A Phase 1b/2, Randomized, Open-Label Study Investigating the Efficacy and Safety of LBL-007 Plus Tislelizumab in Combination With Bevacizumab Plus Fluoropyrimidine Versus Bevacizumab Plus Fluoropyrimidine as Maintenance Therapy in Patients With Unresectable or Metastatic Microsatellite Stable/Mismatch Repair Proficient Colorectal Cancer

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STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-A317-LBL-007-201
Study Protocol Title:	A Phase 1b/2, Randomized, Open-Label Study Investigating the Efficacy and Safety of LBL-007 Plus Tislelizumab in Combination With Bevacizumab Plus Fluoropyrimidine Versus Bevacizumab Plus Fluoropyrimidine as Maintenance Therapy in Patients With unresectable or Metastatic Microsatellite Stable/Mismatch Repair Proficient Colorectal Cancer
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
ADI	Actual dose intensity
AE	Adverse event
AUC	Area under the concentration-time curve
BOR	Best overall response
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FDA	Food and Drug Administration
imAE	Immune-mediated adverse event
IRC	Independent Review Committee
MTD	Maximum tolerated dose
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PK	Pharmacokinetic
PFS	Progression-free survival
PR	Partial response
PS	Performance status
PT	Preferred term
RDI	Relative dose intensity
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-emergent adverse event

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-A317-LBL-007-201. The focus of this SAP is for the planned final analysis specified in the study protocol.

2. STUDY OVERVIEW

The study consists of Phase 1b and Phase 2.

2.1. Phase 1b

A maximum number of 36 patients will be enrolled in Phase 1b. Bayesian optimal interval design with informative prior (Zhou et al 2020) will be used for the evaluation of LBL-007 in different doses. The planned doses for LBL-007 in the safety run-in period is 150 mg, 300 mg, and 600 mg once every 3 weeks or 200 mg and 400 mg once every 2 weeks. However, lower and/or intermediate doses of LBL-007 may be evaluated based on emerging clinical data, as appropriate.

2.2. Phase 2

Approximately 130 patients will be randomized in the PD-L1 positive population group and approximately 60 patients in the PD-L1 negative population group.

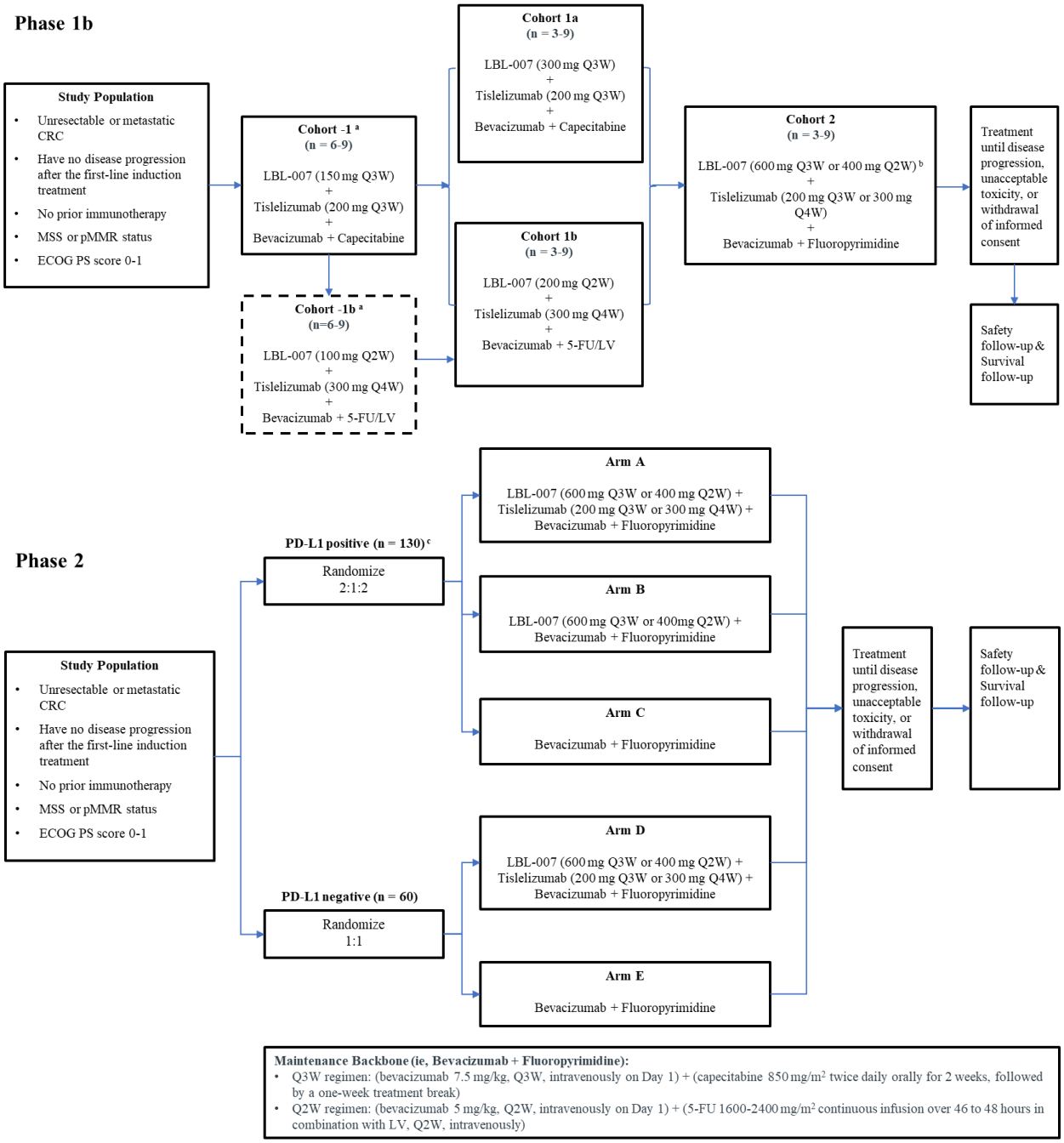
Patients with PD-L1 positive status will be randomized in a 2:1:2 ratio to 1 of 3 treatment arms. The randomization will be stratified according to the following factor: Liver metastases (absent versus present):

