CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	A Phase 2, Open-label, Randomized, Multi-arm Study of BGB-A445 in Combination With Investigational Agents in Non-Small Cell Lung Cancer Patients Previously Treated With Anti-PD-(L)1 Antibody
Protocol Identifier:	BGB-LC-203
Phase:	2
Investigational Medicinal Product(s):	BGB-A445 and investigational agents
Indication:	Anti-PD-(L)1-pretreated non-small cell lung cancer
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive 3rd Floor San Mateo, California 94404 USA
Contact Information:	BeiGene Medical Officer Phone: 1.877.828.5568 Email: clinicaltrials@beigene.com
Original Protocol Version 0.0:	30 March 2023
Amendment 1.0	15 May 2023
Amendment 2.0	13 November 2023
Amendment 3.0	30 September 2024
NCT Number:	NCT06029127

FINAL PROTOCOL APPROVAL SHEET

A Phase 2, Open-label, Randomized, Multi-arm Study of BGB-A445 in Combination With Investigational Agents in Non-Small Cell Lung Cancer Patients Previously Treated With Anti-PD-(L)1 Antibody

BeiGene, Ltd., Approval:

See electronic signature	*See electronic signature*
Sponsor Development Core Team Lead	Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 2, Open-label, Randomized, Multi-arm Study of BGB-A445 in Combination With Investigational Agents in Non-Small Cell Lung Cancer Patients Previously Treated With Anti-PD-(L)1 Antibody

Protocol Identifier: BGB-LC-203

This protocol is a confidential communication of BeiGene, Ltd., and its affiliates. I confirm that I have read this protocol, I understand it, and I will work according to this protocol and the terms of the clinical study agreement governing the study. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its affiliates.

Instructions for Investigator: Please SIGN and DATE this signature page prior to implementation of this sponsor-approved protocol. PRINT your name, title, and the name and address of the center in which the study will be conducted.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

TABLE OF CONTENTS

TITLE PAGE 1
FINAL PROTOCOL APPROVAL SHEET 2
INVESTIGATOR SIGNATURE PAGE 3
SYNOPSIS 12
LIST OF ABBREVIATIONS AND TERMS 18
1. INTRODUCTION 20
1.1. Background Information on Non-Small Cell Lung Cancer 20
1.1.1. Current Treatment of CPI-pretreated Advanced or Metastatic Non-Small Cell Lung Cancer and Unmet Clinical Needs 21
1.2. Background Information on BGB-A445 as an OX40 Agonist 22
1.2.1. Pharmacology 22
1.2.2. Toxicology 22
1.2.3. Clinical Pharmacology 22
1.2.4. Prior Clinical Experience With BGB-A445 23
1.2.4.1. Safety Assessment of BGB-A445 23
1.2.4.2. Efficacy Assessment of BGB-A445 25
1.3. Background Information on Investigational Agents 25
1.4. Study Rationale 25
1.4.1. Rationale for BGB-A445-based Combination Treatment 25
1.4.2. Rationale for Selection of Investigational Agents in Combination With BGB-A445 26
1.4.3. Rationale for Selection of Reference Treatment 26
1.4.4. Rationale for BGB-A445 Dose 26
1.4.5. Rationale for Biomarker Strategy 27
1.5. Benefit-Risk Assessment 27
1.5.1. BGB-A445 27
1.5.2. Investigational Agents 28
2. STUDY OBJECTIVES AND ENDPOINTS 29
2.1. Study Objectives and Endpoints 29
3. STUDY DESIGN 31
3.1. Summary of Study Design 31
3.2. Screening Period 34

3.3. Treatment Period 34
3.4. Details for Safety Lead-in 35
3.4.1. Assessment of Dose-Limiting Toxicity 35
3.4.2. Dose-Limiting Toxicity Definition 35
3.4.3. Safety Lead-in Data Review 36
3.4.3.1. BGB-A445 Combined With Docetaxel 37
3.4.3.2. BGB-A445 Combined With Investigational Agents 37
3.5. Patient Discontinuation From Study Treatment 37
3.6. End of Treatment and Safety Follow-up 38
3.7. Survival Follow-up 38
3.8. Patient Discontinuation From Study (End of Study for an Individual Patient) 38
3.9. End of Study 38
4. STUDY POPULATION 40
4.1. Inclusion Criteria 40
4.2. Exclusion Criteria 41
5. STUDY TREATMENT 46
5.1. Formulation, Packaging, Labeling, and Handling 46
5.1.1. BGB-A445 46
5.1.2. Docetaxel 46
5.1.3. Ramucirumab 46
5.1.4. Investigational Agents 46
5.2. Dosage, Administration, and Compliance 47
5.2.1. BGB-A445 Administration 47
5.2.2. Docetaxel Administration 47
5.2.3. Ramucirumab Administration 48
5.2.4. Investigational Agents Administration 48
5.3. Overdose 48
5.4. Dose Delay and Modification 48
5.4.1. Dose Delay 49
5.4.1.1. Dose Delay for BGB-A445 50
5.4.1.2. Dose Delay for Docetaxel 50
5.4.1.3. Dose Delay for Ramucirumab 50

5.4.1.4. Dose Delay for Investigational Agents 51
5.4.2. Dose Modification 51
5.4.2.1. Dose Modification for BGB-A445 53
5.4.2.2. Dose Modification for Docetaxel 53
5.4.2.3. Dose Modification for Ramucirumab 54
5.4.2.4. Dose Modification for Investigational Agents 55
5.5. Continued Access to Study Drug After the End of the Study 55
6. PRIOR AND CONCOMITANT THERAPY 56
6.1. Prior Therapy 56
6.2. Concomitant Therapy 56
6.2.1. Permitted Concomitant Medications/Procedures 56
6.2.1.1. Systemic Corticosteroids 56
6.2.1.2. Hepatitis B Treatment 56
6.2.1.3. Hepatitis C Treatment 57
6.2.1.4. Radiation Therapy 57
6.2.1.5. COVID-19 Vaccines 57
6.2.2. Prohibited Concomitant Medications/Procedures 57
6.2.3. Restricted Concomitant Medications/Procedures 58
6.3. Potential Interactions Between the Study Drugs and Concomitant Medications 58
7. STUDY ASSESSMENTS AND PROCEDURES 59
7.1. Screening 59
7.1.1. Informed Consent and Screening Log 59
7.1.2. Patient Numbering 60
7.2. Enrollment 60
7.2.1. Confirmation of Eligibility 60
7.2.2. Enrollment and Randomization 60
7.3. Safety Assessments 60
7.3.1. Vital Signs 60
7.3.2. Physical Examinations 60
7.3.3. Ophthalmologic Examination 61
7.3.4. Pulmonary Function Tests 61

