BeiGene

STATISTICAL ANALYSIS PLAN

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug Antibody
AEs	Adverse Events
ATC	Anatomical Therapeutic Chemical
BCLC	Barcelona Clinic Liver Cancer
BOR	Best Overall Response
CI	Confidence Interval
CK	Creatine Kinase
CK-MB	Creatine Kinase Mb
Cmax	Maximum Plasma Concentration
CP-A	Child–Pugh Classes A
CP-B	Child–Pugh Classes B
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
EFF	Efficacy Evaluable Analysis Set
FDA	US Food And Drug Administration
GFR	Glomerular Filtration Rate
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
ICH	International Council For Harmonization
irAE	Immune-Related Adverse Event
iRECIST	Immune-Related Response Evaluation Criteria In Solid Tumors
IV	Intravenous Injection
KIT	KIT Proto-Oncogenes
KM	Kaplan-Meier
MedDRA®	Medical Dictionary For Regulatory Activities
mRECIST	Modified Response Evaluation Criteria In Solid Tumors

Abbreviation	Definition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria For Adverse Events
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Cell Death Protein-1
PD-L1	Programmed Cell Death Protein Ligand-1
PFS	Progression-Free Survival
PI	Principal Investigator
PK	Pharmacokinetic
PO	Orally
PR	Partial Response
PT	Preferred Term
PT	Prothrombin Time
Q3W	Every 3 Weeks
QD	Once A Day
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase 2 Dose/Doses
SAEs	Serious Adverse Events
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Stable Disease
SMC	Safety Monitoring Committee
SOC	System Organ Class
TACE	Transarterial Chemoembolization

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze, and report results for BGB Protocol A317-211 a "A Phase 2 Study to Investigate the Preliminary Antitumor Activity, Safety and Tolerability of Tislelizumab in Combination with Lenvatinib in Patients with Unresectable Locally Advanced or Metastatic Hepatocellular Carcinoma". The focus of this SAP is for the planned analyses specified in the study protocol amendment version 1.0 dated 25 December 2019. If the protocol is amended or updated, then appropriate adjustments to the SAP may be made if they are related to the planned analyses or sample size.

The SAP described hereafter is an a priori plan. This is an open label study with a planned interim analysis (using Simon 2 stage design). The SAP will be finalized and approved before interim analysis. Statistical programming may occur as study data accumulate in order to have analysis programs ready at the time the study finishes.

All statistical analyses will be conducted using SAS® (SAS Institute, Inc., Cary, NC, USA), Version 9.3 or higher.

2 STUDY OVERVIEW

2.1 STUDY DESIGN

This is an open-label, multicenter Phase 2 clinical study for patients with histologically or cytologically confirmed unresectable locally advanced or metastatic HCC. All patients will receive study treatments until confirmed progressive disease assessed by investigator (iCPD) based on iRECIST, unacceptable toxicity, 12-months treatment duration completion, death, withdrawal of consent, study termination by sponsor or patients meet any discontinuation criterion (see protocol Section 3.6 and Section 3.7 for details), whichever comes first. Patients will be closely monitored for safety and tolerability throughout the study. This study consists of the following two parts:

Part 1 (Safety run-in part [21-day DLT assessment] for lenvatinib in combination with tislelizumab): Approximately 6-12 patients with unresectable locally advanced or metastatic HCC will be enrolled in this part.

- The safety and tolerability of starting dose for lenvatinib in combination with tislelizumab will be evaluated. 3 patients with baseline body weight≥60 kg and 3 patients with baseline body weight＜60 kg will be enrolled. These patients will be administered with lenvatinib orally once a day and tislelizumab (200mg) by intravenous injection (IV), on Day 1 of each 21-day cycle (once every 3 weeks, Q3W). The starting dose for lenvatinib in safety run-in part will be based on baseline body weight. 12 mg lenvatinib will be administered once daily if baseline body weight of patient≥60 kg. 8 mg lenvatinib will be administered once daily if baseline body weight of patient＜60 kg.
- If ≤1 of 6 patients experience a dose limiting toxicity (DLT) in lenvatinib starting dose cohort, this dose level is determined as RP2D (Recommended Phase 2 Dose). The part 2 will be started to enroll at RP2D.

- If ＞1 of 6 patients experience a DLT in this cohort, sponsor will decide to terminate the study or to start a new cohort to investigate lenvatinib at a reduced dose. Lenvatinib dose in the dose reduced cohort may be set as 8 mg or 4 mg once daily based on baseline body weight≥60 kg or＜60 kg, respectively. 6 eligible patients, 3≥60 kg and 3＜60 kg will be enrolled in this cohort. Tislelizumab dose is the same, 200 mg IV Q3W.
- If≤1 of 6 patients experience a DLT in lenvatinib dose reduced cohort, this dose level is determined as RP2D. The part 2 will start to enroll at RP2D.
- If＞1 of 6 patients experience a DLT in lenvatinib dose reduced cohort, the part 1 will be stopped, and part 2 won't be proceeded.

The Safety Monitoring Committee (SMC) will determine RP2D of combination treatment based on all available safety data.

