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STATISTICAL ANALYSIS PLAN

Study Protocol Number:	**BGB-900-102**
Study Protocol Title:	**Phase 1-2 Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Various Combinations of BGB-A425 and LBL-007 with Tislelizumab in Patients with Advanced Solid Tumors**
Date:	7-Feb-2025
Version:	2.0
NCT Number:	NCT03744468

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DOCUMENT REVISION HISTORY

Version number	Finalization date	summary of change
1.0	Jan 15, 2025	- Original Issue.
2.0	Jan 23, 2025	- Decision made to conduct a Synoptic CSR following decision to discontinue development of LAG3 and TIM3. - Scope reduced to align with Synoptic CSR: - Section 6.1: Pharmacodynamic Analysis set was removed. - Section 6.4.4: Prior anticancer therapy analysis was removed. - Section 6.4.5: Medical history analysis was removed. - Section 6.6.1: Exposure parameters were removed including summaries of dose reductions, delays, interruptions, modifications and their reasons, along with infusion rate decreases and reasons. - Section 6.6.2: Some safety parameters were removed including (summary of TEAEs with Grade 3 or above, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification, treatment-related TEAEs, and imAEs by category). Listing of IRR was removed. - Section 6.6.3: Laboratory values analysis: clinical chemistry and hematology will be provided as listings. - Section 6.6.6: ECOG shift tables was removed. - Section 6.7: PK analysis was updated. - Section 6.9: Pharmacodynamic Analysis was removed. - Section 8: Changes in the planned analysis are described.

LIST OF BBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
AUC	area under the concentration-time curve
BOR	best overall response
CR	complete response
DCR	disease control rate
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End-of-Treatment
HNSCC	head and neck squamous cell carcinoma
imAE	immune-mediated adverse event
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MSI	microsatellite instability
MMR	mismatch repair
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed death ligand-1
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term

Abbreviation	Definition
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
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 the study BGB-900-102: Phase 1-2 Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Various Combinations of BGB-A425 and LBL-007 with Tislelizumab in Patients with Advanced Solid Tumors. The focus of this SAP is for the planned final analysis specified in the study protocol.

2. STUDY OVERVIEW

This is an open-label, multicenter, nonrandomized Phase 1 and 2 clinical study evaluating various combinations of BGB-A425 and LBL-007 with tislelizumab. The study design schematic is presented in Figure 1.

Priority enrollment for Phase 1 (dose escalation) and Phase 2 (safety lead-in) will be granted to patients with NSCLC, HNSCC, hepatocellular carcinoma, gastric or gastroesophageal carcinoma, nasopharyngeal carcinoma, RCC, cervical cancer, triple-negative breast cancer, and urothelial carcinoma. Prioritization of additional tumor types will also be considered based upon emerging data and after consultation with BeiGene's medical monitor. Enrollment for Phase 2 (dose expansion) will be granted to patients with HNSCC, NSCLC and RCC, and details are described as follows.

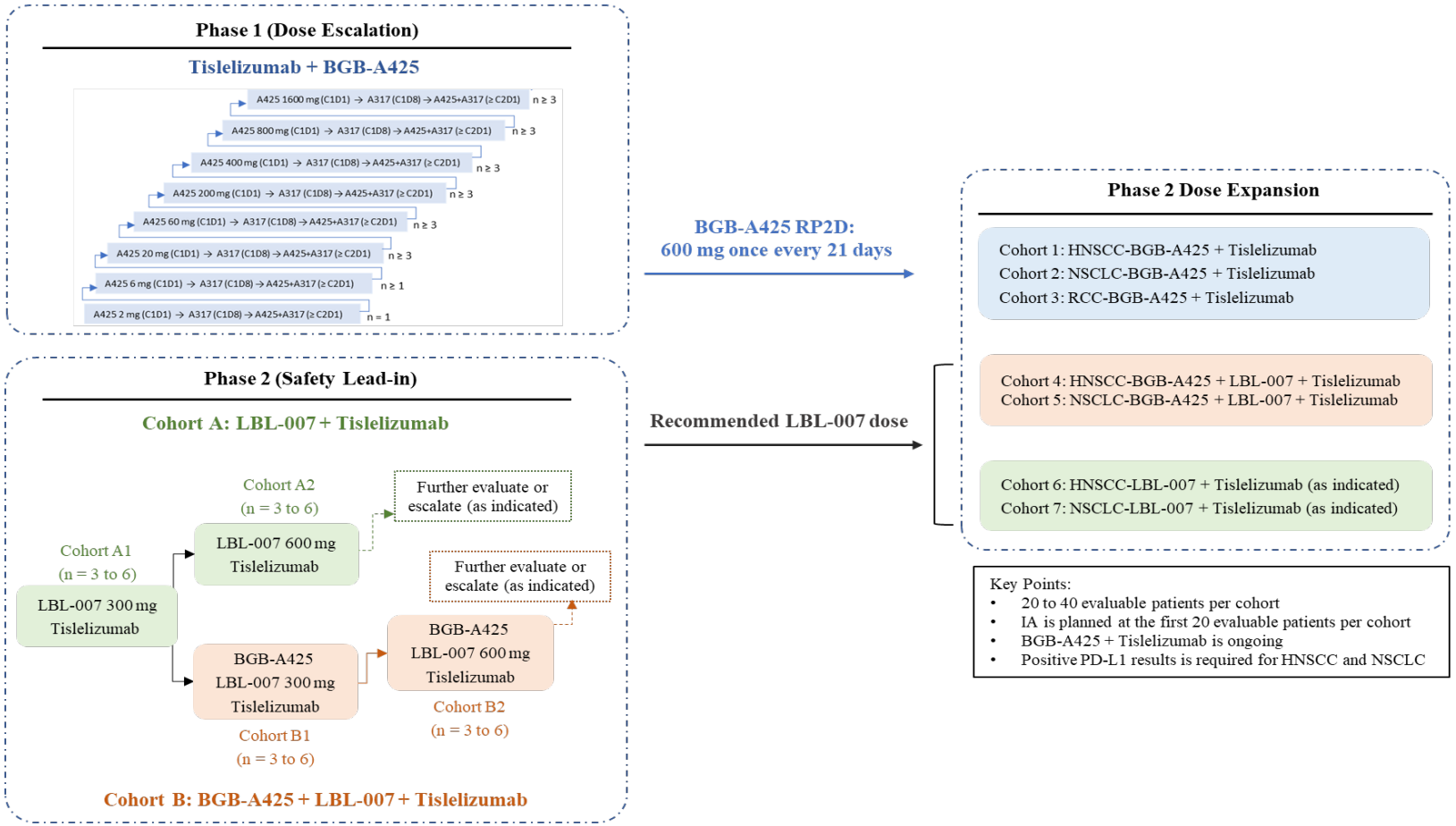
This study consists of the following phases:

