additional dose levels or dosing regimens may be explored)	Intravenous

BGB-A333 and tislelizumab will be administered by IV infusion through an IV line containing a sterile, non-pyrogenic, low-protein-binding filter.

For BGB-A333 monotherapy (Phase 1A), on C1D1, C2D1 and C3D1, the infusion of BGB-A333 will be delivered over 60 (± 5) minutes. After infusion of BGB-A333, patients must be monitored for at least 120 minutes in an area with resuscitation equipment and emergency agents.

If BGB-A333 infusion is well tolerated in the first three cycles, on C4D1 and subsequent cycles, BGB-A333 may be administered over 30 (± 5) minutes and, after infusion of BGB-A333, patients must be monitored for at least 30 minutes in an area with resuscitation equipment and emergency agents.

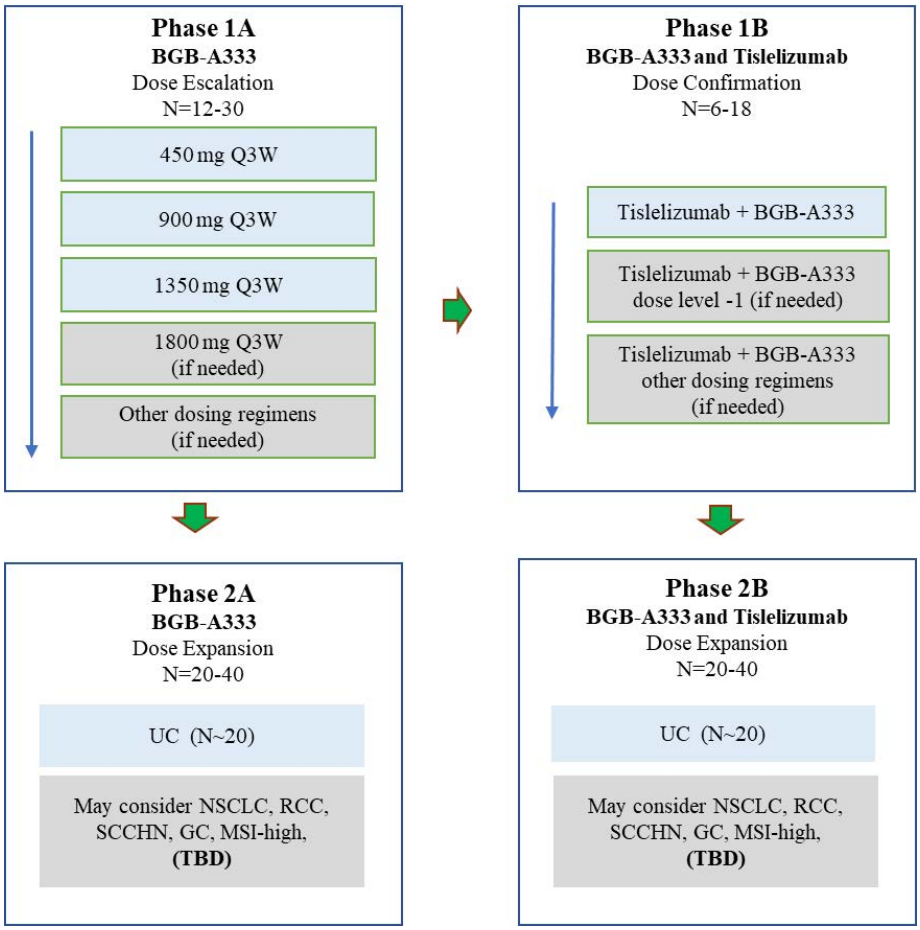
For BGB-A333 and tislelizumab combination arms (Phase 1B and Phase 2B), tislelizumab will be administered first followed by the administration of BGB-A333.

- On C1D1 and C2D1, tislelizumab will be administered over 60 (± 5) minutes followed by the administration of BGB-A333 over 60 (± 5) minutes. After infusion of BGB-A333, patients must be monitored for at least 120 minutes in an area with resuscitation equipment and emergency agents.