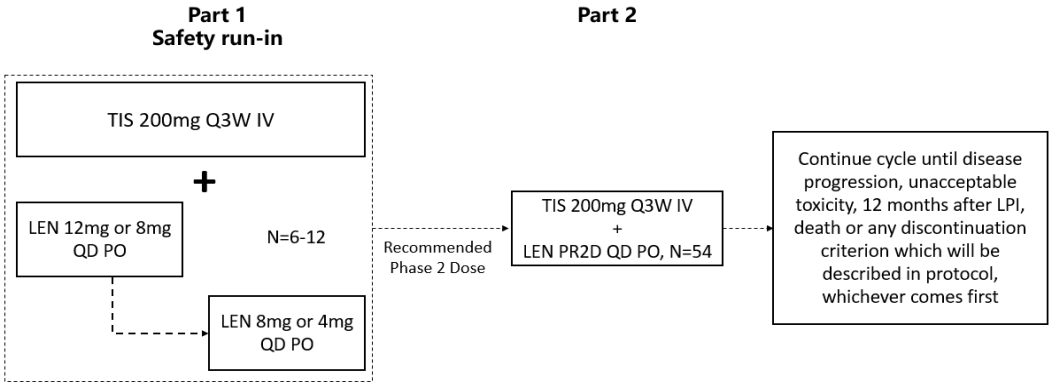
Part 2: The planned 54 patients will be enrolled in this part. Each eligible patient will be administered by lenvatinib in combination with tislelizumab. Lenvatinib in accordance with recommended dose determined in part 1 will be administered orally, once daily continuously, tislelizumab will be administered sequentially starting on Cycle 1 Day 1 and every 21 days thereafter.

The planned 60-66 patients will be enrolled in whole study, including 6-12 patients in part 1 and 54 patients in part 2. A Simon's 2 stage design will be used to test the superiority of studied combination treatment vs. the historical control. When 30 patients dosed at RP2D level (including patients from both part 1 and part 2) are enrolled and all reach their best overall response (BOR) assessed by central site imaging facility for tumor assessment based on RECIST v1.1, the preliminary efficiency and safety of those 30 patients will be assessed as interim analysis.

- If within these 30 patients, ≤6 patients achieve response including complete response (CR) and partial response (PR) as their BOR assessed by central site imaging facility for tumor assessment based on RECIST v1.1, the study will be terminated.
- If within these 30 patients, ＞6 patients achieve response including CR and PR as their BOR assessed by central site imaging facility for tumor assessment based on RECIST v1.1, the study will continue.
- The enrollment won't be interrupted after 30 patients were enrolled.
- If patients don't meet any discontinuation criterion, such as iCPD based on iRECIST, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor, lenvatinib and tislelizumab will be administered until patient completes his/her 12-month treatment duration of study drugs. After 12-month treatment duration completion, if the patients are still under the response (CR, PR) or stable disease (SD) assessed by investigator based on RECIST v1.1 or under the response (complete response [iCR], partial response [iPR]), stable disease (iSD) and unconfirmed progression (iUPD) assessed by investigator based on iRECIST, and may continue receiving benefit based on investigator's assessment, tislelizumab could be further provided by sponsor, this decision must be agreed

with medical monitor and documented in the study records, patients are also required to be reconsented.

2.2 STUDY SCHEMA



Abbreviations: QD, once a day; Q3W, every 3 weeks; PO, orally; IV, intravenous injection; LEN, Lenvatinib; TIS, Tislelizumab.

Note: The dose level of tislelizumab is fixed in the entire study. In part 1 whether to proceed to the lenvatinib dose reduced cohort will depend on safety observations in lenvatinib starting dose cohort and sponsor's decision.

2.3 STUDY ASSESSMENTS

Patients will be closely monitored for safety and tolerability throughout the study.

Assessment of Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) will be assessed among evaluable patients within 21 days after the first dose administration of lenvatinib plus tislelizumab at each dose level. For DLT assessment decision, only DLTs occurring within 21 days will be evaluated. The following patients will not be considered evaluable for DLT, and will be replaced if needed to meet the minimum patient number required for safety evaluation:

- Patients who withdraw or are withdrawn from the study before completing the DLT assessment window for reasons other than a DLT.
- Patients receiving combination therapy who do not receive ≥ 75% of scheduled lenvatinib and ≥ 67% (approximately two-thirds) of scheduled tislelizumab during the DLT assessment window unless they experience a DLT.

Tumor Assessments

Radiological assessment of tumor-response status will be performed approximately every 6 weeks (± 7 days) in the first year, then every 9 weeks (± 7 days) thereafter.

Tumor response will be assessed by investigators and central site imaging facility for tumor assessment respectively based on RECIST v1.1, mRECIST and iRECIST.

After first documentation of response (CR or PR), confirmation of tumor response should occur at 4 weeks or later after the first response or at the next scheduled assessment time point.

If radiographic initial PD is observed by the investigator based on RECIST 1.1, patients should continue treatment with tislelizumab until iCPD (investigator assessed based on iRECIST) is confirmed by repeated imaging ≥ 4 weeks later (but not exceeding 8 weeks from the date of initial documentation of PD, repeated imaging on next scheduled tumor assessment visit date, around 6 weeks from the date of initial documentation of PD is recommended). The criteria which must be met in order to treat patients to continue study drugs beyond initial PD via investigator assessed based on RECIST v1.1 will be described in protocol (see protocol Section 7.4 for details).

The decision to continue study drug(s) beyond investigator-assessed progression must be agreed with the medical monitor and documented in the study records. In such cases, patients are also required to be reconsented.

Central site imaging facility for tumor assessment

Central site imaging facility for tumor assessment is composed of 3 radiology experts at the leading site or the site where the leading PI is located, specialized in tumor radiological assessment. The selection of these experts will be confirmed by leading PI and medical monitor, documented in study records. The executive plan will be described in protocol (see protocol Section 7.4.2 for details).