- Phase 1 (dose escalation): Sequential cohorts of approximately 8 increasing dose levels of BGB-A425 will be evaluated in combination with tislelizumab 200 mg in patients with advanced solid tumors to determine the RP2D, safety, PK, and other key endpoints for BGB-A425 in combination with tislelizumab.
- Phase 2 (safety lead-in): For the safety lead-in, there are two combination cohorts planned to be evaluated:
  - Cohort A: LBL-007 + Tislelizumab
  - Cohort B: BGB-A425 + LBL-007 + Tislelizumab

  For Cohort A, the dose escalation of LBL-007 starts with LBL-007 300 mg intravenously in combination with tislelizumab 200 mg intravenously every 21 days (Cohort A1, n = 3 to 6); the sequential escalating dose is planned to be LBL-007 600 mg intravenously in combination with tislelizumab 200 mg intravenously every 21 days (Cohort A2, n = 3 to 6).

  For Cohort B, the dose escalation of LBL-007 starts with LBL-007 300 mg intravenously in combination with BGB-A425 600 mg and tislelizumab 200 mg intravenously every 21 days (Cohort B1, n = 3 to 6), which will be initiated after the evaluation in Cohort A1; the sequential escalating dose is planned to be LBL-007 600 mg in combination with BGB-A425 600 mg and tislelizumab 200 mg intravenously every 21 days (Cohort B2, n = 3 to 6).

Figure 1: Study Schema



Abbreviations: A317, tislelizumab (BGB-A317); A425, BGB-A425; C, Cycle; D, Day; HNSCC, head and neck squamous cell cancer; IA, interim analysis; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma; RP2D, recommended Phase 2 dose; TBD, to be determined
Notes: For Phase 2 safety lead-in, the dose for BGB-A425 and tislelizumab are 600 mg and 200 mg, respectively; Cohort A1 will be initiated first. For Phase 2 dose expansion, Cohort 3 will be initiated per the results in Cohort 1 and Cohort 2; the enrollment of Cohorts 6 and 7 will be initiated per the emerging clinical data from the ongoing evaluation in Cohorts 4 and 5.

After the evaluation of Cohort A1, which is initiated first, allocation of patients to the respective cohorts (ie, Cohort A2 and Cohort B1) will be carried out through a sequential order of treatment assignment. Up to 6 patients will be evaluated in Cohorts A2, B2, and in subsequent cohort(s) during the dose escalation part of Phase 2 safety lead-in.

During safety lead-in dose escalation, if the combination of BGB-A425 600 mg, LBL-007 600 mg, and tislelizumab 200 mg once every 21 days is deemed safe in Cohort B2, dose expansion will be evaluated in HNSCC and NSCLC cohorts following discussion and in agreement with the Safety Monitoring Committee (SMC). However, in addition to the above-mentioned dose, lower or higher dose levels of LBL-007 may be evaluated in the safety lead-in cohorts based on the analysis of emerging safety, tolerability, PK, biomarker, and other clinical data, if recommended by the SMC.

Enrollment will be open to all eligible patients with advanced solid tumors as described in Phase 1 (dose escalation).

- Phase 2 (dose expansion): Three combination treatments will be evaluated in patients with various tumor types including HNSCC, NSCLC and RCC. A total of 7 cohorts will be conducted as listed below:
  - Cohort 1: HNSCC – BGB-A425 + Tislelizumab
  - Cohort 2: NSCLC - BGB-A425 + Tislelizumab
  - Cohort 3: RCC - BGB-A425 + Tislelizumab
  - Cohort 4: HNSCC - BGB-A425 + LBL-007 + Tislelizumab
  - Cohort 5: NSCLC - BGB-A425 + LBL-007 + Tislelizumab
  - Cohort 6: HNSCC - LBL-007 + Tislelizumab
  - Cohort 7: NSCLC - LBL-007 + Tislelizumab

An interim analysis will be conducted based on approximately the first 20 evaluable patients in each dose expansion cohort. Based upon the interim analysis for a given tumor type cohort, up to approximately 40 evaluable patients for each cohort may be enrolled in that cohort.

In Phase 2 dose expansion, the enrollment of Cohorts 1 and 2 will be initiated first, then Cohorts 4 and 5 will be open followed by the enrollment of Cohorts 6 and 7. The enrollment of Cohorts 6 and 7 will be initiated per the emerging clinical data from the ongoing evaluation in Cohorts 4 and 5.

All patients enrolled in Phase 2 dose expansion must have disease progression that occurred ≥ 10 weeks from the initiation of anti-PD-1/PD-L1 treatment for locally advanced or metastatic disease. All eligible patients will receive the respective combination(s) every 21 days starting on Cycle 1 Day 1. Positive PD-L1 expression from either local or central testing will be required in HNSCC and NSCLC patients in all dose expansion cohorts prior to enrollment. For baseline tumor tissue, fresh biopsy will be mandatory in the absence of

sufficient archival tissue prior to the patient commencing first drug administration on Cycle 1 Day 1.