- If infusions of tislelizumab and BGB-A333 are well tolerated in the first two cycles, on C3D1, tislelizumab may be administered over 30 (± 5) minutes followed by the administration of BGB-A333 over 60 (± 5) minutes and, after infusion of BGB-A333, patients must be monitored for at least 60 minutes in an area with resuscitation equipment and emergency agents.
- If infusions of tislelizumab and BGB-A333 are well tolerated in the first three cycles, on C4D1 and subsequent cycles, tislelizumab may be administered over 30 (± 5) minutes followed by the administration of BGB-A333 over 30 (± 5) minutes and, after infusion of BGB-A333, patients must be monitored for at least 30 minutes in an area with resuscitation equipment and emergency agents.

The infusion rate may be decrease or infusion may be stopped in the evet of infusion-related reactions.

Figure 1 Study Schema



Abbreviations: UC = urothelial carcinoma; Q3W = every 3 weeks.

A Sponsor decision was made not to pursue A333 as a monotherapy treatment beyond the completion of dose escalation in Phase 1A. As such, Phase 2A was not initiated nor conducted in the study. For Phase 2B, only one cohort was opened for dose expansion and a total of 12 patients were treated in the metastatic urothelial carcinoma arm (mUC).

2.2 STUDY ASSESSMENTS

DLT Assessment

For Phase 1A (BGB-A333 dose escalation), at least 3 patients evaluable for dose-limiting toxicity (DLT) assessment will be enrolled per dose level. Dose escalation will proceed to the next dose level if no DLT is observed in the first 3 DLT-evaluable patients. Otherwise, if a DLT has occurred, the cohort is expanded to at least 6 patients. If there is no additional DLT in the first 6 DLT-evaluable patients, dose escalation will continue to the next level. Dose escalation will stop when there are 2 or more DLTs in 6 patients within the same dose level. If 2 or more DLTs are reported in 6 patients at a dose level, a minimum of 6 patients will be enrolled on the next lower dose level, or an intermediate dose level may be evaluated if recommended by the SMC. The MTD dose level is defined as the highest dose at which < 33% of the patients experience a DLT. At least 6 evaluable patients should be enrolled at the MTD level, the RP2D level or at the highest dose level tested if MTD is not reached.

DLTs will be assessed among evaluable patients within 21 days after the first dose of BGB-A333. For dose escalation decision, only DLTs occurring within the first 21 days will be evaluated. For determination of MTD and RP2D, clinically significant toxicities (e.g., irAE) will also be considered.

Adverse Events

Adverse events will be graded and recorded throughout the study according to NCI-CTCAE, version 4.03 (NCI-CTC, June 2010). Characterization of toxicities will include severity, duration, and time to onset.

All toxicities or adverse events will be graded according to the NCI-CTCAE Version 4.03.

Definition of DLT

The occurrence of any of the following toxicities within 21 days after the first dose of BGB-A333 if judged by the Investigator as related to BGB-A333 will be considered a DLT.

Hematologic:

1. Grade 4 neutropenia lasting > 7 days
2. Grade 3 febrile neutropenia (defined as absolute neutrophil count [ANC] <1000/mm^3 with a single temperature of 38.3ºC or a sustained temperature of 38ºC for >1 hour)
3. Grade 3 neutropenia with infection
4. Grade 4 thrombocytopenia with bleeding
5. Grade 4 thrombocytopenia

6. Grade 4 anemia (life-threatening)

Non-hematologic:

1. Grade 4 or above toxicity
2. Grade 3 toxicity lasting more than 7 days despite optimal supportive care

Note: The following AEs will not be considered as DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumors)
- Grade 3 rash
- Grade 3 to Grade 4 laboratory abnormalities that are not associated with clinical sequelae (eg, LDH)

In addition, clinically important or persistent toxicities that are not included above may also be considered a DLT following review by SMC.

Patients who received < two-thirds (67%) of the assigned dose of BGB-A333 (eg, because the infusion had to be stopped due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level.

Tumor Assessments

Radiological assessment of tumor-response status should be performed approximately every 9 weeks (for Q3W dosing) in the first year, then every 12 weeks thereafter. If other dosing intervals are explored (Q2W or Q4W), radiological assessment of tumor response will be performed approximately every 8 weeks.