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

- To assess the preliminary antitumor activity as indicated by overall response rate (ORR) assessed by central site imaging facility for tumor assessment per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1 of tislelizumab in combination with lenvatinib in patients with unresectable locally advanced or metastatic hepatocellular carcinoma

3.2 SECONDARY OBJECTIVES

- To characterize the safety and tolerability of tislelizumab in combination with lenvatinib in patients with unresectable locally advanced or metastatic hepatocellular carcinoma
- To assess the preliminary antitumor activity as indicated by ORR assessed by investigators per RECIST v1.1 of tislelizumab in combination with lenvatinib in patients with unresectable locally advanced or metastatic hepatocellular carcinoma
- To assess the preliminary antitumor activity as indicated by ORR assessed by investigators and central site imaging facility for tumor assessment per modified Response Evaluation Criteria in Solid Tumors (mRECIST) and Immune-related Response Evaluation Criteria in Solid Tumors(iRECIST) respectively of tislelizumab in combination with lenvatinib in patients with unresectable locally advanced or metastatic hepatocellular carcinoma

- To assess the preliminary antitumor activity as indicated by duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) assessed by investigators and central site imaging facility for tumor assessment per RECIST v1.1, mRECIST and iRECIST respectively of tislelizumab in combination with lenvatinib in patients with unresectable locally advanced or metastatic hepatocellular carcinoma

3.3 EXPLORATORY OBJECTIVES

- To characterize the pharmacokinetic (PK) and immunogenicity of tislelizumab when given in combination with lenvatinib in Part I
- To assess OS

4 STUDY ENDPOINTS

4.1 PRIMARY ENDPOINTS

- ORR assessed by central site imaging facility for tumor assessment based on RECIST v1.1

4.2 SECONDARY ENDPOINTS

- The safety and tolerability of tislelizumab in combination with lenvatinib will be evaluated by the incidence, nature, and severity of adverse events (AEs) and serious AEs (SAEs) per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, clinical laboratory abnormalities, relevant physical exam, ECGs, vital signs and DLTs.
- ORR assessed by investigators based on RECIST v1.1
- ORR assessed by investigators and central site imaging facility respectively based on mRECIST and iRECIST
- DOR, DCR, and PFS assessed by investigators and central site imaging facility respectively based on RECIST v1.1, mRECIST and iRECIST

4.3 EXPLORATORY ENDPOINTS

- Serum concentrations of tislelizumab and incidences of anti-tislelizumab-antibodies (ADA) in Part I
- OS

5 SAMPLE SIZE CONSIDERATION

The planned 60-66 patients will be enrolled in whole study, including 6-12 patients in part 1 and 54 patients in part 2.

Part 1 (lenvatinib in combination with tislelizumab safety run-in): Approximately 6 to 12 patients with unresectable locally advanced will be enrolled.

With total of 60 patients at RP2D from both part 1 and part 2, based on Simon's 2 stage design (Simon, 1989), we have about 95% power to detect a statistical significant difference between ORR (assessed based on RECIST v1.1) in studied combination treatment (assumed to be around 40%) to a historical of 18.8% with 1-sided alpha as 0.025. Within first 30 pts (including the 6 patients from part 1 and 24 patients from part 2) in the efficacy analysis set, if we observe≤6 responders, study will be terminated. Otherwise, study will continue. If within the final 60 patients in the efficacy analysis set, we observe≥18 responders, we will claim we are statistically superior than a historical control of 18.8% under the settings. Participants withdraw due to personal reason or AE before first assessment will be replaced, which might need 4-6 extra participants.

6 STATISTICAL METHODS

6.1 ANALYSIS POPULATIONS

- The safety analysis set (SAF) includes all patients who received at least 1 dose of any study drug (any component for the combination therapy).
- The efficacy evaluable analysis set (EFF) includes all dosed patients with measurable disease at baseline per RECIST v1.1 and who had at least one evaluable post-baseline tumor assessment unless treatment was discontinued due to clinical disease progression or death before the first post treatment tumor assessment.
- DLT evaluable analysis set for lenvatinib and tislelizumab combination includes patients who received at least 75% of the assigned total dose of lenvatinib and ≥ 67% (approximately two-thirds) of the assigned total dose of tislelizumab for the DLT assessment window. Additionally, patients who had a DLT event will also be considered evaluable.
- The PK analysis set includes patients who received at least 1 dose of tislelizumab (lenvatinib) study drug and contributed at least 1 post-baseline quantifiable tislelizumab (lenvatinib) PK sample.

6.2 DATA ANALYSIS GENERAL CONSIDERATIONS

6.2.1 Definitions and Computations

Study day: Study days will be calculated in reference to the date of the first dose of study treatment. For assessments conducted on or after the date of the first dose of study treatment, study day will be calculated as (assessment date – date of first dose of study treatment + 1). For assessments conducted before the date of the first dose of study treatment, study day is calculated as (assessment date – date of first dose of study treatment). There is no study day 0.

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings; Study day and any corresponding durations will be presented based on the imputation rules specified in Appendix.

Treatment duration: The treatment duration will be calculated as (date of last dose of study treatment – date of first dose of study treatment + 1) for lenvatinib; and calculated as (date of last

dose of study treatment – date of first dose of study treatment + 21) for Q3W dose regimens (Tislelizumab).

Baseline: Unless otherwise specified, a baseline value is defined as the last non-missing value collected before the time of first dose date.

All calculations and analyses will be conducted using SAS version 9.3 or higher.