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

Except for the Phase 1 DLT period, a 21-day treatment cycle is planned for the remainder of Phase 1 and all of Phase 2 including Phase 2 safety lead-in.

For Phase 1 dose escalation, a 28-day DLT observation period will be utilized for the initial dose-finding recommendations. To incorporate this DLT period into one cycle, only Cycle 1 will have a duration of 28 days from Day 1. During this DLT period, patients must receive BGB-A425 alone on Cycle 1 Day 1 followed by tislelizumab alone on Cycle 1 Day 8 (+2 days) to be DLT evaluable. If no DLT(s) are observed thereafter and through the completion of the initial 28-day cycle, patients will receive both BGB-A425 and tislelizumab sequentially on Day 29 and every 21 days (ie, once every 21 days) until they meet a treatment discontinuation criterion. The occurrence of a DLT during the DLT observation period will result in expansion of that dose level cohort as discussed below.

The first BGB-A425 dose level (2 mg) will initially be evaluated in 1 patient, whereas the second BGB-A425 dose level (6 mg) will be evaluated in 1 or more patients. Accordingly, escalation of the BGB-A425 dose level will proceed if no DLT is observed in the DLT-evaluable patient(s) during the DLT period. However, if a DLT occurs within the DLT observation period for the first or second dose level, enrollment for that dose level will be expanded per the 3+3 design rules described below.

Starting with the BGB-A425 20 mg dose level, escalation of the BGB-A425 dose level will proceed if no DLT is observed during the DLT period in a minimum of 3 DLT-evaluable patients. However, if a DLT occurs within the DLT observation period for a given dose level, enrollment for that dose level will be expanded per the 3+3 design rules as follows:

a) BGB-A425 (Phase 1) dose escalation will advance if the first cycle DLT rate < 33%;
b) BGB-A425 (Phase 1) dose escalation will stop if the first cycle DLT rate is ≥ 33%. A minimum of 6 patients will be enrolled to the current dose level of BGB-A425 (Phase 1), if DLT rate is 33% (eg, 1/3) or the next lower dose level if DLT rate is > 33% (eg, 2/3 or 3/3);
c) The MTD or MAD dose level is defined as the highest dose level at which < 33% of the patients experience a DLT.

More than 3 patients may be enrolled simultaneously during the DLT period(s) for a given dose level. In such cases, the dose escalation decision will be made based upon the above 3+3 rules. Further, for dose escalation decisions, only DLTs occurring within 28 days of Cycle 1 Day 1 for the corresponding dose level will be evaluated. However, additional considerations may be taken into account if clinically significant toxicity(ies) is observed regardless of when it occurred.

Based upon emerging clinical data, lower, intermediate and/or higher dose levels and/or alternative dosing intervals of BGB-A425 may also be evaluated. However, the dosing regimen of tislelizumab will remain fixed for each different BGB-A425 dose level evaluated.

For the Phase 2 safety lead-in, a dose escalation of LBL-007 will be carried out in Cohort A and Cohort B. In Cohort A, the dose escalation will start with Cohort A1; for Cohort B, the dose escalation will be initiated after the evaluation in Cohort A1 and will start with Cohort B1. Specifically, the starting dose of LBL-007 300 mg will be evaluated with a fixed dose of tislelizumab 200 mg in 3 to 6 patients in Cohort A1; likewise, LBL-007 300 mg will be evaluated with BGB-A425 600 mg and tislelizumab 200 mg in 3 to 6 patients in Cohort B1. Moreover, based on the emerging safety, tolerability, PK, and other clinical data, higher dose levels of LBL-007 (eg, 900 mg every 21 days) will be evaluated in the respective combination cohorts, as the other LBL-007 study (LBL-007-CN-003) is being conducted in combination with toripalimab (anti-PD-1 antibody).

In Safety Lead-in Phase, a 21-day DLT observation period will be utilized for all LBL-007 dose finding cohorts. During this DLT period, patients must receive all combination treatments on Cycle 1 Day 1 to be DLT evaluable. Dose escalation to next dose level of LBL-007 will proceed if no DLT is observed in DLT-evaluable patients. However, if a DLT occurs within the DLT observation period for a given dose level, enrollment for that dose level and dose finding decisions will proceed as per the 3+3 design rules described below. All dose escalation(s) will continue based upon the emerging clinical data as determined by the sponsor and the SMC.

Starting with the LBL-007 300 mg dose level, escalation of the LBL-007 dose level will proceed if no DLT is observed during the DLT period in a minimum of 3 DLT-evaluable patients. However, if a DLT occurs within the DLT observation period for a given dose level, enrollment for that dose level will be expanded per the 3+3 design rules as follows:

a) LBL-007 (Phase 2 Safety lead-in) dose escalation will advance if the first cycle DLT rate < 33%;

b) LBL-007 (Phase 2 Safety lead-in) dose escalation will stop if the first cycle DLT rate is ≥ 33%. A minimum of 6 patients will be enrolled to the current dose level of LBL-007, if DLT rate is 33% (eg, 1/3) or the next lower dose level if DLT rate is > 33% (eg, 2/3 or 3/3);

c) The MTD or MAD dose level is defined as the highest dose level at which < 33% of the patients experience a DLT.

In Phase 2 dose expansion (Cohorts 1, 2, and 3 only), the BGB-A425 and tislelizumab RP2D will be administered sequentially starting on Cycle 1 Day 1 and every 21 days (ie, once every 21 days) thereafter until the patient meets a discontinuation criterion.

The recommended dose(s) for the 2 combinations (BGBA425 + LBL007 + tislelizumab and LBL007 + tislelizumab) in Phase 2 dose expansion (Cohorts 4 to 7) will be determined based on safety, tolerability, PK data, pharmacodynamic biomarker, and preliminary antitumor activity from the Phase 2 safety lead-in.