Tumor response will be assessed by Investigators based on the RECIST version 1.1.

For immune therapies, such as BGB-A333 and tislelizumab, pseudoprogression may occur due to immune-cell infiltration and other mechanisms leading to apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, if radiographic progressive disease is suspected by the investigator to reflect pseudoprogression, patients may continue treatment with study drug(s) until PD is confirmed by repeated imaging at least 4 weeks later but not exceeding 8 weeks from the date of initial documentation of PD. The following criteria must be met in order to continue study drug treatment in patients with suspected pseudoprogression:

- Absence of clinical symptoms and signs of disease progression (including clinically significant worsening of laboratory values)
- Stable ECOG performance status
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer

The decision to continue study drug(s) beyond investigator-assessed progression must be agreed with the sponsor's medical monitor and documented in the study records.

3 STUDY OBJECTIVES

Study objectives are presented by study phase in this section.

3.1 PRIMARY OBJECTIVES

Primary Objectives for Phase 1A (Dose Escalation for BGB-A333 Monotherapy) and Phase 1B (Dose Confirmation for BGB-A333 and Tislelizumab Combination)

- To assess the safety and tolerability of BGB-A333 alone and in combination with BGBA317 in patients with advanced solid tumors
- To determine the maximum tolerated dose (MTD), if any, and RP2D for BGB-A333 alone and in combination with tislelizumab

Primary Objectives for Phase 2B (BGB-A333 and Tislelizumab Combination Dose Expansion)

To assess objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 of BGB-A333 alone and in combination with tislelizumab in patients with selected tumor types

3.2 SECONDARY OBJECTIVES

Secondary Objectives for Phase 1A and Phase 1B:

- To assess the preliminary antitumor activity of BGB-A333 alone and in combination with tislelizumab
- To characterize the PK of BGB-A333 alone and in combination with tislelizumab
- To assess host immunogenicity to BGB-A333 alone and in combination with tislelizumab

Secondary Objectives for Phase 2B:

- To assess other tumor assessment outcomes (ie, duration of response [DOR], progression-free survival [PFS] and disease control rate [DCR]) per RECIST version 1.1
- To characterize safety and tolerability of BGB-A333 alone and in combination with tislelizumab

- To characterize the PK of BGB-A333 alone and in combination with tislelizumab
- To assess host immunogenicity to BGB-A333 and tislelizumab

3.3 EXPLORATORY OBJECTIVES

[redacted]

4 STUDY ENDPOINTS

Study endpoints, separated as the primary, secondary and exploratory endpoints, are explained in this section.

4.1 PRIMARY ENDPOINTS

Primary endpoints for Phase 1A and Phase 1B:

- Safety and tolerability: The safety of BGB-A333 alone and in combination with tislelizumab will be assessed throughout the study by monitoring AEs and SAEs per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03, relevant physical examination, electrocardiograms and laboratory assessments as needed
- The MTD, if any, and Recommended Phase 2 Dose (RP2D) for BGB-A333 alone and in combination with tislelizumab will be determined based on safety, tolerability, PK, preliminary efficacy, and other available data

Primary endpoints for Phase 2B:

- Efficacy evaluations: ORR will be determined based on investigators assessment per RECIST version 1.1. The ORR is defined as the proportion of patients who had confirmed CR or PR assessed by investigator using RECIST version 1.1. ORR and its 95% CI will be summarized in the Safety Population

4.2 SECONDARY ENDPOINTS

Secondary endpoints for Phase 1A and Phase 1B:

- Efficacy evaluations: ORR, DOR, and DCR based on investigator assessment per RECIST version 1.1.
    - ORR is defined as the proportion of patients who had confirmed complete response (CR) or partial response (PR) assessed by investigator using RECIST version 1.1. ORR and its 95% confidence interval (CI) will be summarized in the Safety Population and Efficacy Evaluable Population
    - DOR is defined as the time from the first determination of an objective response per RECIST version 1.1, until the first documentation of progression or death, whichever occurs first
    - DCR is defined as the proportion of patients with best overall response of CR, PR and SD. It will be summarized similarly as ORR
- PK: Individual BGB-A333 and tislelizumab concentrations and PK parameters will be tabulated by dose cohort
- Immunogenicity: Immunogenic responses to BGB-A333 and tislelizumab will be assessed by summarizing the number and percentage of patients by dose cohort who develop detectable antidrug antibodies