6.2.2 Conventions

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

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 decimal digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 decimal digit.
- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- Missing efficacy or safety data will not be imputed unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).
- For discrete endpoints, summary statistics will include frequencies and percentages. Percentages will be presented to one decimal place.

6.2.3 Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in the SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures are provided in Appendix 10.1.

By-visit endpoints will be analyzed using observed data, unless otherwise specified. For observed data analyses, missing data will not be imputed and only the observed records will be included.

6.2.4 Adjustment for Covariates

Not applicable.

6.2.5 Multiplicity Adjustment

Not applicable.

6.2.6 Data Integrity

Before pre-specified interim or final statistical analysis begins, 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 a pre-specified cutoff date. Consistency checks and appropriate source data verification should be complete.

6.3 SUBJECT CHARACTERISTICS

6.3.1 Patient Disposition

The number (percentage) of patients with treatment/study ongoing, discontinued from study drug(s) and/or study, and reasons for study drug(s) or study discontinuation will be summarized in the SAF. The end of study status (alive, dead, withdrew consent, or lost to follow-up) at the data cut-off date and study follow-up duration (months) will be summarized using the data from the eCRF.

6.3.2 Protocol Deviations

Protocol deviation criteria will be established; patients with protocol deviations will be identified and documented before the database lock for the interim and primary analyses.

Major protocol deviations will be summarized by each category. A data listing of protocol deviations will be provided.

6.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in the SAF. Continuous variables include age, BMI (in kg/m^2), weight (in kg), height (in cm); categorical variables include gender, age group (<65 vs. ≥65), ECOG status, country, race, child-bearing potential, tobacco use status, alcohol consumption, and HBsAg (positive vs. negative), HCVAb (positive vs. negative), Hepatitis B, and Hepatitis C.

6.3.4 Disease History and Characteristics

The number (percentage) of patients reporting a history of disease and characteristics, as recorded on the CRF, will be summarized.

HCC history and characteristics such as BCLC initial staging, time from initial diagnosis to the first study dose, method of initial HCC diagnosis, histological type of cancer , BCLC staging at study entry, time from BCLC staging at study entry to the first study dose, macrovascular invasion, extrahepatic spread, distant metastases, location of metastases and number of metastatic sites will also be summarized.

Alpha-fetoprotein at baseline (descriptively as well as by category >= 200 ng/mL and >= 400 ng/mL) will be summarized as part of disease history.

HCC relevant medical history (Hepatitis B, Hepatitis C, Cirrhosis, Non-alcoholic steatohepatitis/Fatty Liver, etc.) and ongoing status will be summarized in descriptive statistics.

Total Child-Pugh Score at baseline will be summarized by category (frequency and percentages).

HBV and HCV infection status at baseline based on screening HBV (Hepatitis B Surface Antigen, Hepatitis B Surface Antibody and Hepatitis B Core Antibody) and HCV (Hepatitis C Virus Antibody). Test results will be summarized with HBsAg (Positive vs. Negative), and HCVAb status (Positive vs. Negative).

The number (percentage) of patients reporting clinically significant symptoms at baseline will be summarized by System Organ Class and MedDRA preferred term. Severity of the symptoms according to NCI-CTCAE will be summarized by maximum grade.

Relevant data listings of disease history will be provided.

6.3.5 Prior Anti-Cancer Treatment

Number of regimens of prior anti-cancer drug therapies will be summarized in frequencies and percentages. Regimen names, best response to the last therapy, duration of the last therapy, time from last disease progression to first study dose and reasons of the last therapy discontinued will be summarized.

Total number (percentage) of patients who received any prior liver local regional therapies will be summarized, and the number of types of prior liver local regional therapies will be summarized, and number of patients who received any type of liver local regional therapies will also be summarized by therapy type. Prior liver local regional therapy TACE will be summarized by chemotherapeutic drug names in frequencies and percentages, prior liver local regional therapy HAIC (Hepatic Artery Infusion Chemotherapy) will be summarized by chemotherapeutic drug names in frequencies and percentages, prior liver local regional radiation therapy (EBRT or SIRT) will also be summarized by radiation therapy type. Treatment intention of the above liver local regional therapies will also be summarized in frequencies and percentages (curative or palliative).

Prior systemic radiotherapies (therapy type, treatment intention, sites etc.) and prior surgeries/procedures (name, intention, and anatomic location) will be summarized similarly as prior liver local therapy. Relevant detail listings will be provided for potential narratives use.

6.3.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using current version of World Health Organization Drug Dictionary (WHO DD) drug codes and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

The number (percentage) of patients reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred name.

Prior medications will be defined as medications that stopped before the day of first dose of study

drugs. Concomitant medications will be defined as medications that 1) started before the first dose of study drugs and were continuing at the time of the first dose of study drugs, or 2) started on or after the date of the first dose of study drugs up to 30 days after the patient's last dose. A listing of prior and concomitant medications will be included in the clinical study report (CSR) for this trial. In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, eg, associated with an irAE or is a new anticancer therapy) at 60 and 90 days (±14 days) after the last dose of tislelizumab regardless of whether or not the patient starts a new anticancer therapy.

6.3.7 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) codes of the version currently in effect at BeiGene at the time of databased lock. The number (percentage) of patients reporting a history of any medical condition, as recorded on the eCRF, will be summarized by MedDRA system organ class (SOC) and preferred term (PT) based on the safety analysis set. A listing of medical history will be provided.