3. STUDY OBJECTIVES

3.1. Study Objectives for Phase 1 (Dose Escalation)

3.1.1. Primary Objectives

- To assess the safety and tolerability of BGB-A425 in combination with tislelizumab in patients with advanced solid tumors
- To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and recommended Phase 2 dose (RP2D) of BGB-A425 in combination with tislelizumab

3.1.2. Secondary Objectives

- To assess the preliminary antitumor activity of BGB-A425 in combination with tislelizumab
- To characterize the pharmacokinetics (PK) of BGB-A425 in combination with tislelizumab
- To assess host immunogenicity to BGB-A425 in combination with tislelizumab

3.1.3. Exploratory Objectives

- To explore drug exposure and response (safety and efficacy) correlations
- To assess predictive, prognostic, and pharmacodynamic biomarkers including any association with response to study treatment and mechanism(s) of resistance

3.2. Study Objectives for Phase 2 (Safety Lead-in)

3.2.1. Primary Objectives

- To assess the safety and tolerability of BGB-A425 in combination with LBL-007 and tislelizumab or LBL-007 in combination with tislelizumab in patients with advanced solid tumors
- To determine the MTD or MAD and RP2D/ recommended dose for expansion of LBL-007 in combination with BGB-A425 and tislelizumab, and LBL-007 in combination with tislelizumab

3.2.2. Secondary Objectives

- To assess the preliminary antitumor activity of BGB-A425 in combination with LBL-007 and tislelizumab or the combination of LBL-007 with tislelizumab in patients with advanced solid tumors
- To characterize the PK of BGB-A425, LBL-007, and tislelizumab in the combination treatments

- To assess host immunogenicity to BGB-A425, LBL-007, and tislelizumab in the combination treatments

3.2.3. Exploratory Objectives

- To explore drug exposure and response (safety and efficacy) correlations
- To assess predictive, prognostic, and pharmacodynamic biomarkers including any association with response to study treatment and mechanism(s) of resistance

3.3. Study Objectives for Phase 2 (Dose Expansion)

3.3.1. Primary Objective

- To evaluate antitumor activity based on objective response rate (ORR) of various combinations of BGB-A425 and LBL-007 with tislelizumab in selected tumor types

3.3.2. Secondary Objectives

- To evaluate antitumor activity using other secondary efficacy endpoints of the combination treatments of BGB-A425 and LBL-007 with tislelizumab
- To further characterize the safety and tolerability of various combinations of BGB-A425 and LBL-007 with tislelizumab
- To further characterize the PK of BGB-A425 and LBL-007 in combination with tislelizumab
- To further assess host immunogenicity to BGB-A425 and LBL-007 in combination with tislelizumab

3.3.3. Exploratory Objectives

- To assess overall survival (OS)
- To explore drug exposure and responses (safety and efficacy) correlations
- To assess predictive, prognostic, and pharmacodynamic biomarkers including any association with response to study treatment and mechanism(s) of resistance

4. STUDY ENDPOINTS

4.1. Study Endpoints for Phase 1 (Dose Escalation) and Phase 2 (Safety Lead-in)

4.1.1. Primary Endpoints

- Adverse events (AEs) and serious AE (SAEs) as characterized by type, frequency, severity (as graded by National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE v5.0]), timing, seriousness, and relationship to study

therapy; laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI-CTCAE v5.0), and timing; AEs meeting protocol defined dose limiting toxicity (DLT) criteria

- The MTD or MAD is defined as the highest dose at which < 33% of the patients experience a DLT
- The RP2D/recommended dose for expansion of the combination treatments will be determined based upon the MTD or MAD, and will also take into consideration the long-term tolerability, PK, efficacy, and any other relevant data as available

4.1.2. Secondary Endpoints

- Efficacy evaluations: ORR, duration of response (DOR), and disease control rate (DCR) will be determined from investigator derived tumor assessments per RECIST v1.1
- PK: Maximum observed plasma concentration (C_{max}), minimum observed plasma concentration (C_{min}), time to maximum plasma concentration (T_{max}), half-life ($t_{1/2}$), area under the concentration-time curve from zero to 21 days ($AUC_{0\text{-}21d}$), CL, and apparent volume of distribution (Vz) for BGB-A425 and LBL-007; C_{max} and C_{min} for tislelizumab
- Immunogenicity: Immunogenic responses to BGB-A425, LBL-007, and tislelizumab will be assessed by summarizing the number and percentage of patients who develop detectable antidrug antibodies

4.1.3. Exploratory Endpoints

- Assessments of the correlations between drug exposure and response (efficacy and safety endpoints)
- Evaluation of biomarkers from patient derived tumor tissue(s) and blood (or blood derivatives) samples obtained before, during and/or after the combination treatment. Candidate biomarkers may include, but are not limited to, programmed cell death protein-1 (PD-1), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), and lymphocyte activating gene-3 (LAG-3) RO and immune cell subpopulation in peripheral blood cells, concentrations of cytokine and soluble proteins in plasma or serum, circulating tumor DNA (ctDNA) analysis in peripheral blood, programmed cell death ligand-1 (PD-L1), TIM-3, LAG-3, and ligands expression, TILs, gene expression profiling and tumor mutation analysis in tumor tissue.

4.2. Study Endpoints for Phase 2 (Dose Expansion)

4.2.1. Primary Endpoint

- ORR as determined from investigator derived tumor assessments per RECIST v1.1

4.2.2. Secondary Endpoints

- Progression-free survival (PFS), DOR, and DCR will be determined from investigator derived tumor assessments as per RECIST v1.1

- Safety and tolerability: The safety of various combinations of BGB-A425 and LBL-007 with tislelizumab will be assessed throughout the study by monitoring AEs and SAEs per NCI-CTCAE v5.0, physical examinations, electrocardiograms (ECGs), and laboratory assessments as needed
- PK: PK parameters such as C_{max}, C_{min}, T_{max}, $t_{1/2}$, and $AUC_{0\text{-}21d}$ for BGB-A425 and LBL-007; C_{max} and C_{min} for tislelizumab
- Immunogenicity: Immunogenic responses to BGB-A425, LBL-007, and tislelizumab will be assessed by summarizing the number and percentage of patients who develop detectable antidrug antibodies (ADAs).