- Arm A: LBL-007 + tislelizumab in combination with maintenance backbone
- Arm B: LBL-007 in combination with maintenance backbone
- Arm C: Maintenance backbone, i.e., bevacizumab plus fluoropyrimidine

Patients with PD-L1 negative status will be randomized in a 1:1 ratio to 1 of 2 treatment arms:

- Arm D: LBL-007 + tislelizumab in combination with maintenance backbone
- Arm E: Maintenance backbone, i.e., bevacizumab plus fluoropyrimidine

Figure 1. Study Schema



Abbreviations: 5-FU, 5-fluorouracil; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; LV, leucovorin or levoleucovorin; MSS, microsatellite stable; PD-L1, programmed cell death protein ligand-1; pMMR, mismatch repair proficient; PS, Performance Status; Q2W, once every 2 weeks; Q3W, once every 3 weeks; Q4W, once every 4 weeks; SMC, Safety Monitoring Committee.

Notes:

[a] Cohort -1b will be initiated only if Cohort -1 is not tolerable due to capecitabine, assessed by the SMC. In this case, only a regimen containing 5-FU will be implemented in the subsequent study treatment.

[b] The doses of LBL-007 between 300 mg and 600 mg once every 3 weeks, or 200 mg to 400 mg once every 2 weeks, may be assessed based on a review of tolerability and exposure data by the SMC.

[c] The randomization of PD-L1 positive population in Phase 2 will be stratified according to the following factor: liver metastases (absent versus present).

3. STUDY OBJECTIVES

3.1. Primary Objective

Phase 1b

- To assess the safety and tolerability of LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine.

Phase 2

- To evaluate the efficacy between LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine (Arm A) and bevacizumab plus fluoropyrimidine (Arm C) as maintenance therapy in the PD-L1 positive population (defined as TAP score ≥ 1% by the Ventana PD-L1 [SP263] assay) through PFS, as assessed by the investigator according to RECIST v1.1 in patients with unresectable or metastatic MSS/pMMR CRC.

3.2. Secondary Objective

- To evaluate the efficacy of LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine (Arm A) and bevacizumab plus fluoropyrimidine (Arm C) as maintenance therapy in the PD-L1 positive population through overall response rate (ORR), and duration of response (DOR).
- To assess the efficacy of LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine (Arm D) and bevacizumab plus fluoropyrimidine (Arm E) in PD-L1 negative population (TAP < 1%) through PFS, ORR, and DOR.
- To assess the safety and tolerability of LBL-007 with or without tislelizumab, in combination with bevacizumab plus fluoropyrimidine.