6.4 EFFICACY ANALYSIS

Since this study may start a new cohort with Lenvatinib at a reduced dose (Tis 200mg Q3W IV+ Len 8mg or 4mg QD PO), if so, we need to specify the dose level for all below efficacy analyses and the analyses will be conducted by dose (high vs. low) and combined. High dose refers to Tis 200mg Q3W IV + Len 12mg or 8mg OD PO, low dose refers to Tis 200mg Q3W IV + Len 8mg or 4mg OD PO.

6.4.1 Primary Efficacy Endpoints

Primary endpoint for Part 1 is safety endpoint (DLT), no hypothesis testing will be done for Part 1 safety run-in.

Objective Response Rate (ORR) at RP2D

ORR is defined as the proportion of subjects achieving a best overall response (BOR) of CR or PR.

For part 2, hypothesis testing of confirmed ORR in the EFF evaluated based on RECIST v1.1 by central site imaging facility for tumor assessment will be the primary efficacy analysis.

The ORR in studied BGB-A317 combination treatment is assumed as 40% in patients with previously treated unresectable HCC. The historical rate in a similar population is estimated as 18.8% for mono Lenvatinib (Kudo, 2018). The null and alternative hypotheses are set as follows:

H_0: ORR = 18.8%

Ha: ORR > 18.8%

A Simon's 2 stage design will be used to test the superiority of studied combination treatment vs. the historical control. If the obtained 1-sided p-value is less than 0.025, it will be concluded that

the combination treatment statistically significantly increases ORR compared to the historical control. Therefore, the superiority of the combination treatment will be demonstrated.

As stated in Section 2, if ⩽6 responses are observed within the first 30 patients, the study will be terminated.

The number and proportion of ORR will be summarized by dose and combined. The precision of the estimators will be assessed by two-sided Clopper-Pearson 95% confidence intervals (CI). Patients without post-baseline tumor assessment will not be included into EFF, and patients discontinued treatment due to early clinical PD or death before the first post treatment tumor assessment will be included into EFF and considered as non-responders for ORR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, PR, stable disease [SD], and progressive disease [PD]) will also be presented.

The primary efficacy analysis will be conducted when mature response rate data have been observed, estimated as no more than 6 months after the last subject received the first dose of study drug. Additional efficacy analysis will be conducted approximately 12 months after the last subject received the first dose of study drug.

6.4.2 Secondary Efficacy Endpoints

Below analyses are all based on EFF population and will be analyzed by dose and combined.

6.4.2.1 Response Rate

- ORR assessed by investigators based on RECIST v1.1
- ORR assessed by investigators and central site imaging facility for tumor assessment respectively based on mRECIST and iRECIST.
- DCR assessed by investigators and central site imaging facility based on RECIST v1.1, mRECIST, and iRECIST

ORR is defined as the proportion of subjects achieving a best overall response (BOR) of CR or PR.

DCR is defined as the proportion of patients with BOR of CR, PR or SD. Patients without post-baseline tumor assessment will be considered as failure in DCR.

A point estimate and a 2-sided Clopper-Pearson 95% confident interval (CI) will be provided for ORR or DCR by dose and combined, respectively.

6.4.2.2 Duration of Response (DOR)

DOR is defined as the time interval between the date of the earliest qualifying response (CR or PR) and the date of PD or death (whichever occurs earlier). DOR analysis will only include responders.

DOR = (The earlier of PD or death date − The earlier of PR or CR date + 1) / 7 in weeks.

The KM method will be used to estimate the key secondary endpoint DOR assessed by investigators and central site imaging facility based on RECIST v1.1, mRECIST, and iRECIST, and corresponding quantiles (including the medians), if estimable, in the responders. A two-sided 95% CIs of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley, 1982).

The DOR censoring rule will follow the FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA, 2018) with some modifications (See Appendix 10.2).

6.4.2.3 Progression Free Survival (PFS)

PFS is defined as the time from the date of the first dose of study drug(s) to the date of the confirmed documentation of PD or death, whichever occurs first.

PFS = (The earlier of PD or death date − Date of treatment initiation + 1) / 30.4375 in =months.

PFS, assessed by investigators and central site imaging facility based on RECIST v1.1, mRECIST, and iRECIST, will be similarly analyzed in the efficacy evaluable population using the Kaplan-Meier (KM) method as described above. KM method along with the corresponding 95% CI based on Greenwood's formula (Greenwood, 1926) will be used to construct the PFS time point estimates which are defined as the percentages of patients in the analysis population who remain alive and progression-free at the specified time points (ie, 3, 6, or 12 month). KM curves will be constructed to provide a visual description of the PFS rate versus time.

Censoring rule for PFS will follow DOR censoring rule (see Appendix 10.2).

In addition, number of patients who received post-treatment anti-cancer therapies (surgery/procedure, radiation, or systemic therapies) and regiment names will be summarized.

6.4.3 Subgroup Analyses

Subgroup analysis on key efficacy endpoints (ORR, DOR, DCR, PFS) will be conducted to explore the consistence of efficacy across variety of subgroups, as appropriate (ie. when there is sufficient number of patients in the subgroup, otherwise relevant subgroups may be combined). Subgroup analyses will be performed per RECIST v1.1 by both investigator and central site imaging facility. Subgroup variables may include, but not limited to,

- age (< 65 vs. ≥ 65 years)
- gender (female vs. male)
- macrovascular invasion and/or extrahepatic spread (present vs. absent)
- macrovascular invasion (present vs. absent)
- extrahepatic spread (present vs. absent)

- hepatitis virus infection (HBV vs. HCV vs. uninfected)
- ECOG PS (0 vs. 1)
- Child-Pugh Classification Score (5 vs. 6)
- alpha-fetoprotein (< 400 ng/mL vs. >= 400 ng/mL)
- BCLC stage (Stage B vs. Stage C)
- Prior liver loco-regional therapy (yes vs. no)
- # of prior TACE loco-regional therapy (1 vs. 2+)

Subgroup results in proportions will also be presented in forest plots. The subgroup variables and their respective categories are subject to change if warranted to better represent the data.