4.2.3. Exploratory Endpoints

- OS is defined as the time from the date of the first dose of study drug(s) to the date of death due to any cause
- Assessments of the correlations between drug exposure and response (efficacy and safety endpoints)
- Evaluation of biomarkers from patient derived tumor tissue(s) and blood (or blood derivatives) samples obtained before, during and/or after treatment. Candidate biomarkers may include, but are not limited to, LAG-3 RO in peripheral blood cells, concentrations of cytokine and soluble proteins in plasma or serum, ctDNA analysis in peripheral blood, PD-L1, TIM-3, LAG-3, and ligands expression, TILs, gene expression profiling and tumor mutation analysis in tumor tissue.

5. SAMPLE SIZE CONSIDERATIONS

The study plans to enroll approximately 178 to 358 patients:

- Phase 1 (dose escalation for BGB-A425 + tislelizumab): Approximately 20 to 42 patients
- Phase 2 (safety lead-in for Cohort A and Cohort B): Approximately 18 to 36 patients
- Phase 2 (dose expansion for 3 combinations in 7 cohorts): Approximately 140 to 280 evaluable patients in 3 prespecified tumor type (HNSCC, NSCLC, and RCC) with a total of 7 cohorts (approximately 40 evaluable patients/cohort) and a built-in interim analysis of approximately the first 20 evaluable patients per cohort

For Phase 1, 20 to 42 patients are sufficient to evaluate the safety and tolerability of increasing dose levels of BGB-A425 per the 3+3 design rules.

For Phase 2 safety lead-in, approximately 18 to 36 patients will be enrolled to evaluate the safety and tolerability of increasing dose levels of Cohort A and Cohort B per the 3+3 design rules.

In the Phase 2 dose expansion, 7 cohorts (approximately 40 evaluable patients per cohort) with 3 combinations in 3 tumor types (HNSCC, NSCLC, and RCC) will be created:

- Cohort 1: HNSCC - BGB-A425 + Tislelizumab

- Cohort 2: NSCLC - BGB-A425 + Tislelizumab
- Cohort 3: RCC - BGB-A425 + Tislelizumab
- Cohort 4: HNSCC - BGB-A425 + LBL-007 + Tislelizumab
- Cohort 5: NSCLC - BGB-A425 + LBL-007 + Tislelizumab
- Cohort 6: HNSCC - LBL-007 + Tislelizumab
- Cohort 7: NSCLC - LBL-007 + Tislelizumab

There will be approximately 40 evaluable patients planned per cohort (up to 280 evaluable patients in total). An interim analysis will be performed for each cohort when approximately 20 evaluable patients in the cohort have completed at least 1 tumor assessment. Details of interim analyses are provided in Section 7.

6. STATISTICAL METHODS

6.1. Analysis Sets

The following analysis sets are defined for this study. Some data may be summarized for multiple analysis sets as deemed necessary.

- The Safety Analysis Set includes all patients who received at least 1 dose of study drug(s). It will be the population for the safety and efficacy analyses.
- The Efficacy-Evaluable Analysis Set includes all dosed patients who have evaluable disease at baseline, and at least 1 evaluable postbaseline tumor response assessment unless any clinical PD or death occurred before the first scheduled postbaseline tumor assessment.
- The DLT Evaluable Analysis Set for Phase 1 includes patients who received at least 80% each of the assigned dose of BGB-A425 on Cycle 1 Day 1 and tislelizumab on Cycle 1 Day 8 (+2 days) and remained on the study during the 28-day DLT observation period for safety evaluation. For safety lead-in in Phase 2 with Cohort A and Cohort B, DLT Evaluable Analysis Set includes patients who received at least 80% each of the assigned dose of study drug(s) in the combination treatments and remained on the study during the 21-day DLT observation period for safety evaluation. Patients who experienced a DLT within the DLT observation period will be included in the DLT Evaluable Analysis Set.
- The PK Analysis Set includes all patients who received at least 1 dose of study drug(s) and have at least 1 derivable PK parameter of BGB-A425 or LBL-007 or tislelizumab.
- The ADA Analysis Set includes all patients who received ≥ 1 dose of study drug(s) and in whom both baseline ADA and ≥ 1 postbaseline ADA results of BGB-A425 or LBL-007 or tislelizumab are available.

6.2. Multiplicity Adjustment

Since no formal hypothesis is tested in this study, multiplicity adjustment is not applicable.

6.3. Data Analysis General Considerations

6.3.1. Study drugs

Study drugs include BGB-A425, LBL-007, and tislelizumab (BGB-A317).

6.3.2. Study day

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

6.3.3. Baseline

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

6.3.4. Conventions

No formal hypothesis will be tested in this study. Data will be mainly analyzed descriptively. Confidence intervals will be constructed to describe the precision of the point estimates of interest.

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 place.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 decimal place.
- 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.

6.3.5. Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in this SAP. Partial missing dates will be imputed conservatively. Specific rules are provided in Appendix 1.

By-visit endpoints will be analyzed using observed data unless otherwise specified.

6.3.6. Data presentation

Data from the Phase 1 and Phase 2 safety lead-in will be summarized by dose level; while data from the Phase 2 dose expansion will be summarized by cohort. The data in Phase 1 Dose Escalation, Phase 2 Safety Lead-in, and Phase 2 Dose Expansion will be presented on separate outputs. If deemed necessary, pooled analyses, e.g., pooling patients in the same indication (e.g., HNSCC or NSCLC) or with the same treatment regimen, may be carried out.

6.4. Patient Characteristics

Patient characteristics will be summarized in the Safety Analysis Set, unless otherwise specified.

6.4.1. Patient Disposition

The number (percentage) of patients treated, discontinued treatment, reasons for treatment discontinuation, discontinued from the study, reasons for discontinued from the study, and the duration of study follow-up will be summarized.