4. STUDY ENDPOINTS

4.1. Primary Endpoints

Phase 1b

- Adverse events (AE) and serious AEs (SAE) as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 [NCI-CTCAE v5.0]), timing, seriousness, and relationship to study treatments; physical examinations, electrocardiograms (ECGs), and laboratory assessments as needed; and AEs meeting protocol-defined dose-limiting toxicity (DLT) criteria.

Phase 2

- PFS, as assessed by the investigator per RECIST v1.1, defined as the time from the date of randomization to the date of first documentation of disease progression or death, whichever occurs first, in the ITT Analysis Set of Arms A and C for PD-L1 positive population.

4.2. Secondary Endpoints

- ORR, and DOR as assessed by the investigator, in the ITT Analysis Set of Arms A and C for PD-L1 positive population
    - ORR, defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) from the time of randomization
    - DOR, defined as the time from the first confirmed objective response after randomization until the first documentation of disease progression or death, whichever comes first
- PFS, ORR, and DOR as assessed by the investigator, in the ITT Analysis Set of Arms D and E for PD-L1 negative population.
- The incidence and severity of adverse events according to NCI-CTCAE v5.0.

5. SAMPLE SIZE CONSIDERATIONS

The study plans to enroll approximately 226 patients:

- Phase 1b (safety run-in): a maximum number of 36 patients.
- Phase 2 (proof-of-concept): Approximately 130 patients with PD-L1 positive status (TAP ≥ 1%) and approximately 60 patients with PD-L1 negative status (TAP < 1%).

Phase 2 is designed to obtain preliminary efficacy and safety data for LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine as maintenance treatment in patients with unresectable or metastatic MSS/pMMR CRC. It is not designed to make explicit power and Type I error considerations so there is no formal statistical hypothesis.

Approximately 130 patients with PD-L1 positive status will be randomized in a 2:1:2 ratio into 3 arms. With 72 PFS events observed in Arm A vs Arm C, there will be 70% power to detect PFS difference with a one-sided alpha level of 0.05 if the true PFS HR equals 0.60. The efficacy data collected from patients in Arm B will be used to describe the component contribution of LBL-007.

Approximately 60 patients with PD-L1 negative status will be randomized in a 1:1 ratio into 2 arms. With a sample size of 30 patients in each arm, the binomial probabilities of detecting ≥ 1 TEAEs with a frequency of 5% and 1% are approximately 79% and 26%, respectively.

6. STATISTICAL METHODS

In general, data from Phase 1 and Phase 2 will be summarized separately by phase.

The table layout for Phase 1b is presented in Table 1. Data from Phase 2 will be summarized by treatment arm.

Table 1: Layout for Tables in Phase 1b

	LBL-007 150mg Q3W+Tisle 200mg Q3W+Bev+FPs (N = XX)	LBL-007 300mg Q3W or 200mg Q2W+Tisle 200mg Q3W or 300mg Q4W+Bev+FPs (N = XX)	LBL-007 600mg Q3W or 400mg Q2W+Tisle 200mg Q3W or 300mg Q4W+Bev+FPs (N = XX)
Row 1			

* Bev, Bevacizumab; FPs, Fluoropyrimidine; Q2W, once every 2 weeks; Q3W, once every 3 weeks; Tisle, Tislelizumab.

6.1. Analysis Sets

- The ITT Analysis Set includes all randomized patients. Patients will be analyzed according to their randomized treatment arm. This will be the primary analysis set used for Phase 2 efficacy analysis.
- The Safety Analysis Set includes all patients who have received ≥ 1 dose of any component of study treatment.
- The DLT-Evaluable Analysis Set will include patients who received ≥ 70% of fluoropyrimidine and ≥ 95% dose of other assigned study treatment (LBL-007, tislelizumab, and bevacizumab) and remain on the study for the 21-day DLT observation period for safety assessments or who have experienced any DLT during the 21-day DLT observation period. This analysis set will be used in DLT evaluation period.