6.5 SAFETY ANALYSES

The sponsor, leading investigator and maybe other investigators will establish a SMC for ongoing safety assessment throughout the study. The SMC charter will define the organization members and procedures. The SMC will evaluate safety data from Part 1 and decide the dose level for next group or if enroll more eligible patients, based on the safety data from the former dose level. The SMC will continue monitoring safety data during Part 2 periodically as needed.

Since this study may start a new cohort with Lenvatinib at a reduced dose (Tis 200mg Q3W IV+ Len 8mg or 4mg QD PO), if so, we need to specify the dose level for all below safety analyses and the analyses will be conducted by dose (high vs. low) and combined. High dose refers to Tis 200mg Q3W IV + Len 12mg or 8mg OD PO, low dose refers to Tis 200mg Q3W IV + Len 8mg or 4mg OD PO.

All subjects who are exposed to (or started receiving) any study drug (any component for the combination therapy) will be evaluated for safety by dose. Safety will be determined by the spontaneous reporting of AEs and by laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, ECOG and ECGs findings will also be used in determining the safety profile. The severity of AEs will be graded according to the CTCAE v5.0. The incidence of DLT events and TEAEs will be reported as the number (percentage) of patients with DLT/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 by dose.

Patients who have an AE leading to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a different antitumor therapy.

6.5.1 Dose-Limiting Toxicity Analysis

Dose-limiting toxicity (DLT) will be assessed among evaluable patients within 21 days after the first dose administration of lenvatinib plus tislelizumab at each dose level. For DLT assessment

decision, only DLTs occurring within 21 days will be evaluated. The following patients will not be considered evaluable for DLT, and will be replaced if needed to meet the minimum patient number required for safety evaluation:

- Patients who withdraw or are withdrawn from the study before completing the DLT assessment window for reasons other than a DLT.
- Patients receiving combination therapy who do not receive ≥ 75% of scheduled lenvatinib and ≥ 67% (approximately two-thirds) of scheduled tislelizumab during the DLT assessment window unless they experience a DLT.

The DLT events will be summarized descriptively for each combination dosing level in the DLT evaluable analysis set.

6.5.2 Extent of Exposure

Extent of exposure to the study drug will be summarized descriptively by study drug, and by dose level with respect to the following:

- Number of treatment cycles received: defined as the total number of treatment cycles in which at least one dose of the study drug is administered
- Duration of exposure (months): defined as the duration (in month) from the date of the first dose to the last exposure of the study drug
- Total dose received per patient (mg): defined as the cumulative dose of the study drug during the treatment period of the study
- Actual dose intensity (ADI) per patient (mg/day for Lenvatinib; mg/cycle for Tislelizumab): defined as sum of actual dose received by a patient divided by duration of treatment
- Relative dose intensity (RDI) per patient (%): defined as the ratio of actual dose intensity(mg/day) and planned dose intensity

The number (percentage) of patients requiring dose reduction will be summarized for Lenvatinib. The number (percentage) of patients requiring dose delay, dose interruption, and overdose will be summarized for Tislelizumab. Frequency of does delay and frequency of dose interruption will be summarized by categories (0, 1, ≥2). The cycle in which the first dose delay/interruption occurred will be summarized for Tislelizumab using descriptive statistics. The cycle in which the first dose reduction/interruption occurred will be summarized for Lenvatinib using descriptive statistics. Frequency of dose delay and interruption as well as reason for dose delay and interruption will be summarized descriptively for Tislelizumab. Frequency of dose reduction and interruption as well as reason for dose reduction and interruption will be summarized descriptively for Lenvatinib.

Dose interruption is defined as any dose temporary discontinuation due to AE or held for procedure. Dose reduction for Lenvatinib is defined as any planned dose reduced from the original planned dose, regardless of reasons. Dose missing is defined as any dose temporary discontinuation due to reasons other than AE or held for procedure. Overdose for Lenvatinib is defined as any dose excess compare with original planned dose based on RP2D determined in

part 1. Overdose for Tislelizumab is defined as any dose administered more than 200mg in each treatment cycle. If the patient misses any once dose of Lenvatinib and is able to take it within 12 hours, this case should not belong to dose interruption or dose missing.

6.5.3 Adverse Events

AEs will be graded by the investigators using CTCAE v5.0. The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) and up to 30 days following study drug(s) discontinuation or initiation of new anticancer therapy, whichever occurs first. TEAE classification also applies to irAEs recorded up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. 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.

An overview table, including the incidence of and the number of patients with TEAEs, treatment-emergent serious adverse events (SAEs), treatment-related TEAEs, TEAEs with grade 3 or above, treatment-related SAEs, TEAEs that led to death, and TEAEs that led to treatment discontinuation, TEAEs that led to Tislelizumab dose delay, dose interruption, overdose, and dose modification (dose delay or dose interruption), TEAEs that led to Lenvatinib dose interruption, dose missed, dose reduction, overdose, and dose modification (dose reduction or dose interruption), adjudicated immune-related TEAEs, and infusion related reactions will be provided. Treatment-related AEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship.