Secondary endpoints for Phase 2B:

- DOR, PFS, and DCR based on investigator assessment per RECIST version 1.1.
    - PFS is defined as the time from the date of the first dose of study drug(s) to the date of the first documentation of disease progression assessed by investigator using RECIST v1.1 or death, whichever occurs first
- Safety and tolerability: The safety of BGB-A333 in combination with tislelizumab will be assessed throughout the study by monitoring AEs and SAEs per NCI-CTCAE Version 4.03, relevant physical examination, electrocardiograms and laboratory assessments as needed
- PK: Individual concentrations and PK parameters of BGB-A333 and tislelizumab
- Immunogenicity: Immunogenic responses to BGB-A333 and tislelizumab will be assessed by summarizing the number and percentage of patients who develop detectable antidrug antibodies (ADAs)

5 SAMPLE SIZE CONSIDERATIONS

The study plans to enroll approximately 98 to 128 patients.

- Phase 1A (BGB-A333 dose escalation): Approximately 12 to 30 patients with advanced solid tumors in 4 to 5 dose levels or dosing regimens per modified 3+3 design
- Phase 1B (BGB-A333 and tislelizumab combination): Approximately 6 patients with advanced solid tumors in one combination dosing regimen. An additional 12 patients may be enrolled to test different dosing regimens
- Phase 2B (BGB A333 and tislelizumab combination dose expansion): Approximately 20 patients with UC

In Phase 2, approximately 20 patients per cohort will be enrolled to evaluate the preliminary efficacy. No formal hypothesis testing will be performed in the efficacy evaluation. With 20 patients, the probabilities of observing at least one responder under different underlying ORR assumptions are summarized in Table 2, indicating the proposed sample size is adequate to detect any preliminary anti-cancer activities of the treatment. The 95% CIs of the ORR estimate when observing 1 to 6 responders are included in Table 3, depicting the precision achieved with 20 patients.

Table 2. Time Probabilities of Observing at least One Responder in 20 Patients under Various ORR Assumptions

ORR	**0.10**	**0.20**	**0.30**	**0.40**
Probability (observing ≥ 1 responder)	0.88	0.99	> 0.99	> 0.99

Table 3. 95% CI (%) when Observing 1 to 6 Responders in 20 Patients

# of responders	**1**	**2**	**3**	**4**	**5**	**6**
95% CI	(0.1, 24.8)	(1.2, 31.7)	(3.2, 37.9)	(5.7, 43.7)	(8.7, 49.1)	(11.9, 54.3)

6 STATISTICAL METHODS

6.1 ANALYSIS POPULATIONS

Safety Population includes all patients who received at least 1 dose of study drug. It is the population for the safety and efficacy analyses.

The PK analysis population includes all patients with valid PK sampling after treatment with study drug(s)

6.2 DATA ANALYSIS GENERAL CONSIDERATIONS

All the reporting of data analyses, including summary tables and listings, is presented by phase and cohort (per dose level for Phase 1A and Phase 1B, or tumor type for Phase 2B). All data will be listed as well.

All efficacy and safety analyses will be performed for safety population. The analyses of ORR and its 95% confidence interval will be repeated for efficacy evaluable population as well. All listings will be presented for safety population unless otherwise specified.

6.2.1 Definitions and Computations

Reference date: is the first date of any study drug (A333 or A317) taken per patient. This date is noted as Day 1 of Cycle 1.

Study day: is the relative day of an assessment (for any event or observation) in reference to a patient's date of first dose of study drug, calculated as (assessment date – reference date +1) for any assessment conducted on or after the reference date, or as (assessment date – reference date) for any assessment conducted before the reference date. So, the study day for the first dose is 1, noted as study day 1 (also, as explained above, as Day 1 of Cycle 1). Correspondingly, the study month of an assessment if needed is defined as the study day of the assessment divided by 365.25 and by 12 (i.e., 365.25/12), rounded to 2 decimal places. When the event date is partial or missing, the date will appear partial or missing in the listings.