6.4.2. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using descriptive statistics, including the following variables:

- Age (continuously and by categories [<65 or ≥65 years])
- Sex
- Race
- Ethnicity
- Weight
- BMI
- ECOG at Baseline

6.4.3. Disease History

Disease history and characteristics, as recorded on the eCRF, will be summarized using descriptive statistics, including the following variables:

- Tumor type
- Disease status at study entry (Metastatic disease, Locally advanced disease, Recurrent disease)
- Primary location

- Histology
- Location(s) of metastases at study entry
- MSI or MMR status
- Current Stage of disease
- Time from initial diagnosis to the first dose date (months)
- Time from diagnosis of metastatic disease to the first dose date (months)

6.5. Efficacy Analysis

Efficacy response analyses will be performed on the Efficacy-Evaluable Analysis Set only, and progression free survival will be analyzed on the Safety Analysis Set as needed.

Responses will be assessed by the investigators per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1. The confirmed objective response rate (ORR) is defined as the percentage of participants with a confirmed best overall response (BOR) of either complete response (CR) or partial response (PR). The ORR and corresponding two-sided 95% confidence interval calculated from Clopper-Pearson exact method will be presented.

The best overall response (BOR) is defined as the best response recorded from the date of the first dose until progressive disease (PD), death, cut-off date, or up to the initiation of post-treatment anti-cancer therapies, whichever comes first. If the first tumor assessment occurs after the new anticancer therapy, the BOR is considered as NE.

- Confirmed CR is defined as at least 4 weeks apart (in-between) 2 CRs. Single "Not Evaluable (NE)" between two CRs, CR NE CR is considered as confirmed CR. More than one NE between CR is considered as unconfirmed. Any assessments, except NE, between two CRs are considered as data issue and need to be queried.
- Confirmed PR is defined as at least 4 weeks apart (in-between) the first PR and the last PR/CR. Single "NE" or "SD" between two PRs, (PR NE PR, or PR SD PR) is considered as confirmed. More than one NE/SD after PR is considered as unconfirmed. If it is found that there is a PD in between 2 PRs, query of the data.
- Stable Disease (SD) is defined as assessments of SD which are at least 5 weeks after the first dose date.
- For the best overall response, the priority order of responses reported will be CR, PR, SD, Progressive disease, and NE.

Other efficacy endpoints will include the followings:

- **DCR** is defined as the proportion of patients with a best overall response of a confirmed CR, a confirmed PR, or an SD.

  The DCR will be analyzed similarly to ORR.

- **DOR** is defined as the time from the first documentation of a confirmed response, until the first documentation of progression or death, whichever comes first. The censoring rules for PFS will be applied to DOR.

A listing of response data including DOR will be also provided.

Progression Free Survival

The distribution of PFS, including median, Q1 and Q3, and event-free rates at 6, 9 and 12 months, 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).

PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after a new anticancer therapy is given; the event occurred after two or more consecutive missing tumor assessments. For the cases of missing baseline tumor assessment, an early death occurring within 13 weeks (i.e., 12 weeks for two tumor assessments + 1 week) from the first dose date will be considered a PFS event. Clinical or symptomatic progressions without supporting radiologic data will not be considered as PFS events. The censoring rules PFS are presented in Table 1.

Table 1: Handling of Intercurrent Events and Missing Tumor Assessments of Progression-free Survival Per RECIST Version 1.1

	Derivation rules	**Outcome**
No progression at the time of data cut-off or withdrawal from study or lost to follow up	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study*	Censored
Intercurrent events		
Discontinuation of the treatment	Tumor assessment data collected after discontinuation of study treatment will be used for analysis	No impact
New anticancer therapy started prior to disease progression or death	Last adequate disease assessment before the new anticancer therapy*	Censored
Missing values not related to intercurrent events		
Patients' withdrawal from the study or lost to follow-up	Last adequate disease assessment prior to patients withdrawal from the study*	Censored
No baseline or post-baseline tumor assessments without death within 13 weeks after the first dose date	Date of the first dose	Censored
No baseline or post-baseline tumor assessments with death within 13 weeks after the first dose date	Date of death	Event

Death or progression after more than one missed tumor assessment	Date of last adequate radiologic assessment before missed tumor assessments	Censored

6.5.1. Subgroup Analyses

No subgroup analysis will be performed.

6.5.2. Exploratory Efficacy Endpoints

No exploratory efficacy analysis will be performed.

6.6. Safety Analyses

The safety profile will be determined by reporting of AEs and by laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, ECG, and other findings will also be used in determining the safety profile. Safety data will be analyzed using the Safety Analysis Set.

6.6.1. Extent of Exposure

The extent of exposure to each study drug will be summarized descriptively with parameters such as duration of exposure (Months), cumulative total dose received per patient, dose intensity, and relative dose intensity.

- **Treatment Duration (TD):** calculated as last date of exposure – first dose date + 1
  a) If patients discontinued treatment (with non-missing EOT date), "last date of exposure" will be defined as min (cutoff date, study discontinuation date, death date, last dose date + 20, last dose date + 27 (for patients in Phase 1 who use BGB-A425 only)).
  b) Otherwise for treatment ongoing patient, using cutoff date as the "last date of exposure"
  c) The TD will be summarized individually for each study drug as well as overall for the combination therapy cohorts. For Phase 1, the first dose date for tislelizumab should be the date when tislelizumab was initially administered (e.g., Cycle 1 Day 8 (+2 days) following the Assessment Schedule). Overall TD for a combination therapy will be calculated as the latest date of exposure among all treatment components – the earliest date of exposure among all treatment components + 1.
- **Total Cumulative Dose**
  Total cumulative dose will be defined as the sum of all actual dosages per administration at all visits up to the cutoff date
- **Actual Dose Intensity (ADI)**
  ADI (mg/cycle) = total cumulative dose (mg) / total number of treatment cycles
- **Planed Dose Intensity (PDI)**
  PDI (mg/cycle) = planned one cycle dose (mg), i.e. 200mg for tislelizumab
- **Relative Dose Intensity (RDI)**
  RDI (%) = Actual Dose Intensity (mg/cycle) /Planned Dose Intensity (mg/cycle) *100 (%)
- **Total number of treatment cycles**
  Total number of treatment cycles is defined as the total number of cycles in which at least one dose of the study drug is administered.