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 according to CTCAE v.5.0 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 treatment-emergent SAEs, treatment-related TEAEs, TEAEs with grade 3 or above, treatment-related TEAE with grade 3 or above, treatment-related SAEs, TEAEs that led to death, Tislelizumab treatment-related TEAE leading to death, Lenvatinib treatment-related TEAE leading to death, TEAEs that led to treatment discontinuation, TEAEs that led to Tislelizumab dose delay, dose interruption, overdose, and dose modification (dose delay or dose interruption), TEAEs that led to Lenvatinib dose interruption, dose missed, dose reduction, overdose, and dose modification (dose reduction or dose interruption), Tislelizumab treatment-related TEAE leading to treatment discontinuation, Lenvatinib treatment-related TEAE leading to treatment discontinuation, Tislelizumab treatment-related TEAE leading to dose delay, dose interruption, overdose, and dose modification (dose delay or dose interruption), Lenvatinib treatment-related TEAE leading to dose interruption, dose missed, dose reduction, overdose, and

dose modification (dose reduction or dose interruption), most frequently reported (incidence ≥5%) treatment-related TEAE for Tislelizumab, most frequently reported (incidence ≥5%) treatment-related TEAE for Lenvatinib, most frequently reported (incidence ≥ 2 %) treatment-related TEAE with grade 3 or above for Tislelizumab, most frequently reported (incidence ≥ 2 %) treatment-related TEAE with grade 3 or above for Lenvatinib, infusion related reactions (IRRs), IRRs with grade 3 or above, and IRRs leading to treatment discontinuation will be summarized by SOC and PT.

6.5.4 Immune-related TEAEs

- Immune-related TEAEs (irTEAEs) will be summarized by irTEAE category.
- irTEAEs with grade 3 or above by irTEAE category
- irTEAEs leading to treatment discontinuation by category
- irTEAEs leading to death by category
- irTEAEs leading to dose delay and dose interruption by category
- irTEAEs treated with glucocorticoids by category
- irTEAEs treated with high dose glucocorticoids by category

Patient data listings of all AEs, SAEs, AEs that led to death and AEs that led to treatment discontinuation will be provided.

All deaths and causes of death will be reported, including those occurred during the study treatment period and those reported during the survival follow-up period after treatment completion/discontinuation.

6.5.5 Laboratory Values

Clinical laboratory (e.g., hematology, serum chemistry, coagulation, thyroid function and urinalysis) values will be evaluated for each laboratory parameter as appropriate. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. For all quantitative parameters listed in Table 1, the actual value and the change from baseline to each post-baseline visit and to the end of treatment will be summarized by visit using descriptive statistics (n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables).

Laboratory parameters (Alkaline phosphatase, Alanine aminotransferase, Aspartate etc.) that are graded in NCI CTCAE (v. 5.0) will be summarized by shifts from baseline CTCAE grades to worst post-baseline grades. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions will be summarized separately. Shift tables will be used to summarize the grade change from baseline to worst post baseline value with counts and percentages.

Table1 Clinical Laboratory Assessments

Clinical Chemistry	Hematology	Coagulation	Thyroid function	Urinalysis
Alkaline phosphatase*	Hematocrit	Prothrombin time or INR	TSH Free T3 Free T4	Glucose
Alanine aminotransferase*	Hemoglobin*	aPTT		Protein*
Aspartate aminotransferase*	Platelet counts*			Blood
Albumin*	WBC count*			Ketones
Total protein*	Lymphocyte count*			24-hour protein*
Lactate dehydrogenase*	Neutrophil count*			Random protein/creatinine ratio*
Total bilirubin*				
Direct bilirubin*				
Blood urea nitrogen or urea				
Potassium				
Sodium				
Corrected calcium				
Creatinine*				
Glucose				
CK				
CK-MB				
Lipase				
Serum amylase				

Note: parameters with * are our primary interests.

Furthermore, to evaluate liver injury, potential Hy's Law cases will also be summarized.

6.5.6 Alpha-fetoprotein

The actual value and change from baseline in alpha-fetoprotein will be summarized descriptively over time by visit.

6.5.7 HBV DNA

The actual value and change from baseline in HBV DNA will be summarized descriptively over time by visit.

6.5.8 Vital Signs

The change from baseline and Potentially Clinically Significant (PCS) vital signs in blood pressure, pulse rate, weight, temperature in Celsius will be summarized in descriptive statistics. Vital signs will be listed by patient and visit.

Blood pressure that are graded in NCI CTCAE (v. 5.0) will be summarized by shifts from baseline CTCAE grades to worst post-baseline grades.

6.5.9 Physical Examination

Physical examination will be assessed during screening and study visits. Physical examination findings prior to first dose of study treatment will be collected in medical history, clinically significant abnormalities found in physical examination will be reported in adverse events. No separate physical examination data will be collected and reported in this study.

6.5.10 Electrocardiograms (ECG)

ECG will be performed at the baseline and multiple time points (refer the time points to the protocol study assessments and procedures schedule) after the start of treatment. Observed and change from baseline in ECG will be summarized descriptively over time by visit. Observed post-baseline QTc interval measurement and increase from baseline by pre-specified thresholds will be summarized by category.

6.5.11 Eastern Cooperative Oncology Group (ECOG)

A shift table from baseline to worst post-baseline in ECOG performance status will be summarized.

6.6 PHARMACOKINETIC ANALYSES

Blood samples for PK analysis of tislelizumab will be collected at specified time points (refer to Appendix 2 of protocol). The actual collection date and time of each blood sample will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points upon sponsor approval to ensure thorough PK monitoring.