Baseline assessment: is the last non-missing assessment collected prior to the first study drug.

6.2.2 Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- Summary analyses for continuous endpoints or variables will include n, mean, standard deviation, median, and range (minimum and maximum); summary analyses for categorical or discrete endpoints or variables will be in number (%) of patients reached the endpoint or variable, unless otherwise specified. For the second, the denominator to be used for the percentage will be the total number of patients by cohort of the analysis population, unless otherwise specified.
- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 decimal place.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 decimal place.
- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25
- Duration of event endpoints will be based on the actual date of event obtained rather than the associated visit date.
- Missing efficacy or safety data will not be imputed unless otherwise specified.
- For laboratory results collected as < or >, a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator, unless otherwise specified. Unscheduled measurements will not be included but will contribute to the worst if required in the analyses. Listings will include all, the scheduled and the unscheduled.
- Data will be presented to the original number of decimal places. The mean and medians will be presented to 1 more decimal place than the raw data. The standard deviations will be presented to 2 more decimal places than the raw data.

6.2.3 Handling of Missing Data

Missing data will not be imputed unless otherwise specified in the footnote of an output. Missing data will not be included in any analysis unless otherwise specified as well. When relevant, the number of patients with missing data will be presented.

6.2.3.1 Date of medication missing or partially missing

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and cannot be determined whether it was taken prior or concomitantly, it will be considered concomitant.

6.2.3.2 Onset date of adverse event missing or partially missing

When an AE has a missing or partially onset date, if the missing or partially onset date does not indicate that the AE started prior to the study treatment or after the 30th day post last study treatment, it will be classified conservatively as the treatment-emergent AE (TEAE, defined in Section 6.5.2). This data handling is just for the determination of treatment emergent adverse events and no imputation will be performed to AE start/end dates in datasets and listings.

6.2.3.3 Relationship of adverse event to study treatment

If the assessment of the relationship of an AE to study drug is missing, the event will be considered related to the study drug. This handling is only for the classification and no imputation will be done at the data level.

6.2.3.4 Severity (grade) of adverse event

If a severity is missing for an AE interested, and the maximal severity on the remaining occurrences of this AE is mild or moderate, then the worst severity of the event cannot be determined. Therefore, whenever a summary of AEs by severity is to be presented, this event will be in a separate “missing” category.

6.2.4 Adjustment for Covariates

Not applicable.

6.2.5 Multiplicity Adjustment

No multiplicity adjustments will be made.

6.2.6 Data Integrity

Before final statistical, the integrity of the data should be reviewed to assure fit-for-purpose. The data set for analysis should be an accurate and complete representation of the patients' relevant outcomes from the clinical database. All data should be complete and reviewed up to data cutoff date. Consistency checks and appropriate source data verification should be complete.

6.3 SUBJECT CHARACTERISTICS

6.3.1 Patient Disposition

The number of patients treated, discontinued from study drug and/or study and those with major protocol deviations will be summarized. The primary reason for study drug and/or study discontinuation will be summarized according to the categories in the eCRF. The end of study status (alive, dead, withdrew consent, lost to follow-up or compassionate use) at the data cut-off date will be summarized using the data from the eCRF.

6.3.2 Protocol Deviations

Major protocol deviations/violations will be summarized by category. All major protocol deviations/violations will be listed.

6.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized for the Safety Population using descriptive statistics. Continuous variables include age, weight, vital signs, etc. Categorical variables include race, gender, ECOG, country etc.

6.3.4 Disease History and Baseline Disease Characteristics

Disease history and baseline characteristics include time since initial cancer diagnosis to date of signed consent, type of solid tumor at initial diagnosis, metastatic disease status at initial diagnosis, and metastatic disease status at study entry.

Cancer associated symptoms at baseline will also be summarized by System Organ Class (SOC), preferred term.

6.3.5 Prior Anti-Cancer Drug Therapies and Radiotherapies

The number (%) of prior anti-cancer drug therapies and prior radiotherapies will be summarized. The systemic therapies with the same sequence/regimen number are counted as one prior therapy.