7.3.5. Eastern Cooperative Oncology Group Performance Status....61
7.3.6. Laboratory Safety Tests....61
7.3.6.1. Cardiac Enzyme Monitoring....62
7.3.7. Electrocardiograms....62
7.3.8. Adverse Events....62
7.3.9. Hepatitis B and C Testing....62
7.4. Tumor and Response Evaluations....63
7.5. Pharmacokinetic and Antidrug Antibody Testing....64
7.6. Biomarkers....65
8. SAFETY MONITORING AND REPORTING....66
8.1. Risks Associated With Study Drug....66
8.1.1. Risks Associated With BGB-A445....66
8.1.2. Risks Associated With Docetaxel....66
8.1.3. Risks Associated With Ramucirumab....67
8.1.4. Risks Associated With Investigational Agent....67
8.2. General Plan to Manage Safety Concerns....68
8.2.1. Eligibility Criteria....68
8.2.2. Safety Monitoring Plan....68
8.3. Adverse Events....68
8.3.1. Definitions and Reporting....68
8.3.2. Assessment of Severity....69
8.3.3. Assessment of Causality....69
8.3.4. Follow-up of Adverse Events....70
8.3.5. Laboratory Test Abnormalities....71
8.4. Definition of a Serious Adverse Event....71
8.5. Suspected Unexpected Serious Adverse Reaction....72
8.6. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events....72
8.6.1. Adverse Event Recording Period....72
8.6.2. Reporting Serious Adverse Events....73
8.6.2.1. Prompt Reporting of Serious Adverse Events....73
8.6.2.2. Completion and Transmission of the Serious Adverse Event Report....74

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events 74
8.6.3. Eliciting Adverse Events 74
8.6.4. Progressive Disease 74
8.6.5. Deaths 75
8.6.6. Adverse Events of Special Interest 75
8.6.7. Pregnancies 76
8.6.8. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent Ethics Committees 76
8.6.9. Assessing and Recording Immune-Mediated Adverse Events 76
8.6.10. Recording Infusion-Related Reactions 77
8.6.11. Recording Anaphylaxis 77
8.7. Management of Events to be Monitored 77
8.7.1. Infusion-Related Reactions 77
8.7.2. Immune-Mediated Adverse Events 78
8.7.3. Hepatic Function Abnormalities 79
9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION 80
9.1. Statistical Analysis 80
9.1.1. Randomization 80
9.1.2. Analysis Sets 80
9.1.3. Patient Disposition 80
9.1.4. Demographic and Other Baseline Characteristics 80
9.1.5. Prior and Concomitant Medications 80
9.2. Efficacy Analyses 81
9.2.1. Primary Efficacy Analysis 81
9.2.1.1. Stage 1 Primary Efficacy Analysis 81
9.2.1.2. Stage 2 Primary Efficacy Analysis 81
9.2.2. Secondary Efficacy Analysis 82
9.2.3. Exploratory Efficacy Analysis 82
9.3. Safety Analyses 82
9.3.1. Extent of Exposure 82
9.3.2. Adverse Events 82
9.3.3. Laboratory Analyses 83

9.3.4. Vital Signs 83
9.4. Pharmacokinetic Analysis 83
9.5. Immunogenicity Analyses 84
9.6. Other Exploratory Analyses 84
9.7. Sample Size Consideration 84
9.8. Interim Monitoring 84
10. STUDY COMMITTEES AND COMMUNICATION 86
11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS 87
11.1. Access to Information for Monitoring 87
11.2. Access to Information for Auditing or Inspections 87
12. QUALITY ASSURANCE AND QUALITY CONTROL 88
12.1. Regulatory Authority Approval 88
12.2. Quality Assurance 88
12.3. Study Site Inspections 88
12.4. Drug Accountability 88
13. ETHICS/PROTECTION OF HUMAN PATIENTS 90
13.1. Ethical Standard 90
13.2. Institutional Review Board/Independent Ethics Committee 90
13.2.1. Protocol Amendments 90
13.3. Informed Consent 90
13.4. Patient and Data Confidentiality 91
13.5. Financial Disclosure 92
14. DATA HANDLING AND RECORD KEEPING 94
14.1. Data Collection and Management Responsibilities 94
14.1.1. Data Entry in the Electronic Case Report Form 94
14.1.2. Data Collection 94
14.1.3. Data Management/Coding 94
14.2. Data Integrity and In-House Blinding 95
14.3. Study Records Retention 95
14.4. Protocol Deviations 96
14.5. Study Report and Publications 96

14.6. Study and Study Center Closure 97
14.7. Information Disclosure and Inventions 97
15. REFERENCES 99
APPENDIX 1. SCHEDULE OF ASSESSMENTS 104
APPENDIX 2. BLOOD AND TUMOR TISSUE BIOMARKER ANALYSIS 109
APPENDIX 3. CLINICAL LABORATORY ASSESSMENTS 111
APPENDIX 4. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS 112
APPENDIX 5. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1 113
APPENDIX 6. PREEXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES 123
APPENDIX 7. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION 125
APPENDIX 8. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT 126
APPENDIX 9. MANAGEMENT OF INFUSION-RELATED REACTIONS 140
APPENDIX 10. MANAGEMENT OF ANAPHYLAXIS 141
APPENDIX 11. FORMULAE FOR ESTIMATING RENAL FUNCTION 142
APPENDIX 12. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL" 143
APPENDIX 13. LIST OF PROHIBITED CHINESE HERBAL AND PATENT MEDICINES 145
APPENDIX 14. BGB-15025 147

LIST OF TABLES

Table 1: Primary Objectives and Endpoints 29
Table 2: Secondary Objectives and Endpoints 29
Table 3: Exploratory Objectives and Endpoints 30
Table 4: Administration of BGB-A445 47
Table 5: Administration of BGB-A445 and Docetaxel and Monitoring Time 48
Table 6: Management of Nonimmune-Mediated Adverse Events 51
Table 7: BGB-A445 Dose Reduction Levels 53

Table 8: Guidelines for Docetaxel Dose Modifications 54
Table 9: A Summary of the Commonly Reported Toxicities of Docetaxel 66
Table 10: A Summary of Adverse Drug Reactions Reported in Patients Treated With Ramucirumab in Combination With Chemotherapy or Erlotinib In Phase 3 Clinical Trials 67
Table 11: Guidance for Duration of Recording New or Worsening Adverse Events in All Treatment Cohorts 73
Table 12: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee 73
Table 13: Examples of Immune-Mediated Adverse Events 79
Table 14: Safety Stopping Boundaries for Number of Patients With TR-Deaths 85

LIST OF FIGURES

Figure 1: Study Schema 33

SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.

Investigational Medicinal Product(s): BGB-A445 and investigational agents

Title of Study: A Phase 2, Open-label, Randomized, Multi-arm Study of BGB-A445 in Combination With Investigational Agents in Non-Small Cell Lung Cancer Patients Previously Treated With Anti-PD-(L)1 Antibody

Protocol Identifier: BGB-LC-203

Phase of Development: 2

Number of Patients: The total number of patients of this study may vary depending on the number combinations where investigational agents are combined with BGB-A445 and the timing of when these agents are added to the study. In both Stage 1 and Stage 2, approximately 20 patients will be enrolled or randomized into each treatment cohort.