The tislelizumab concentration data collected sparsely at predose and around T_{max} will be tabulated and summarized by visit/cycle and dose level. Descriptive statistics will include means, standard deviations, medians, and ranges as appropriate.

Additional PK, including population PK analyses, may be conducted as appropriate, and the results of such analysis may be reported separately from the CSR.

6.7 IMMUNOGENIC ANALYSES

Human anti-drug antibodies (ADA) to tislelizumab will be assessed during the study as defined in the protocol.

ADA attributes:

- Treatment boosted ADA is defined as ADA positive at baseline that was boosted to a 4-fold or higher level following drug administration.
- Treatment-induced ADA is defined as ADA negative at baseline and ADA positive post-baseline.

- Persistent ADA response is defined as Treatment-induced ADA detected at 2 or more time points during treatment or follow-up, where the first and last ADA positive samples are separated by 16 weeks or longer; or detected in the last time point.
- Transient ADA response is defined as a treatment-induced response that is not considered persistent.
- Neutralizing ADA is defined as ADA that inhibits or reduces the pharmacological activity.

ADA response endpoints:

- ADA incidence is defined as sum of treatment-emergent ADA, which include both treatment-induced and treatment-boosted ADA-positive patients, as a proportion of the ADA evaluable population.
- ADA prevalence is defined as proportion of all patients that are ADA positive, including pre-existing ADA, at any time point.

Samples to assess anti-tislelizumab-antibodies will be collected. The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADA. The incidence of positive ADA and neutralizing ADA will be reported for evaluable patients. The effect of immunogenicity on PK, efficacy, and safety may be evaluated if data allow.

6.8 EXPLORATORY EFFICACY ENDPOINT

Overall Survival (OS)

OS is defined as the time (in month) from the date of the first dose of study drug(s) to the date of death. Patients who remained alive at data cutoff or discontinuation of the study (discontinued study due to reasons other than "Death") will be censored at the time of the last date the patient was known to be alive.

The OS time point estimates, defined as the percentages of patients in the analysis population who remain alive at the specified time points (e.g., 3, 6 or 12 month), will be estimated using the KM method along with the corresponding 95% CI constructed using Greenwood's formula. The KM estimates of OS will be plotted over time.

6.9 BIOMARKER ANALYSES

Not applicable.

7 INTERIM ANALYSIS

For Part 2, one futility interim analysis will be conducted based on the Simon's 2-stage design (see Section 6.4.1 for details).

8 CHANGES IN THE PLANNED ANALYSIS

NA

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10 APPENDIX

10.1 IMPUTATION OF MISSING/PARTIALLY MISSING DATES

Missing data will not be imputed unless otherwise specified. The imputation rule for the safety analyses will be used to address the issues with partial dates.

i) When the start date or end date of an adverse event is partially missing, the date will be imputed to determine whether the adverse event is treatment-emergent. When in doubt, the adverse event will be considered treatment emergent by default. The following rules will be applied to impute partial dates for adverse events:

If start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, the set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, the set to first of the month

If year of the start date is missing, or start date is completely missing, do not impute.

If end date of an adverse event is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

If year of the end date is missing, end date is completely missing, do not impute

ii) When the start date or end date of a medical or disease history/medication/therapy (systematic or radiotherapy)/surgery or procedure is partially missing, the date will be imputed to determine whether the medical or disease history/medication/therapy (systematic or radiotherapy)/surgery or procedure is prior or concomitant or post. The following rules will be applied to impute partial dates:

If the start date is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month

If the end date is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

If the year of start date or year of end date of a medication/therapy/procedure is missing, or the start date or end date is completely missing, do not impute.

If the date is known to be prior study treatment, e.g. for medical history, disease history, or prior therapies etc., the imputed date should be compared against the first dose date. If it is after the first dose date, then replace the imputed date with the first dose date – 1.

If the date is known to be post study treatment, e.g. for post-treatment subsequent therapies, the imputed date should be compared against the last dose date. If it is before the last dose date, then replace the imputed date with the last dose date + 1.

iii) Deaths

If death date is partial, impute death date as the first day of the month, and JAN as the month. if month is missing, then take the max of (the imputed date and the last known alive date +1); if death date is completely missing, set as the last known alive date +1.

10.2 HANDLING OF CENSORING TIME TO EVENT DATA

Table 2 shows the primary censoring rules for the derivation of PFS using RECIST v1.1 criteria.

The censoring rule for time to event data (DOR, PFS) using RECIST v1.1 will follow FDA Guidance for Industry Clinical Study Endpoints for the Approval of Cancer Drugs and Biologics (Food and Drug Administration Center for Drug Evaluation and Research ; Center for Biologics Evaluation and Research, 2018); see the following table.

Table 2 Censoring Rules for Analysis of Progression-Free Survival Per RECIST v1.1

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline tumor assessments	Date of the first dose	Censored
2	Progression documented on scheduled visit or between scheduled visits	Date of first radiologic PD assessment	Progressed
3	No progression at the time of data cut-off or withdrawal from study	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored
5	Death before first PD assessment	Date of death	Progressed
6	Death between adequate assessment visits*	Date of death	Progressed
7	Death or progression after more than one missed visit**	Date of last adequate radiologic assessment prior to missing occurred	Censored

Abbreviations: CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease,

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

** More than one missed visit is defined as the duration between the last tumor assessment and death or PD is longer than 13 weeks week in the first 18 weeks, and longer than 19 weeks thereafter.

Details of censoring rules for time to event data (DOR, PFS) using iRECIST and mRECIST, please see Supplemental Data Definition.