For prior anti-cancer drug therapy, number of regimens, time from end of last systemic therapy to study entry, best response for last therapy, and reason for therapy discontinuation will be summarized.

6.3.6 Prior and Concomitant Medications

Concomitant medications will be assigned an 11-digit code using the World Health Organization (WHO) Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class and WHO drug preferred term for the safety population.

Prior medications are defined as medications that stopped before the first dose of study drug. Concomitant medications are defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose.

6.3.7 Medical History

Medical History will be coded using MedDRA (version 20.0 or newer). The number (%) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class and preferred term for safety population.

6.4 EFFICACY ANALYSIS

The efficacy per RECIST 1.1 (ie, ORR, DOR, PFS, and DCR) will be summarized by dose cohort in Phase 1A and Phase 1B. Efficacy will be summarized by tumor type in Phase 2B.

All efficacy analyses will be performed for safety population. All time-to-event endpoints (PFS, DOR) will be analyzed by Kaplan-Meier (KM) method.

6.4.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the objective response rate (ORR) for Phase 2B. Objective response rate is defined as proportion of patients with best overall response (BOR) of CR or PR. Confirmation of CR or PR is required for BOR of CR or PR. Patients without BOR of CR or PR will be considered as non-responders.

The analyses will include number (%) of patients achieved the confirmed overall response as CR or PR and the 2-sided 95% confidence interval (CI) to the ORR by Clopper-Pearson method.

ORR for Phase 1A and Phase 1B will also be summarized similarly by cohort.

Best overall response is defined as the best response recorded from administration of study drug(s) until data cut or the start of new anticancer treatment. Patients with no post-baseline response assessment (due to any reason) will be considered as not evaluable for best overall response (BOR). The proportion of response categories (CR, PR, SD, and PD) will be presented.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints, including progression-free survival (PFS), duration of response (DOR), disease control rate (DCR), and clinical benefit rate (CBR). All the analyses will be performed for safety population.

PFS will be estimated using the Kaplan-Meier (KM) method. The median PFS and landmark PFS at every 3 months will be calculated and presented with 2-sided 95% CIs.

PFS is defined as the time from the date of first dose of study drug to the date of PD or death, whichever occurs first. Patients without PD/death will be censored at date of last adequate tumor assessment. The PFS censoring rule will follow United States Food and Drug Administration

(FDA) Guidance for Industry, Clinical Trial Endpoints for Approval of Cancer drugs and Biologics (2007) (FDA Guidance for Industry 2007).

DOR will be analyzed for the responders. DOR is defined as the time from the date of first response to the date of PD or death, whichever occurs first. DOR analysis will follow the same censoring rule as used for PFS.

Disease control rate (DCR) is defined as the proportion of patients who achieve the best overall response of CR, PR, or SD.

Clinical benefit rate (CBR) is defined as the proportion of patients who achieve the best overall response of CR, PR, or durable SD [BOR of SD with duration ≥ 24 weeks].

The DCR and CBR will be analyzed the same way as for ORR.

In addition, the best change in sum of diameters of target lesions (i.e., the maximum tumor shrinkage) will be plotted using waterfall plot.

6.5 SAFETY ANALYSES

Safety will be determined by the spontaneous reporting of adverse events and by laboratory values (hematology, serum chemistry, coagulation, and urinalysis). Vital signs, physical examination and ECG findings will also be used in determining the safety profile. The severity of adverse events will be graded according to the CTCAE v4.03. The incidence of DLT events, treatment-emergent AEs (TEAEs) will be reported as the number (percentage) of patients with TEAEs by system organ class (SOC) and preferred term (PT). Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs.

Safety data will be summarized in the Safety Population by study phase and cohort.

6.5.1 Extent of Exposure

Extent of exposure to each study drug will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient (mg), dose intensity, and relative dose intensity.

- Treatment duration = date of last exposure – date of first dose + 21.
- The number of cycles received defined as the number of cycles with non-missing doses (dose>0) will be summarized by phase and cohort.
- Dose intensity = cumulative total dose (mg) / (duration of exposure (day)/21). Relative dose intensity = Dose intensity / planned dose intensity. The planned dose intensity = Total planned dose in a cycle.