6.2. Multiplicity Adjustment

Not applicable

6.3. Data Analysis General Considerations

6.3.1. Definitions and Computations

Study drugs include LBL-007, tislelizumab, bevacizumab and fluoropyrimidine to be used in this study.

Study day will be calculated in reference to the date of the first dose of study drug in phase 1b or the date of randomization for phase 2. For assessments conducted on or after the date of reference date, the study day will be calculated as (assessment date – reference date + 1). For assessments conducted before the date of reference date study day is calculated as (assessment date – reference date. 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 imputations specified in Appendix 1.

Unless otherwise specified, a baseline value is defined as the last non-missing value collected before the first dose of study drug.

All calculations and analyses will be conducted using SAS® Version 9.4 or higher.

6.3.2. 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 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.
- P-values will be rounded to 4 decimal places. P-values that is less than 0.0001 will be presented as '< 0.0001' and p-values that is larger than 0.9999 will be presented as '> 0.9999'.
- Duration of image-based event endpoints (such as PFS) will be based on the actual date the radiograph was obtained rather than the associated visit date.
- 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.
- 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.

6.3.3. Handling of Missing Data

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

Patients without postbaseline tumor assessment will be considered as non-responders for ORR.

6.4. Patient Characteristics

6.4.1. Patient Disposition

The number (percentage) of patients randomized (only for phase 2), treated, discontinued from the study, reasons for discontinued from the study, and the duration of study follow-up will be summarized in the safety analysis set for phase 1b and ITT analysis set for phase 2. The patients who discontinued treatment and the primary reason for the end of treatment will be summarized among patients who were treated.

6.4.2. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using descriptive statistics in the safety analysis set for phase 1b and ITT analysis set for phase 2, including the following variables:

- Age (continuously and by categories [< 65 or ≥ 65 years])
- Weight
- Sex
- Race
- Ethnicity
- Region
- Liver metastases

6.5. Efficacy Analysis

6.5.1. Primary Efficacy Endpoint(s) for Phase 2

PFS in the PD-L1 positive population is the primary endpoint for Phase 2, which will be summarized for patients in Arms A and C.

Hazard ratio in Arm A versus Arm C and corresponding 2-sided 95% CI will be estimated using an unstratified Cox proportional hazards model.

The distribution of PFS, including median, Q1 and Q3, and event-free rates at selected landmark timepoints will be estimated using the Kaplan-Meier method for each treatment group. Ninety-five percent CIs for median and Q1 and Q3 of PFS will be estimated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley, 1982). And 95% CIs for event-free rates will be estimated using Greenwood's formula (Greenwood, 1926). The censoring rules for the primary analysis of PFS are presented in Table 2.

Table 2: Censoring Rules for Progression-free Survival per RECIST v1.1

No.	Situation	Date of Progression or Censoring	Primary Analysis

1	No baseline and/or any post-baseline tumor assessments and without death within the two scheduled disease assessment windows (19 weeks) from reference start date *	Reference start date	Censored
2	No baseline and/or any post-baseline tumor assessments, but died within the two scheduled disease assessment windows from reference start date	Date of death	Event
3	Progression documented between/at scheduled visits**	Date of first radiologic PD assessment	Event
4	No progression or death by the time of data cut-off or withdrawal from study or lost to follow up or other EOS reasons	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study or lost to follow up or other EOS reasons	Censored
5	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored
6	Death before first documented PD assessment	Date of death	Event
7	Progression or death after two or more consecutive missing visits***	Date of last adequate radiologic assessment before the missing tumor assessments or reference start date	Censored

* Reference start date is defined as first dose date for phase 1b and randomization date for phase 2 in this study.

**Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by the reviewers. Clinical PD without documented radiologic assessment is not considered as PD event, unless otherwise specified by protocol.

*** Two (or more) consecutive missing visits are identified as described in Appendix 2.

6.5.2. Secondary Efficacy Endpoint(s) for Phase 2

ORR, and DOR will be summarized for PD-L1 positive population in Arm A and Arm C.

ORR is defined as the proportion of patients achieving confirmed BOR of CR or PR. BOR is defined as the best response recorded from randomization date until data cutoff or the initiation of new anticancer treatment, whichever occurs earlier. Patients with no postbaseline response assessment will be considered as non-responders. ORR and its Clopper-Pearson 95% CI will be calculated for each arm.