Study Centers: Approximately 30 centers in the Asia Pacific region for Stage 1 and expanded to North America, Europe, and additional Asia Pacific countries in Stage 2

Study Objectives and Endpoints:

Primary:

Objectives	Endpoints
To assess the antitumor activity of BGB-A445 plus investigational agent(s) in non-small cell lung cancer (NSCLC) patients pretreated with anti-programmed cell death protein-1 (anti-PD-1)/anti-programmed cell death protein ligand-1 (anti-PD-L1) antibody	Overall response rate (ORR) as assessed by the investigators per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1

Secondary:

Objectives	Endpoints
To assess the safety and tolerability of BGB-A445 plus investigational agent(s)	The incidence and severity of adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 in experimental cohorts (BGB-A445 plus investigational agent)
To further assess the antitumor activity of BGB-A445 plus investigational agent(s)	Duration of response (DOR), disease control rate (DCR), and clinical benefit rate (CBR) as assessed by the investigator per RECIST v1.1
To characterize the pharmacokinetics (PK) of BGB-A445 and investigational agent(s)	Plasma or serum concentrations of BGB-A445 and investigational agents at specified timepoints
To assess host immunogenicity to BGB-A445 and investigational protein therapeutics	Immunogenic responses to BGB-A445 and investigational protein therapeutics, evaluated through the detection of antidrug antibodies (ADA)

Exploratory:

Objectives	Endpoints
To evaluate the potential association of exploratory biomarkers with response or resistance to study treatment and with patient prognosis	Evaluate exploratory biomarkers in various sample types (ie, tumor tissue and/or blood) at various timepoints (ie, before study treatment, after study treatment, and/or at disease progression or recurrence) and the association between these biomarkers and clinical efficacy, disease status, and resistance Exploratory biomarkers may include, but are not limited to: tumor necrosis factor receptor superfamily, member 4 (CD134, OX40) expression; PD-L1 expression; soluble OX40 (sOX40); investigational agent-specific protein expression; gene expression profiling; tumor-infiltrating immune cells in tumor tissue; tumor mutation burden/microsatellite instability/genetic mutation profile; circulating tumor DNA (ctDNA), cytokines, and soluble proteins in plasma or serum Other assessments may be conducted as indicated and as allowed by local regulations
To further assess the preliminary antitumor activity including by time-to-event of BGB-A445 plus investigational agent(s)	Progression-free survival (PFS) as determined from tumor assessments by investigators per RECIST v1.1
To assess overall survival (OS)	OS defined as the date of randomization to the date of death because of any cause

Study Design:

This is a Phase 2, open-label, randomized, multicenter, multi-arm study designed to evaluate the efficacy and safety of BGB-A445 in combination with investigational agent(s) in patients with advanced or metastatic NSCLC whose tumors do not harbor actionable gene alterations and who have received no more than 2 lines of prior systemic therapies which must include anti-PD-(L)1 treatment.

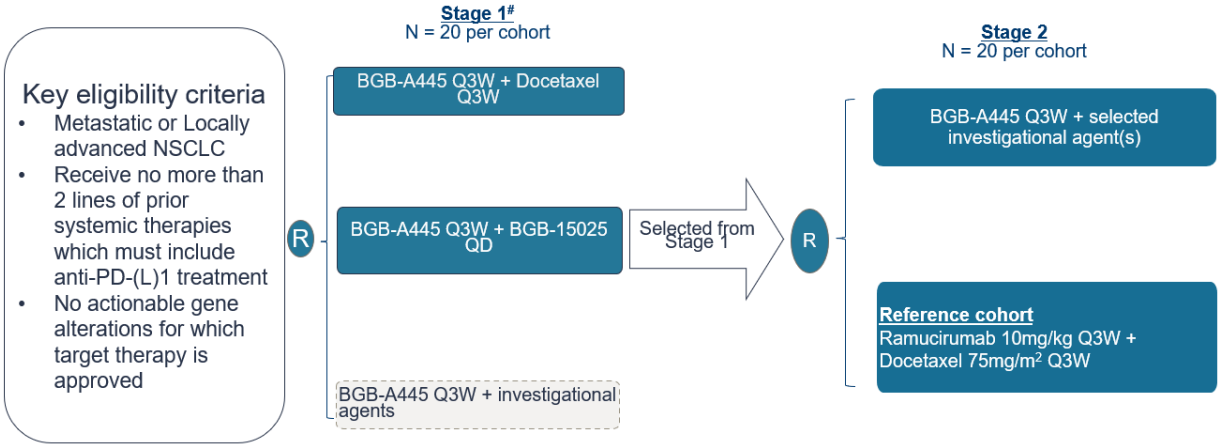
The study is designed to include 2 stages, with the flexibility of adding treatment cohorts become available or discontinuing treatment cohorts that demonstrate minimal clinical activity or unacceptable toxicity.

Stage 1: Patients will be equally enrolled or randomized into different experimental cohorts to receive BGB-A445 plus investigational agent(s). Approximately 20 patients per cohort will be enrolled. For an investigational agent in combination with BGB-A445, a safety lead-in with approximately 6 patients enrolled/randomized will be initiated for the confirmation of the safe dosage. After the dosage is deemed as safe, enrollment or randomization will be continued until approximately 20 patients are enrolled into a cohort.

Stage 2: Only investigational agent(s) with promising efficacy signal and acceptable safety and tolerability in Stage 1 will be selected for each cohort in Stage 2. Patients will be equally enrolled or randomized into different cohorts including: 1) experimental cohorts with treatments of BGB-A445 plus selected investigational agent(s), 2) the reference cohort, and 3) the selected cohort for dose optimization. Approximately 20 patients per cohort will be enrolled.

The study design schematic is presented below.

Study Schema



Abbreviations: NSCLC, non-small cell lung cancer; PD-(L)1, programmed cell death protein-1 /programmed cell death protein ligand-1; Q3W, once every 3 weeks; QD, once a day; R, randomization.

In the current protocol, the treatments in either stage will be administered as follows:

Stage 1

- Experimental cohorts: BGB-A445 + investigational agent(s)
  - Investigational agents include, but are not limited to, BGB-15025 and docetaxel in Stage 1.
  - A safety lead-in will be implemented for the combination of investigational agents with BGB-A445.

Stage 2

- Experimental cohorts: BGB-A445 + selected investigational agent(s)
  - Investigational agents are selected based on the efficacy signal and acceptable safety and tolerability shown in Stage 1.
- Reference cohort: Docetaxel + ramucirumab
- Dose optimization for selected cohort: Different dose levels of the investigational agents may be explored to more fully characterize exposure-response relationships to enable future development

In both stages, study treatments in all cohorts will be administered until disease progression, intolerable toxicity, withdrawal of informed consent, or another discontinuation criterion is met, whichever occurs first (see Section 3.8).

Tumor response will be assessed by investigators using standard RECIST v1.1 criteria. Tumor imaging (computed tomography [CT] with or without contrast and/or magnetic resonance imaging [MRI]) must be performed within 28 days before randomization. Tumor assessments will occur every 6 weeks (± 7 days) from randomization for the first 9 months, and every 12 weeks (± 7 days) thereafter. Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient experiences disease progression, dies, withdraws consent, is lost to follow-up, or until the study terminates, whichever occurs first.

Safety will be assessed throughout the study by monitoring adverse events (AE), serious adverse events (SAEs) (toxicity grades assigned per NCI-CTCAE v5.0), and laboratory results. Vital signs, physical examinations, Eastern Cooperative Oncology Group (ECOG) Performance Status changes, electrocardiogram (ECG) results, and other examinations will also be used for safety assessments.