Patient level listings will be provided for all dosing records and for calculated summary statistics.

6.6.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be coded using Medical Dictionary for Regulatory Activities (MedDRA). 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 after the last dose of study drug(s) or initiation of new anticancer therapy, whichever occurs first. Only those AEs that are treatment emergent will be included in summary tables of TEAE.

An AE overview table, including the number and percentage of patients with TEAEs, treatment-emergent serious adverse events (SAEs), TEAEs with Grade 3 or above, TEAEs leading to death, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification (including dose reduction, dose delay, dose interruption, and infusion rate decreased), and treatment-related TEAEs will be provided. 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, serious TEAE, TEAEs leading to death, serious treatment-related TEAEs will be reported as the number (percentage) of patients with the events by SOC and PT in descending order. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 within a System Organ Class and Preferred Term, even if the patient experienced more than 1 event within a specific System Organ Class and Preferred Term.

An immune-mediated adverse event (imAE) is defined as an adverse event reported up to 90 days of the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy, and for which a coded MedDRA PT meets imAE criteria based on Company Custom Queries (CCQ), as summarized in Appendix 2. Overview of imAEs will be provided.

IRR is defined as events with the IRR checkbox checked on the AE eCRF page. Overview of infusion-related reactions (IRRs) will be provided.

Patient data listings of all AEs including imAEs will be provided.

A listing of DLTs for Dose Escalation in Phase 1 and Safety Lead-In Cohorts will be also provided.

All deaths and causes of death will be summarized and listed including those occurred during the study treatment period and those reported after treatment completion/discontinuation.

6.6.3. Laboratory Values

Clinical laboratory (i.e., hematology, clinical chemistry, coagulation, urinalysis, and as presented in Table 3) 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. All post-baseline assessments using the same source (local or central) as their baseline assessment source will be included in the analysis. A listing of clinical laboratory values will be provided.

Laboratory parameters (e.g., clinical chemistry and hematology) will be provided as listings.

Table 3: Key Clinical laboratory tests

Clinical Chemistry	Hematology
Alkaline phosphatase	Hematocrit
Alanine aminotransferase	Hemoglobin
Aspartate aminotransferase	Platelet counts
Albumin	WBC count
Total bilirubin	Neutrophil count
Blood urea nitrogen or urea	Lymphocyte count
Potassium	
Sodium	
Calcium	
Creatinine	
Glucose	
Lactate dehydrogenase	
Total protein	
Testosterone[a]	
Lipase	
Amylase	
Creatine Kinase (CK)	
CK-MB[c]	
Cortisol (blood test)[d]	

[a] Testosterone test is only applied for patients with mCRPC.
[b] On routine urinalysis, if urine protein is ≥ 2+ by dipstick, then obtain a 24 hour urine sample for total protein and a random urine sample for total protein and creatinine to determine a protein to creatinine ratio
[c] In the event that CK-MB fractionation is not available, troponin I and/or troponin T will be assessed instead.
[d] Cortisol testing will be performed only for patients in Phase 2 (safety lead-in and dose expansion).

A summary table(s) of Hy's law for liver functions will be provided.

6.6.4. Vital Signs

Vital signs (such as body temperature, pulse rate, systolic and diastolic blood pressure) will be listed by patient and visit.

6.6.5. Electrocardiograms (ECG)

ECG will be performed during baseline and multiple post-baseline time points in Phase 1 or as clinically indicated post-baseline in Phase 2. The ECG data will be listed by patient and visit.

6.7. Pharmacokinetic Analyses

Noncompartmental analysis will be carried out for BGB-A425, LBL-007 and Tislelizumab serum concentrations as needed. The PK analyses will include only patients with sufficient data to enable estimation of key parameters, and the parameters such as C_{max}, minimum observed serum concentration (C_{min}), time to maximum plasma concentration (t_{max}), $t_{1/2}$, $AUC_{0\text{-}21d}$, clearance (CL), volume of distribution in the terminal phase (V_z), and accumulation ratio of $AUC_{0\text{-}21d}$ and C_{max} (as appropriate for data collected) may be derived, tabulated and summarized with descriptive statistics (mean, standard deviation, and coefficient of variation) by dose level and by treatment.

Reporting of PK concentrations and parameters for Descriptive Statistics

The following conventions will be used for reporting descriptive statistics for concentration data obtained from dose expansion. The PK analyst will appropriately flag and annotate treatment of any anomalous PK parameters, exclusions and any special treatment for descriptive statistics.

- All the PK parameters except t_{max} should have the following summary statistics: sample size (n), mean, standard deviation (SD), coefficient of variance (CV%), median, minimum, maximum, geometric mean, geometric CV%; t_{max} should be presented as median, range (minimum, maximum), and sample size (n) when presenting the summary statistics. Geometric mean (geometric CV%) should be the default method of reporting PK parameters within in-text tables. For any parameters that have $n \leq 2$, SD should not be presented.
  - If a concentration at a given time point is below the assay quantification limit (BLQ), the concentration shall be reported as the term "BLQ" with the lower limit of quantitation (LLOQ) defined in the footnotes. BLQ values shall be treated as zero for computation of descriptive statistics. BLQ values will not be included for calculations of geometric mean and geometric coefficient of variation (CV%).
  - Mean and median values should be reported to 2 decimal places, SD values to 3 decimal places, max and min values to 1 decimal places, and CV values as whole numbers (no decimal places).