In addition, PFS, ORR, and DOR will also be summarized for the PD-L1 negative population in Arm D and Arm E. Unstratified analysis for PFS and DOR will be conducted.

6.6. Safety Analyses

All safety analyses will be performed based on safety analysis set. For phase 1b, safety analyses will follow the layout defined in Table 1, including an additional 'Total' column. For Phase 2, analyses will be performed by treatment arm. Safety and tolerability will be assessed, where applicable, by incidence, for relevant parameters including, laboratory values, ECG findings.

6.6.1. Extent of Exposure

The following measures of the extent of exposure will be summarized for phase 1b and phase 2:

Duration of exposure (months): defined as (last date of exposure - first dose date + 1) / 30.4375.

- For tislelizumab, if patients discontinued treatment (with non-missing EOT date), the 'last date of exposure' is defined as min(date of the last dose of Tislelizumab + 20 days, cutoff date, study discontinuation date, death date) for Q3W, as min(date of the last dose of Tislelizumab + 27 days, cutoff date, study discontinuation date, death date) for Q4W. For treatment ongoing patient, use cutoff date as the 'last date of exposure'.
- For LBL-007, if patients discontinued treatment (with non-missing EOT date), the 'last date of exposure' is defined as min(date of the last dose of LBL-007 + 20 days, cutoff date, study discontinuation date, death date) for Q3W, as min(date of the last dose of LBL-007 + 13 days, cutoff date, study discontinuation date, death date) for Q2W. For treatment ongoing patient, use cutoff date as the 'last date of exposure'.
- For bevacizumab, if patients discontinued treatment (with non-missing EOT date), the 'last date of exposure' is defined as min(date of the last dose of Bevacizumab + 20 days, cutoff date, study discontinuation date, death date) for Q3W, as min(date of the last dose of Bevacizumab + 13 days, cutoff date, study discontinuation date, death date) for Q2W. For treatment ongoing patient, use cutoff date as the 'last date of exposure'.
- For capecitabine, if patients discontinued treatment (with non-missing EOT date), the 'last date of exposure' is defined as min(date of the last dose of Capecitabine + 7 days, cutoff date, study discontinuation date, death date). For treatment ongoing patient, use cutoff date as the 'last date of exposure'.
- For 5-FU, if patients discontinued treatment (with non-missing EOT date), the 'last date of exposure' is defined as min(date of the last dose of 5-FU + 12 days, cutoff date, study

discontinuation date, death date). For treatment ongoing patient, use cutoff date as the 'last date of exposure'.

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.

Total dose received per patient is defined as the cumulative dose of the study drug during the treatment period of the study. The dose unit is mg for tislelizumab, LBL-007, bevacizumab and chemotherapy.

Actual dose intensity (ADI) (mg/cycle) is defined as the cumulative dose administration (mg) received by a patient divided by the duration of exposure (cycles).

- For tislelizumab, duration of exposure (cycles) was calculated as (last dose date up to cutoff date - first dose date + 21)/21 for Q3W and (last dose date up to cutoff date - first dose date + 28)/28 for Q4W.
- For LBL-007 and bevacizumab, duration of exposure (cycles) was calculated as (last dose date up to cutoff date - first dose date + 21)/21 for Q3W and (last dose date up to cutoff date - first dose date + 14)/14 for Q2W.
- For capecitabine, duration of exposure (cycles) was calculated as (last dose date up to cutoff date - first dose date + 8)/21.
- For 5-FU, duration of exposure (cycles) was calculated as (last dose date up to cutoff date - first dose date + 13)/14.

Relative dose intensity (RDI) is defined as the actual dose intensity divided by the planned dose intensity *100. The planned dose intensity is specified in Table 9, Section 6 of the study protocol amendment 4.0.

6.6.2. Adverse Events

AEs will be graded by the investigators using CTCAE version 5.0. The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA (Version 26.0 or higher) lowest level term closest to the verbatim term, along with the linked MedDRA preferred term (PT) and primary system organ class (SOC).

A treatment-emergent adverse event (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 treatment(s) and up to 30 days after last dose of study treatment(s), or initiation of new anticancer therapy, whichever occurs first. Summary tables will generally focus on those AEs that were treatment-emergent (TE). All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

DLT events will be listed in the phase 1b.