A Safety Monitoring Committee (SMC) will be established to review safety data for patients enrolled in the safety lead-in and to perform regular safety monitoring on this study. The SMC will review available safety and other relevant data, as appropriate, to make recommendations regarding dose selection, modification, and further enrollment.

Duration of Patient Participation:

This study will consist of 5 periods:

- The Screening Period is within 28 days before the randomization.
- The Treatment Period starts with the first study drug administration and ends when the patient is discontinued from study treatment for any reason. Patients will receive study drug until they 1) are no longer considered to be achieving clinical benefit, 2) have unacceptable toxicity, or 3) withdraw informed consent, whichever occurs first.
- The End-of-Treatment (EOT) or Safety Follow-up Period: Patients who discontinue treatment for any reason will be asked to return to the clinic for the EOT or Safety Follow-up Visit (to occur approximately 30 days [± 7 days] after the last dose of study drug[s] or before the initiation of a new anticancer treatment, whichever occurs first). In addition, patients should be contacted by telephone to assess AEs (serious and non-serious) and related concomitant medications, if appropriate, at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of study drug(s), regardless of whether the patient starts a new anticancer therapy. If a patient reports a suspected new or worsening AE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.
- The Efficacy Follow-up Period: Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient meets any of the discontinuation criteria or starts a new anticancer therapy.
- The Survival Follow-up Period: Overall survival data will be collected via telephone calls approximately every 8 weeks (± 7 days) after the Safety Follow-up Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or the end of the study by the sponsor.

Study Population: Patients with NSCLC who have advanced disease during or after anti-PD-(L)1 treatment with no more than 2 lines of prior systemic therapies and whose tumors do not harbor actionable gene alterations.

Key Eligibility Criteria:

Inclusion Criteria

- Patients (age ≥ 18 years) with advanced or metastatic NSCLC (nonsquamous or squamous) that is histologically or cytologically confirmed.
- Patients who have received no more than 2 lines of prior systemic therapies which must include anti-PD-(L)1 treatment and a platinum-based chemotherapy administered in combination with, or sequentially before or after the anti-PD-(L)1 treatment.

- Patients must agree to provide archival tissue.
- At least 1 measurable lesion as defined per RECIST v1.1.
- ECOG Performance Status of 0 or 1.
- Adequate organ function.

Exclusion Criteria

- Patients who received prior therapy containing docetaxel and/or ramucirumab for advanced or metastatic NSCLC.
- Patients with known gene actionable alterations.
- Patients with active leptomeningeal disease or uncontrolled and untreated brain metastasis.
- Patients who received prior therapy targeting OX40 or any other T-cell agonists.
- Patients with active autoimmune diseases or history of autoimmune diseases that may relapse, or history of life-threatening toxicity related to prior immune therapy.
- Patients with prior immunodeficiency or who received allogenic stem cell transplantation or organ transplantation.
- Patients with a history of severe hypersensitivity reactions to other monoclonal antibodies.

Investigational Product, Dose, and Mode of Administration:

- BGB-A445: [redacted] administered by intravenous infusion once every 3 weeks.
- Refer to the respective appendix for detailed instructions on drug dosage, preparation, storage, and administration of other investigational products.

Reference Therapy, Dose, and Mode of Administration:

- Docetaxel: 75 mg/m^2 administered by intravenous infusion once every 3 weeks.
- Ramucirumab: 10 mg/kg administered by intravenous infusion once every 3 weeks.

Statistical Methods:

Sample Size:

The total number of patients of this study may vary depending on the number of combinations where investigational agents are combined with BGB-A445 and the timing of when these agents are added to the study. In both Stage 1 and Stage 2, approximately 20 patients will be enrolled or randomized into each treatment cohort.

Statistical Analysis:

Efficacy

The Intent-to-Treat (ITT) Analysis Set will be used as the primary efficacy analysis population. The ORR assessed by the investigator and the corresponding 95% CIs will be reported using the Clopper-Pearson method. The CBR and DCR will be analyzed similarly to ORR. The time-to-event endpoints, including DOR, PFS, and OS, will be estimated using the Kaplan-Meier method.

Stage 1 Efficacy Analysis:

Confirmed ORR assessed by the investigator will be reported for each cohort. The corresponding 95% CIs will be reported using the Clopper-Pearson method.

Stage 2 Efficacy Analysis:

In Stage 2, the ORR difference between any experimental cohort and the concurrent reference cohort (ΔORR) and the corresponding 95% CIs will be reported. For investigational agents evaluated in both stages, an analysis by combing the data from two stages will be conducted if deemed necessary.

Safety

Safety and tolerability will be determined by the AEs observed and by laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and ECG findings will also be used in determining the safety profile of the study treatment(s). The severity of AEs will be graded according to NCI-CTCAE v5.0. The incidence of treatment-emergent adverse events (TEAE) will be reported as the number (percentage) of patients with TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs.

Pharmacokinetics

Serum or plasma concentration of BGB-A445 and other investigational agent(s) will be tabulated and summarized by the visit/cycle when these samples are collected. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Immunogenicity

Antidrug antibody (ADA) samples will be collected for BGB-A445 and relevant investigational agents, as appropriate. The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs.

Interim Monitoring:

Futility Analysis

A futility analysis will be conducted when approximately 20 patients are enrolled or randomized in any of the experimental cohorts at the end of Stage 1 and when these patients have been followed up for ≥ 2 postbaseline tumor assessments. Bayesian posterior probability will be used to evaluate clinical antitumor activity in Stage 1 for BGB-A445 in combination with investigational agents in each cohort. An experimental cohort will be considered futile and not proceed to Stage 2 if the ORR in this group is unlikely to exceed a historical benchmark (eg, Posterior Probability [true ORR ≥ 23%] ≤ 20%). The historical benchmark will be assessed periodically and may be updated based on the emergent data during the cause of the study.

Safety Stopping Rules

To control the number of patients at risk in the event of a major safety concern, a pause in enrollment will be triggered by unacceptable conditions, including any death because of reasons other than disease progression and at least possibly related to the study treatment. After evaluating the totality of the data, recommendations from the SMC, and benefit-risk evaluation, the sponsor will take appropriate actions for safety concern.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BGB-A317	Tislelizumab
CR	complete response
CPI	checkpoint inhibitor
CT	computed tomography
DLT	dose-limiting toxicity
ECG	Electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
EDC	electronic data capture (system)
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
imAE	immune-mediated adverse event
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
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

Abbreviation	Definition
PK	pharmacokinetic(s)
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SMC	Safety Monitoring Committee
TEAE	treatment-emergent adverse event
TME	tumor microenvironment
ULN	upper limit of normal

1. INTRODUCTION

1.1. Background Information on Non-Small Cell Lung Cancer

Lung cancer is one of the most common malignancies in adults, with approximately 2.21 million new diagnoses and 1.8 million deaths worldwide in 2020, which corresponds to the second highest incidence among cancers and the most common cancer-related mortality (Sung et al 2021). In 2022, an estimated 236,740 new cases of lung cancer will be diagnosed, and 130,180 deaths are estimated to occur because of the disease in the United States of America (USA) (NCCN Guideline v1 2023). Lung cancer is also the most commonly diagnosed malignancy, and it remains one of the deadliest in China, with an estimated 787,000 diagnoses and 630,500 deaths in 2015 (Gao et al 2020). The prognosis of advanced stage non-small cell lung cancer (NSCLC) remains poor despite the availability of newer anti-cancer therapy. The overall 5-year survival rate for patients with Stage IV NSCLC is 5% (Goldstraw et al 2016; Sung et al 2021).