6.8. Immunogenicity Analyses

The immunogenicity results of BGB-A425, LBL-007 and Tislelizumab will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs as needed. The incidence of treatment emergent-, treatment boosted-, treatment induced-, persistent-, transient-, and neutralizing- ADA will be reported for evaluable patients (if available).

7. INTERIM ANALYSES

An interim analysis will be performed for cohorts in Phase 2. For each cohort, the "success" is defined as posterior probability of true ORR exceeding the historical ORR is higher than 0.75; where historical ORRs from representative populations for HNSCC, NSCLC, and RCC are 15%,

20%, and 25%, respectively. A two-stage design is implemented in which Bayesian predictive probability of success (PPoS) based on unconfirmed response rate will be used at the interim analysis after approximately 20 evaluable patients in a cohort have completed at least 1 tumor assessment. The use of response without confirmation requirement is to allow timely evaluation of preliminary efficacy results. If the PPoS is > 0.5 for a given cohort, enrollment of that cohort will continue to approximately 40 evaluable patients. If the PPoS is < 0.05 for a given cohort, enrollment may stop due to futility. If the PPoS is between 0.05 and 0.5, additional efficacy endpoints (eg, PFS, DOR) will be evaluated. The final decision to stop enrollment or terminate the cohorts early will be based on the totality of available data, such as additional efficacy endpoints, all available safety information, biomarker data, and internal and external emergent data.

Given the criteria described above, HNSCC patients will be populated based on whether ≥ 4 responders are observed in the first 20 evaluable patients of each cohort, enrollment will be allowed to proceed to approximately 40 evaluable patients, or if ≤ 1 responder out of the first 20 evaluable patients are observed, enrollment will be stopped. Similarly, in NSCLC patients, if ≥ 5 responders are observed in the first 20 evaluable patients of each cohort, enrollment will be allowed to proceed to approximately 40 evaluable patients, if ≤ 2 responders out of the first 20 evaluable patients are observed, enrollment will be stopped. Finally, in RCC patients (planned to be initiated only after Cohorts 1 and 2 being evaluated in interim analysis), if ≥ 7 responders are observed in the first 20 evaluable patients of each cohort, enrollment will be allowed to proceed to approximately 40 evaluable patients; if ≤ 4 responders out of the first 20 evaluable patients are observed, enrollment will be stopped.

Interim analysis results that fall in-between the 2 thresholds may lead to further evaluation of additional efficacy endpoints (eg, PFS, DOR) for a GO/or NO-GO decision. If additional time is required to obtain sufficient data points for the interim analysis, enrollment may continue to approximately 25 to 30 evaluable patients for a respective cohort in order to accumulate sufficient data points without negatively impacting potential future enrollment of additional patients.

8. CHANGES IN THE PLANNED ANALYSIS

The Phase 2 Dose Expansion Cohorts 1, 2, 4 and 5 were not expanded after their interim futility assessments, and the cohorts 3, 6, and 7 were not initiated. In December 2024 the decision was made to stop further development of the LAG3 and TIM3 programs. As a result, the scope of the statistical analysis was reduced to generate and inform the content of a Synoptic CSR. For instance, the overall survival (OS) as exploratory endpoint will not be analyzed. ORR, DCR, and DOR will be analyzed on the Efficacy-Evaluable Analysis set only (i.e., the analyses on the Safety Analysis Set will not be performed). By-visit summary of laboratory parameters and vital sign parameters and their changes from baseline will not be performed. The end of study status will not be shown in Patient Disposition. The analysis of TEAE will be based on the definition in the SAP. The ADA Analysis Set is added for the corresponding analysis.

9. REFERENCES

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Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38:29-41.

Greenwood M. The Natural Duration of Cancer. Reports on Public health and medical subjects. 1926;33:1-26.

APPENDIX 1. IMPUTATION RULES FOR PARTIAL DATES

Please note: all the imputed start date should be prior to/or by last known alive date. **The last known alive date only is based on complete dates without imputation.**

1. Impute partial dates for concomitant medication

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

2. Impute partial dates for adverse events

If year of the start date is missing or start date is completely missing, do not impute. Impute AE end date first if both AE start date and end date are partially missing.

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 the imputed end date > min(death date, end of study date), then set to min (death date, end of study date)

If year of the end date is missing or end date is completely missing, <u>do not impute.</u>

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 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

3. Impute partial dates related to disease history and prior therapy (Drug, surgery/procedure, radiotherapy)

The following rules will be applied to impute partial dates.

Impute end date first. If 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 the last day of the month
- For prior radiotherapy/locoregional therapy, if imputed end date > the first dose date, then set to the first dose date - 1

If 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 imputed start date > end date, then set to the end date

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.

4. Impute partial dates for subsequent anti-cancer therapy as collected in the post-treatment page (same rule applies to safety and efficacy flag)

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

5. Impute partial dates for deaths in case complete death dates are not recorded.

- 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 (only applies for safety analysis).
- 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. imAE DEFINITION

An immune-mediated adverse event is defined as an adverse event reported up to 90 days of the last dose of study treatment and for which a coded MedDRA PT meets 1 of 2 components below:

- A narrow list of PTs from the immune-mediated adverse event CCQ for which the immune-mediated etiology is specified within the PT itself are always considered to be immune-mediated adverse events (eg, immune-mediated hypothyroidism).
- A broad list of PTs from the immune-mediated adverse event CCQ that are known or possible immune-mediated adverse events, and that are considered immune-mediated adverse events when any of the following additional criteria are met (if applicable):
  - Investigator causality assessment reported as related to any study drug
  - Investigator assessment reported as an immune-mediated adverse event in the case report form
  - Action taken with any study drug as dose interruption or drug discontinuation
  - Treatment of the adverse event with systemic corticosteroids or other immunosuppressants
  - Treatment of adverse events from the categories of immune-mediated hypothyroidism, hyperthyroidism, and thyroiditis with thyroid replacement/antithyroid agents
  - Treatment of adverse events from the category of immune-mediated type 1 diabetes mellitus treated with insulin