An AE overview table includes the number and percentage of patients with

- TEAEs
- TEAEs with Grade 3 or above

- Serious treatment-emergent adverse events
- Serious treatment-related treatment-emergent adverse events
- TEAEs that led to death
- TEAEs that led to treatment discontinuation
- Immune-mediated TEAEs
- Infusion related reaction

Treatment-related AEs include those events considered by the investigator to be related to study drug or with a 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 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 serious treatment-emergent adverse events, serious treatment-related treatment-emergent adverse events will be summarized by SOC and PT. TEAEs leading to death, and TEAEs leading to treatment discontinuation will also be summarized by PT in descending order.

An immune-mediated adverse event (imAE) overview table, including the number and percentage of patients with imAE, imAE with grade 3 or above, serious imAE, imAE that led to treatment discontinuation, imAE that lead to death, imAE treated with systematic corticosteroid, imAE treated with other immunosuppressant, imAE treated with hormone therapy will be provided.

All deaths, including death due to disease under study and causes of death will be summarized in phase 1b and phase2, including those occurred during the study treatment period and those reported during the survival follow-up period after treatment completion/discontinuation.

6.6.3. Laboratory Values

Laboratory safety tests in local lab will be evaluated for selected parameters described in Table 3.

In the summary of laboratory parameters by CTCAE grade, parameters with laboratory abnormalities worsened by >= 2 grades from baseline will be summarized by treatment arms in phase 2.

Incidence of patients who meet potential Hy's law criteria will be summarized in phase 1b and phase 2, respectively. A listing of patients who meet Hy's law criteria will be provided for both phase 1b and phase 2.

Table 3: Serum Chemistry and Hematology Laboratory Tests

Serum Chemistry	Hematology
Alkaline phosphatase	Hemoglobin
ALT	Platelet counts

Serum Chemistry	Hematology
AST	White blood cell count
Total bilirubin	Neutrophil count
Albumin	Lymphocyte count
Creatinine	
Glucose	
Lactate dehydrogenase	
Creatine kinase/CK-MB [a]	
Calcium	
Potassium	
Sodium	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine-kinase-cardiac muscle isoenzyme.

[a] Cardiac enzyme testing has been added to monitor for potential event of immune-mediated myocarditis. If CK-MB fractionation is not available, assess troponin I and/or troponin T instead. Investigators should make every effort to perform either CK-MB, troponin I and/or troponin T consistently at screening and at follow-up visits.

6.6.4. Electrocardiograms (ECG)

ECG results, such as Overall ECG Interpretation and QTcF interval, will be listed for each patient in Phase 1b and Phase 2.

7. INTERIM ANALYSES

No interim analysis is planned.

8. CHANGES IN THE PLANNED ANALYSIS

Table 4 summarizes the major changes in the planned analyses from BGB-A317-LBL-007-201 Protocol Amendment 4.0, dated on 26 February 2025. The changes are all made before database lock and not based on any comparative data.

Table 4: Statistical Analysis Plan Changes

SAP version	Approval date	Change made from	Rationale of the change	Description of the change
1.0	This version	Protocol v4.0	Site-level rounding when calculating drug volume based on concentration may result in patients receiving slightly less than the full planned dose. To avoid unnecessary exclusions and ensure clinically meaningful evaluations, the DLT evaluable set criterion is updated from 100% to ≥95% of the planned dose.	Change the 'full dose of other assigned study treatment (LBL-007, tislelizumab, and bevacizumab)' to '≥ 95% dose of other assigned study treatment (LBL-007, tislelizumab, and bevacizumab)' in DLT evaluable set definition.

9. REFERENCES

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Sato T. On the Variance Estimator of the Mantel-Haenszel Risk Difference. Biometrics. 1989; 45:1323–1324.

Zhou Y, Lee JJ, Wang S, Bailey S, Yuan Y. Incorporating historical information to improve phase I clinical trials. Pharm Stat. 2021 Nov;20(6):1017-1034.

APPENDIX 1. IMPUTATION OF MISSING OR PARTIALLY MISSING DATES

In general, missing or partial dates will not be imputed at the data level. The following rules will apply for the specific analysis and summary purposes mentioned below only.

1.1 Prior/Concomitant Medications/Procedures or Study Drugs Administration

When the start date or end date of medication /therapy/procedure or study drugs is partially missing, the date will be imputed to determine whether the medication/therapy/procedure is prior or concomitant. The following rules will be applied to impute partial dates for medications:

If the start date of medication 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 imputed start date > min (death date, cutoff date, concomitant medication end date), then set to min (death date, cutoff date, concomitant medication end date).