NSCLC accounts for 80% to 85% of all lung cancers (American Cancer Society 2020). The disease is more common in men than women, representing 16.8% of all cancers in men and 8.8% of all cancers in women. For NSCLC patients without driver molecular alterations, the treatment strategy has shifted from traditional doublet chemotherapy to immunotherapy-based treatments with or without chemotherapy because of significant improvements in overall survival when compared with standard platinum-based chemotherapy (Planchard et al 2018). In these patients with pretreated late-stage advanced NSCLC, overall survival (OS) remains at approximately 9 to 13 months. The improvements of approximately 3 to 4 months have been achieved with anti-programmed cell death protein-1 (anti-PD-1) or anti-programmed cell death protein ligand-1 (anti-PD-L1) monotherapy compared with docetaxel (Borghaei et al 2015; Brahmer et al 2015; Herbst et al 2016; Rittmeyer et al 2017). However, for these NSCLC patients without actionable gene alterations, 7% to 27% and 20% to 44% of them will develop primary resistance to the CPI-based treatments in the first-line or the second-line settings, respectively (Walsh and Soo 2020), and there are limited treatment options for checkpoint inhibitor (CPI)-pretreated patients.

Different biomarkers have been proposed or are currently under investigation to better select patients that could benefit from immunotherapy (Di Liello et al 2020). Nevertheless, beyond the established role of PD-L1 expression (with all its limitations), none of these new biomarkers are able to guide clinicians to establish a targeted therapeutic algorithm for individual patients. The best treatment option remains challenging both in first line and after immunotherapy failure. Currently available options of treatment after the failure of a first line immunotherapy with or without with chemotherapy are represented by single agent chemotherapy eventually combined with anti-angiogenic drugs (Insa et al 2022).

The therapeutic index of these second-line NSCLC therapies has been restricted both by limited survival benefit and significant toxicities, such as myelosuppression and neuropathy (docetaxel), diarrhea (pemetrexed and erlotinib), and rash (erlotinib) (Stinchcombe and Socinski 2008). Outcomes are poor for patients with previously treated, advanced or metastatic NSCLC; systemic chemotherapy (eg, docetaxel) or erlotinib provide modest benefits (Al-Farsi and Ellis 2014; Stinchcombe and Socinski 2008).

1.1.1. Current Treatment of CPI-pretreated Advanced or Metastatic Non-Small Cell Lung Cancer and Unmet Clinical Needs

Chemotherapy is used in the subsequent-line setting for NSCLC after the first-line treatment including CPI treatments. Chemotherapy including docetaxel or docetaxel plus ramucirumab demonstrated an overall response rate (ORR) ranging from 10% to 20% but did not translate to durable disease control or OS benefit, with significant toxicities reported in patients who received docetaxel.

Docetaxel was the first agent to demonstrate a survival benefit in comparison with best supportive care (BSC) in patients with relapsed NSCLC following platinum-containing therapy. In the first randomized Phase 3 study (TAX317), 103 eligible patients were stratified by performance status (PS) and best response to cisplatin chemotherapy and were then randomized to treatment with docetaxel 100 mg/m^2 or 75 mg/m^2 (55 patients) or BSC. Time to progression was longer for docetaxel-treated patients than for BSC-treated patients (10.6 versus 6.7 weeks, respectively; $p < 0.001$), as was median OS (7.0 versus 4.6 months; log-rank test, $p = 0.047$). The difference was more significant for patients treated with docetaxel 75 mg/m^2 than with docetaxel 100 mg/m^2 and there was less toxicity with docetaxel 75 mg/m^2 than with docetaxel 100 mg/m^2 (Shepherd et al 2000). Subsequent studies comparing other treatment options with docetaxel in a second-line setting showed a response rate of 6% to 11% and median OS of 5 to 10 months (Barnfield and Ellis 2016).

Pemetrexed appears to be a non-inferior agent compared with docetaxel. A Phase 3 study demonstrated non-inferiority for OS between pemetrexed and docetaxel (8.3 versus 7.9 months; hazard ratio [HR] 0.99; 95% CI: 0.8 to 1.2). However, pemetrexed showed a better toxicity profile with a significantly lower rate of neutropenia and alopecia, as well as lower rates of gastrointestinal adverse events (AEs) (Hanna et al 2004). The use of pemetrexed is limited to patients with nonsquamous histology. In addition, its use as a first-line agent has become much more prevalent, thus limiting its administration in the second-line setting.

Ramucirumab was approved by the Food and Drug Administration (FDA) in combination with docetaxel for treatment of patients with metastatic NSCLC with whose disease progressed on or after platinum-based chemotherapy. The efficacy of ramucirumab was evaluated in REVEL (NCT01168973), a multinational, randomized, double-blind study in patients with NSCLC whose disease progressed on or after one platinum-based therapy for locally advanced or metastatic disease. The major efficacy outcome measure was OS. Additional efficacy outcome measures included progression free survival (PFS) and ORR. A total of 1253 patients were randomized: 628 to the ramucirumab with docetaxel group and 625 to the placebo with docetaxel group. Median overall survival was 10.5 months (interquartile range [IQR] 5.1 to 21.2) for 628 patients allocated ramucirumab plus docetaxel and 9.1 months (IQR 4.2 to 18.0) for 625 patients who received placebo plus docetaxel (HR 0.86; 95% CI 0.75 to 0.98; $p = 0.023$). Median progression-free survival was 4.5 months (IQR 2.3 to 8.3) for the ramucirumab group compared with 3.0 months (IQR 1.4 to 6.9) for the control group (HR 0.76; 95% CI 0.68 to 0.86; $p < 0.0001$). The overall response rate (complete response plus partial response) was 23% (95% CI: 20 to 26) for ramucirumab with docetaxel and 14% (95% CI: 11 to17) for placebo with docetaxel, $p < 0.001$ (Garon et al 2014).

Nintedanib was approved in the European Union (EU) for patients with lung cancer with advanced adenocarcinoma after first-line chemotherapy. The Phase 3 LUME-Lung 1 study assessed the efficacy and safety of docetaxel plus nintedanib as second-line therapy for NSCLC; A total of 655 patients were randomly assigned to receive docetaxel plus nintedanib and 659 to receive docetaxel plus placebo. Data from the study demonstrated that compared to docetaxel alone, nintedanib when added to docetaxel significantly extended median overall survival from 10.3 to 12.6 months (p = 0.0359; HR: 0.83) for patients with adenocarcinoma, with a quarter of patients surviving for 2 years or more (survival at 24 months: nintedanib plus docetaxel [25.7% of patients] versus placebo plus docetaxel [19.1% of patients], p = 0.0359; HR: 0.83) (Reck et al 2014).

1.2. Background Information on BGB-A445 as an OX40 Agonist

BGB-A445 is a humanized IgG 1, Fc-competent, monoclonal agonist antibody against OX40 under clinical development for the treatment of human malignancies.