- Cumulative total dose (mg) per subject will be computed as the sum of all of the doses received in each cycle for each study drug.

The number (percentage) of patients requiring dose interruption, dose delay will be summarized for each cohort.

6.5.2 Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be coded using Medical Dictionary for Regulatory Activities (MedDRA®). Adverse events will be coded to MedDRA (Version 18.1 or higher) lower level term, preferred term and primary system organ class (SOC).

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pre-treatment) on or after the first dose of study drug and up to 30 days following study drug discontinuation or initiation of new anticancer therapy, whichever occurs first. TEAE also includes immune-related AEs recorded up to 90 days after the last dose of study drug. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and PT. A patient will be counted only once by the highest severity grade per NCI-CTCAE v.4.03 within an SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug. TEAEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. SAEs, deaths, TEAE with ≥ Grade 3 severity, irAE, treatment-related AEs, and TEAEs that led to treatment discontinuation, dose interruption, or dose delay will be summarized.

The AE summary analyses will include:

1) An overview summary table will be provided for TEAEs.
2) TEAEs will be summarized by SOC and PT. TEAEs will also summarized by PT in descending frequency.
3) Treatment-related AEs will be summarized by SOC and PT.
4) Treatment-emergent SAEs, treatment-related SAEs will be summarized by SOC and PT.
5) AEs with fatal outcomes will be summarized by SOC and PT.
6) AEs leading to treatment discontinuation/dose modification will be summarized by SOC and PT.
7) irAEs will be summarized by SOC and PT.

6.5.3 Laboratory Values

Clinical laboratory (eg. hematology and serum chemistry) values will be evaluated for each laboratory parameter by patient. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this protocol. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit.

Serum Chemistry	**Hematology**
Alkaline phosphatase	RBC count
Alanine aminotransferase	Hematocrit
Aspartate aminotransferase	Hemoglobin
Albumin	Platelet counts
Total bilirubin	WBC count with differential
Direct bilirubin	
Creatine kinase	
Creatine kinase-cardiac muscle isoenzyme (CK-MB)	Neutrophil count
Blood urea nitrogen or urea	Lymphocyte count
Testosterone	Monocyte count
Creatinine	Basophil count
Calcium	Neutrophil count
Chloride	Lymphocyte (Absolute)
Phosphate	Monocyte (Absolute)
Phosphorus	Basophil (Absolute)
Glucose	Eosinophil (Absolute)
Lactate dehydrogenase	
Total Protein	
Potassium	
Sodium	

Laboratory parameters that are graded in NCI-CTCAE v.4.03 will be summarized by NCI-CTCAE grade. In the summary of laboratory parameters by NCI-CTCAE grade, parameters with NCI-CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately. The graded laboratory parameters (ALP, ALT, AST, total bilirubin, albumin, hemoglobin, platelet counts, WBC count, neutrophil and lymphocyte) will be summarized by grade shift from baseline to maximum post-baseline grades.

6.5.4 Vital Signs

Descriptive statistics for vital sign parameters and changes from baseline will be presented by visit.

6.5.5 Electrocardiograms (ECG)

A centralized ECG laboratory may be used in this study in selected study sites. Calibrated ECG machines will be provided to these sites and ECG collected from these sites will be reviewed centrally. In other sites, local ECG machines will be used.

Abnormal post-baseline ECG parameters will be summarized by cohort. QTcF results will be categorized with the following categories: increase of >30 msec, increase of > 60 msec, value of > 450 msec, value of > 480 msec, value of > 500.

6.5.6 Eastern Cooperative Oncology Group (ECOG)

The ECOG Performance Status will be summarized by study cohort. A shift table from baseline to worst post-baseline in ECOG performance score will be provided.

6.6 PHARMACOKINETIC ANALYSES

Refer to a separate PK analysis plan.

6.7 IMMUNOGENIC ANALYSES

Refer to a separate analysis plan.

7 INTERIM ANALYSIS

Not applicable.

8 CHANGES IN THE PLANNED ANALYSIS

Due to the limitation of data collection and development of study program, Sponsor will not plan exploratory analyses specified in protocol in line of the exploratory objectives.