If the end date of medication 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 imputed end date > min (death date, study discontinuation date), then set to min (death date, study discontinuation date).

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

1.2 Adverse Events

The imputation rule for the safety analyses will be used to address the issues with partial dates. 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 the 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 the imputed AE start date is after AE end date (maybe imputed), then update AE start date with AE end date as final imputed AE start date.

If the end date of an AE 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 imputed end date > min (death date, study discontinuation date), then set to min (death date, study discontinuation date).

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

1.3.1 Subsequent anti-cancer therapy

If start date of subsequent anti-cancer therapy 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 imputed start date > min (death date, study discontinuation date, data cutoff date, end date of subsequent anti-cancer therapy, start/end date of the next subsequent anti-cancer therapy), then set to min (death date, study discontinuation date, data cutoff date, end date of subsequent anti-cancer therapy, start/end date of the next subsequent therapy).

If stop date of 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 imputed stop date > min (death date, study discontinuation date, start date of the next subsequent anti-cancer therapy), then set to min (death date, study discontinuation date, start date of the next subsequent therapy).

The (imputed) stop date must be after or equal to the (imputed) start date.

If year of the start date/stop date is missing, do not impute.

Note: if the imputed subsequent anti-cancer therapy date collected from CRF “post-treatment discontinuation anti-cancer systemic therapy” or “post-treatment discontinuation anti-cancer procedure” page is before the last dosing date, send data query.

1.4 Deaths

In case complete death dates are not recorded, impute as follows:

- If both month and day are missing, then the imputed month and day will be 01Jan or the last date of a patient known to be alive + 1, whichever is later.

- If only day is missing, the death will be assumed to be on the first day of the month or the last date of a patient known to be alive +1, whichever is later.

APPENDIX 2. RULES FOR IDENTIYING MISSING TUMOR ASSESSMENTS

1) Input scheduled TA visit list

a. 9wk-18wk-27wk-36wk-45wk-54wk-66wk- 78wk…

2) Identify last evaluable TA before PD or death (--LPTADT) and map it to the closest scheduled visit (--LPTADT_WK).

a. In the event of unscheduled TA, choose the closest scheduled visit number as –LPTADT_WK. It can be achieved programmatically by following the classification rule (e.g. defining thresholds) depicted in Table 5 below. (The team can consider to map all tumor visits if the scheduled visits code are uncleaned or questionable.)

b. Otherwise, assign the scheduled visit number (assuming it is coded correctly) to --LPTADT_WK.

3) Find the 2nd TA visit after LPTADT_WK according to the list in step 1 (--LPTADT_WK_2)

a. If LPTADT_WK_2+1wk < earliest of PD/death date, then censor PFS at the –LPTADT

b. Otherwise, PFS event at the earliest of PD/death date

Table 5 shows how to assign unscheduled TA to a schedule visit. The Threshold column is defined as the mid-point between current and next visit (except for baseline); it is the upper limit for LPTADT to be mapped to the prior scheduled assessment (step 2a above). For example, if LPTADT is Week 48 for an unscheduled visit, it will be mapped to Week 45 TA since it is within the Threshold for Week 45. Assuming it is SD and the subsequent TA of the patient is PD after Week 64 (i.e., 2 consecutive missing assessments), PFS will be censored at LPTADT (Week 48); had the PD occurred prior to/at Week 64, it would be counted as an PFS event.

Table 5: An example of scheduled tumor assessments with time window

Weeks	Scheduled week -1	**Scheduled week**	Scheduled week+1	Threshold
Baseline		Baseline		
Every 9 weeks	Week 8	Week 9	Week 10	Week 13.5
	Week 17	Week 18	Week 19	Week 22.5
	Week 26	Week 27	Week 28	Week 31.5
	Week 35	Week 36	Week 37	Week 40.5
	Week 44	Week 45	Week 46	Week 49.5
	Week 53	Week 54	Week 55	Week 58.5
	Week 62	Week 63	Week 64	Week 67.5
	Week 71	Week 72	Week 73	Week 76.5
	Week 80	Week 81	Week 82	Week 85.5
	…	…	…	…