1.2.1. Pharmacology

BGB-A445 binds to the extracellular domain of human OX40 with high specificity and affinity, while it does not block the binding of OX40 to its native ligand OX40L. In in vitro cell-based assays and in the mouse models, BGB-A445 functions as an agonist of the OX40 receptor to costimulate T cells secreting Interleukin-2 (IL-2) and shows antitumor activities alone or in combination with anti-mouse PD-1 antibody. Refer to the BGB-A445 Investigator's Brochure for detailed information regarding pharmacology studies.

1.2.2. Toxicology

The acute toxicity was evaluated in the single-dose pharmacokinetics (PK) study at doses up to 50 mg/kg and in the repeated-dose toxicity study at doses up to 100 mg/kg intravenous in cynomolgus monkeys. No acute toxicity was observed in cynomolgus monkeys in toxicity studies. Also, overall, no apparent test article-related toxicity, including local effects, was noted at ≤ 20 mg/kg following repeated administration once every 2 weeks for 13 weeks in cynomolgus monkeys.

Refer to the BGB-A445 Investigator's Brochure for detailed information regarding additional toxicology studies.

1.2.3. Clinical Pharmacology

Preliminary pharmacokinetic data in humans indicate that BGB-A445 exposure (C_{max} and AUC_{21d}) increased approximately [redacted] in the [redacted] monotherapy dose range and [redacted] dose range in combination with [redacted] tislelizumab. Serum concentrations declined in a biexponential manner after intravenous infusion, and preliminary terminal half-life ($t_{1/2}$) estimates range from 7.9 to 12.7 days.

Preliminary immunogenicity data are available from a total of 99 patients treated with BGB-A445 monotherapy or combination therapy at dose levels ranging from [redacted] (up to [redacted] for combination therapy) in the ongoing Phase 1a/1b Study BGB-A317-A445-101. Fifteen of 71 patients (21.1%) treated with BGB-A445 ranging from [redacted]

monotherapy and 9 of 28 patients (32.1%) treated with BGB-A445 ranging from [redacted] in combination with [redacted] of BGB-A317, which is a BeiGene-developed anti-PD-1 monoclonal antibody, namely tislelizumab, tested positive for BGB-A445 treatment-emergent antidrug antibody (ADAs). Neutralizing antibody (NAb) information is not available yet. The immunogenicity assessments will be continued in this study and other planned BGB-A445 studies.

Preliminary immunogenicity data for tislelizumab (dosed at [redacted] once every 3 weeks) are available from a total of 23 ADA-evaluable patients treated with tislelizumab in combination with BGB-A445. Ten of 23 patients (43.5%) tested positive for tislelizumab treatment-emergent ADAs. The ADA positivity rate for the tislelizumab in combination with BGB-A445 was found to be somewhat higher than that observed for tislelizumab monotherapy based on historical data.

In both treatment parts, OX40 receptor occupancy was saturated (> 90%) at dose levels ≥ [redacted]. In both treatment parts, a stronger trend of soluble OX40 induction was found after long term treatment at higher doses (≥ [redacted]).

Refer to the BGB-A445 Investigator's Brochure for detailed information regarding additional toxicology studies.

1.2.4. Prior Clinical Experience With BGB-A445

BGB-A317-A445-101 is an ongoing, open-label, multicenter, nonrandomized, first-in-human Phase 1a/1b study investigating the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of the anti-OX40 agonist monoclonal antibody BGB-A445 alone or in combination with the anti-PD-1 monoclonal antibody tislelizumab in patients with advanced solid tumors. As of the 05 January 2023 data cutoff date, 166 patients had received study drug across monotherapy and in combination dose escalation cohorts as follows:

- BGB-A445 monotherapy in dose escalation and expansion phases (n = 119): As of the data cutoff date, 8 dose levels have been evaluated including [redacted] (n = 1), [redacted] (n = 4), [redacted] (n = 3), [redacted] (n = 6), [redacted] (n = 12), [redacted] (n = 44), [redacted] (n = 45), and [redacted] (n = 4) every 3 weeks.
- BGB-A445 in combination with tislelizumab [redacted] in dose escalation phase (n = 47): As of the data cutoff date, 6 dose levels of BGB-A445 have been evaluated including [redacted] (n = 6), [redacted] (n = 5), [redacted] (n = 8), [redacted] (n = 14), [redacted] (n = 10), and [redacted] (n = 4) every 3 weeks.

1.2.4.1. Safety Assessment of BGB-A445

As of 05 January 2023, 119 dose-limiting toxicity (DLT)-evaluable patients had received ≥ 1 dose of BGB-A445 alone, and 47 patients received a combined dose of BGB-A445 with tislelizumab [redacted] every 3 weeks in the dose-escalation stage. No DLTs were observed, and no deaths were reported related to the treatment. BGB-A445, alone up to [redacted] and in combination up to [redacted], was generally safe and well-tolerated. The safety profile of BGB-A445 given as monotherapy or in combination with tislelizumab is well tolerated in patients with advanced solid tumors at doses up to [redacted] both in monotherapy and in combination with tislelizumab [redacted] once every 3 weeks.

BGB-A445 monotherapy

Among 119 patients who received BGB-A445 monotherapy, 99 (83.2%) had at least 1 treatment-emergent adverse event (TEAE). Fifty-six patients (47.1%) experienced TEAEs that were assessed as related to treatment. Thirty-seven patients (31.1%) experienced TEAEs of ≥ Grade 3, 5 (4.2%) of which were considered related to treatment. Thirty-eight patients (31.9%) experienced serious TEAEs, 6 (5.0%) of which were considered related to treatment.

Among 37 patients (31.1%) who experienced ≥ 1 TEAE of ≥ Grade 3 severity, the most commonly occurring ≥ Grade 3 TEAEs were Death (4 patients, 3.4%), followed by Haemoptysis, Pleural effusion, and Hypertension (3 patients each, 2.5%), as well as Nausea, Pneumonia, Sepsis, Arthralgia, Back pain, Cancer pain, and Anaemia (2 patients each, 1.7%).

A total of 20 of 119 patients (16.8%) experienced ≥ 1 immune-mediated AEs (imAEs) which are of Grade 1 to 2 in severity. The most commonly occurring immune-mediated AEs were Pruritus and Rash maculo-papular (4 patients each, 3.4%), followed by Pyrexia (2 patients, 1.7%). The remaining immune-mediated AEs occurred in single instances (0.8% each). Additionally, 16 (13.4%) of 119 patients experienced ≥ 1 infusion-related reactions, with 1 patient at the dose level of [redacted] experiencing ≥ 1 infusion-related reactions of Grade 3 severity.

Ten patients (8.4%) had a TEAE leading to death; 1 patient each from the [redacted] and [redacted] cohorts, 5 patients from the [redacted] cohort, and 3 patients from the [redacted] cohort. None of these fatal TEAEs were assessed as related to the study treatment.

BGB-A445 in combination with tislelizumab

Among 47 patients who received BGB-A445 in combination with tislelizumab, 46 (97.9%) had at least 1 TEAE, with 34 patients (72.3%) experienced TEAEs assessed as related to treatment. Twenty-three patients (48.9%) experienced a ≥ Grade 3 TEAE, 6 (12.8%) of which were considered related to treatment. Twenty patients (42.6%) experienced serious TEAEs, 4 (8.5%) of which were considered related to treatment.

Among 23 patients (48.9%) who experienced ≥ 1 TEAE of ≥ Grade 3 severity, the most commonly occurring ≥ Grade 3 TEAEs were Abdominal pain and Diarrhoea (3 patients each, 6.4%), followed by Fatigue, Pyrexia, and Pleural effusion (2 patients each, 4.3%). The remaining ≥ Grade 3 TEAEs were single occurrences.

Immune-mediated AEs were reported in 17 patients (36.2%), including imAEs with incidence ≥ 5% of Rash maculo-papular (5 patients, 10.6%), Diarrhoea (4 patients, 8.5%), Arthralgia and Hypothyroidism (3 patients each, 6.4%). Three of 47 patients experienced ≥ 1 imAEs of Grade 3 severity. These imAEs included Immune-mediated arthritis, Rash maculo-papular, Diarrhoea, and Rash, and all of them occurred only once. Nine patients (19.1%) experienced an infusion-related reaction, with 1 patient that experienced 1 infusion-related reaction with Grade 3 severity at the dose level of [redacted].

Of the 47 patients in the BGB-A445 combination therapy with tislelizumab cohort, 3 patients (6.4%) experienced a TEAE leading to death in the BGB-A445 [redacted] + tislelizumab [redacted] cohort. None of these fatal TEAEs were assessed as related to the study treatment.

1.2.4.2. Efficacy Assessment of BGB-A445

As of the data cutoff date, 06 January 2023, 2 patients with unconfirmed partial response (PR) and 2 patients with stable disease ≥ 24 weeks in BGB-A445 monotherapy and 9 patients with unconfirmed PR in the combination therapy of BGB-A445 and tislelizumab have been observed in the BGB-A317-A445-101 study.

1.3. Background Information on Investigational Agents

Background information on each investigational agent is presented in the appendices.

1.4. Study Rationale

1.4.1. Rationale for BGB-A445-based Combination Treatment

Successful antitumor immune response following immunotherapy with PD-1/PD-L1 immune checkpoint inhibitors, requires the reactivation and clonal proliferation of antigen-experienced T cells present in the tumor microenvironment (TME) (Jenkins et al 2018; Sharma et al 2017). Additionally, an immunosuppressive TME, which is characterized by high levels of immune-suppressing cytokines and/or metabolites with high levels of immune suppressive cells (eg, myeloid-derived suppressor cells, and regulatory T cells [Tregs]) is also growing in recognition as another driver of acquired resistance to treatment with anti-PD-1/PD-L1 antibodies (Jenkins et al 2018; Topalian et al 2015).

One strategy for increasing tumor immunity would be to activate and expand tumor-associated antigen T cells via activation of immunogenic costimulatory pathways such as OX40 (Jensen et al 2010). The mechanisms of action of agonistic anti-OX40 monoclonal antibody-mediated antitumor effects are attributed to their ability to directly improve the effector function of T cells while counteracting the immunosuppressive effects of Tregs (Ito et al 2006; St Rose et al 2013; Voo et al 2013; Aspeslagh et al 2016).

OX40 (also known as ACT35, CD134, or tumor necrosis factor receptor [TNFR] superfamily, member 4 [TNFRSF4]) is an immune costimulatory receptor primarily expressed on activated T cells and to a lesser extent on neutrophils, natural killer cells, and natural killer T cells. A large body of literature suggests that OX40 plays a key role in promoting T-cell survival, proliferation, and proinflammatory cytokine expression in the tumor microenvironment. When expressed on effector T cells, OX40 binds with its sole ligand (OX40L) and activates both the NF-κB1 and NF-κB2 pathways, which play key roles in the regulation of T-cell survival, differentiation, expansion, cytokine production, and effector function.

Some studies reported that higher expression of OX40 on tumor-infiltrating lymphocytes was correlated with better OS (Petty et al 2002; Ladanyi et al 2004; Sarff et al 2008). Indeed, the sponsor and others have shown nonclinically that treatment with an OX40 agonist induces tumor regression in a large number of distinct in vivo tumor models (Redmond and Weinberg 2007; Piconese et al 2008).

It was hypothesized that the BGB-A445-based combination treatment may overcome the resistance to anti-PD-(L)1 antibodies in NSCLC. This study is designed to establish proof of concept for multiple novel investigational agents, in a randomized setting, in combination with

OX40 agonist BGB-A445, to identify novel combination therapies that could improve responses and clinical benefit in the second or third line treatment for anti-PD-(L)1-pretreated patients with NSCLC without actionable gene alterations.

1.4.2. Rationale for Selection of Investigational Agents in Combination With BGB-A445

In this study, docetaxel is selected to be administered in combination with BGB-A445.

In the second- and third-line treatment setting for NSCLC, docetaxel remains a commonly used standard treatment option for both squamous and non-squamous histologies in China and worldwide. It has demonstrated a survival benefit relative to BSC in patients with relapsed NSCLC following first-line therapy and is associated with a response rate between 6% and 11% and a median OS of 5 to 10 months as mentioned in Section 1.1.1. The doses of docetaxel in combination of BGB-A445 are based on product labelling, literature, and local guidelines.

While docetaxel alone or combined with ramucirumab has previously demonstrated a tolerable safety profile in the second- and third-line treatment of NSCLC regardless of the add-on of CPI such as anti-PD-(L)1 antibody, the response rate and OS of docetaxel remain far from satisfactory. The addition of immunotherapy to chemotherapy has been proven to be a good strategy with improved ORR and survival in NSCLC, but for those patients who already had been treated with PD-1/PD-L1 inhibitors, rechallenge with PD-1/PD-L1 inhibitors in the second- and third-lines settings yielded limited efficacy (Furuya et al 2021; Takahara et al 2022) and was associated with an increased toxicity burden.

Accumulating preclinical data suggest that BGB-A445 can modulate the tumor microenvironment as mentioned above, and synergic effects were observed for BGB-A445 in combination with chemotherapy in mouse models. Collectively, the add-on of BGB-A445 may benefit the NSCLC patients in the second and third lines of treatment setting.

For other investigational agents selected to be administered in combination with BGB-A445 in the treatment of anti-PD-(L)1-pretreated NSCLC, the rationale is provided in Appendix 14.

1.4.3. Rationale for Selection of Reference Treatment

As described in Section 1.1.1, patients with anti-PD-(L)1-pretreated NSCLC that do not have actionable gene alterations typically receive a standard of care that includes ramucirumab in combination with docetaxel, which depends on the local guidelines (NCCN Guideline v1 2023). Reference treatments may be amended in this study accordingly because the standard of care may evolve in the future.

1.4.4. Rationale for BGB-A445 Dose

BGB-A445 will be administered by intravenous infusion at a dose of [redacted] once every 3 weeks with additional investigational agents. This dose was selected based on acceptable safety, tolerability, PK, pharmacodynamic activity, and antitumor activity of BGB-A445 observed in the ongoing Phase 1 study BGB-A317-A445-101. Most antitumor activity was observed in the [redacted], leading to 2 patients with unconfirmed partial responses (1 patient each at the [redacted] and [redacted] monotherapy dose levels), while 2 patients at the [redacted] dose level have presented ongoing durable stable disease lasting > 36 weeks. Although

saturation of receptor occupancy in peripheral blood at dose levels of ≥ [redacted] has been observed, peripheral receptor occupancy is not a robust measure of occupancy at the tumor tissue target, which could be because of several contributing factors, such as lower biodistribution of monoclonal antibodies into tissue (Shah and Betts 2013) or kinetics of OX40 expression on T cells (Willoughby et al 2017). Data from this study and Study BGB-A317-A445-101 dose expansion will inform and may further refine the dose of BGB-A445 in clinical development.

1.4.5. Rationale for Biomarker Strategy

Exploratory biomarker analyses will be performed to study the following aspects of BGB-A445 in combination with investigational agent(s): 1) potential predictive biomarkers for response and resistance of each combination therapy; 2) treatment and pharmacodynamic effects induced in patients. Soluble OX40 is a marker of T-cell activation and can serve as a predictive biomarker and for mechanisms of action (MOA) exploration (Wang et al 2018). OX40 agonist antibodies have been shown to enhance naive T-cell differentiation to effector T cells or memory T cells, increase pro-inflammatory cytokines and deplete regulatory T cells through antibody-dependent cellular cytotoxicity (ADCC) (Piconese et al 2008; Aspeslagh et al 2016). The expression levels of OX40, PD-L1, and other investigational agent-specific proteins at baseline as determined by immunohistochemistry will be correlated to response and may serve as predictive biomarkers. Tumor-mutation, gene-expression profiles, and tumor-infiltrating lymphocytes may be explored in these tissues as possible predictive markers.

Circulating tumor DNA (ctDNA) levels, as well as cytokines/soluble proteins in peripheral blood at baseline and after treatment, may serve as possible predictive markers and/or pharmacodynamic markers that may help to explore the depth of response and the understanding of MOA for the combination treatment effect of each investigational agent (Ricciuti et al 2021).

Besides predictive biomarkers, mechanisms of resistance to immunotherapy are also not well understood and need more exploration. Identifying tumor and immune-mediated features that are associated with progressive disease or acquired resistance to the treatments may increase the understanding of disease pathobiology and provide biological evidence for combination strategies.

1.5. Benefit-Risk Assessment

The BGB-LC-203 study will evaluate the efficacy, pharmacodynamics, and safety of BGB-A445 in combination with investigational agents in checkpoint inhibitors-pretreated patients with NSCLC. Based on general assessment, the sponsor hypothesizes that BGB-A445 in combination with investigational agents may provide clinical benefit by enhancing the tumor response and reducing disease recurrence.

1.5.1. BGB-A445

The human experience with BGB-A445 as either monotherapy or in combination with other antitumor agents is still evolving; therefore, clinical benefit in patients with advanced solid tumors has not been assessed. Based on the BGB-A445 MOA, in vivo and in vitro preclinical data, and preliminary antitumor activity observed in the ongoing dose-escalation phase of

Study BGB-A317-A445-101, BGB-A445 as a single agent or in combination with tislelizumab has the potential to address unmet medical needs in patients with advanced solid tumors.

A total of 166 patients as of 05 January 2023 have been treated with BGB-A445 monotherapy or in combination with tislelizumab in multiple tumor types. Generally, BGB-A445 is well tolerated when used in combination with tislelizumab therapy. However, these data should be interpreted with some caution because the sample sizes are relatively small for the ongoing studies. Refer to the Investigator's Brochure for more detailed information on BGB-A445 safety and efficacy data when given as monotherapy or in combination.

1.5.2. Investigational Agents

The agent-specific benefit-risk assessment is presented in the respective appendix.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives and Endpoints

Table 1: Primary Objectives and Endpoints

Objectives	Endpoints
To assess the antitumor activity of BGB-A445 plus investigational agent(s) in non-small cell lung cancer (NSCLC) patients pretreated with anti-programmed cell death protein 1 (anti-PD-1)/anti-programmed cell death protein ligand 1 (anti-PD-L1) antibody	Overall response rate (ORR) as assessed by the investigators per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1 (as described in Section 9.2)

Table 2: Secondary Objectives and Endpoints

Objectives	Endpoints
To assess the safety and tolerability of BGB-A445 plus investigational agent(s)	The incidence and severity of adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 in experimental cohorts (BGB-A445 plus investigational agent)
To further assess the antitumor activity of BGB-A445 plus investigational agent(s)	Duration of response (DOR), disease control rate (DCR), and clinical benefit rate (CBR) as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (as described in Section 9.2)
To characterize the pharmacokinetics (PK) of BGB-A445 and investigational agent(s)	Plasma or serum concentrations of BGB-A445 and investigational agents at specified timepoints
To assess host immunogenicity to BGB-A445 and investigational protein therapeutics	Immunogenic responses to BGB-A445 and investigational protein therapeutics, evaluated through the detection of antidrug antibodies (ADA)

Table 3: Exploratory Objectives and Endpoints

Objectives	Endpoints
To evaluate the potential association of exploratory biomarkers with response or resistance to study treatment and with patient prognosis	Evaluate exploratory biomarkers in various sample types (ie, tumor tissue and/or blood) at various timepoints (ie, before study treatment, after study treatment, and/or at disease progression or recurrence) and the association between these biomarkers and clinical efficacy, disease status, and resistance Exploratory biomarkers may include, but are not limited to: tumor necrosis factor receptor superfamily, member 4 (CD134, OX40) expression; PD-L1 expression; soluble OX40 (sOX40); investigational agent-specific protein expression; gene expression profiling; tumor-infiltrating immune cells in tumor tissue; tumor mutation burden/microsatellite instability/genetic mutation profiles; circulating tumor DNA (ctDNA), cytokines, and soluble proteins in plasma or serum Other assessments may be conducted as indicated and as allowed by local regulations
To further assess the preliminary antitumor activity including by time-to-event of BGB-A445 plus investigational agent(s)	Progression-free survival (PFS) as determined from tumor assessments by investigators per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
To assess overall survival (OS)	OS defined as the date of randomization to the date of death because of any cause (as described in Section 9.2)

3. STUDY DESIGN

3.1. Summary of Study Design

This is a Phase 2, open-label, randomized, multicenter, multi-arm study designed to evaluate the efficacy and safety of BGB-A445 in combination with investigational agent(s) in previously treated NSCLC patients whose tumors do not harbor *EGFR*-sensitizing mutations, *ALK* translocations, *BRAF* V600E mutations, *RET* rearrangement, *ROS1* mutations, or another actionable mutation with targeted therapy approved by the local health authority. The patient must not have received more than 2 lines of prior systemic therapies, which must include an anti-PD-(L)1 treatment.

The study is designed to include 2 stages, with the flexibility of adding treatment cohorts when new treatments become available or discontinuing treatment cohorts that demonstrate minimal clinical activity or unacceptable toxicity. Approximately 20 patients will be enrolled or randomized into each cohort in Stage 1 and Stage 2. New BGB-A445-based combination cohort(s) may be added in accordance with emerging preclinical or clinical evidence via a protocol amendment. The total number of patients in this study may vary depending on the number of combinations where investigational agents are combined with BGB-A445 and the timing of when these agents are added to the study.

Stage 1: Patients will be equally enrolled or randomized into different experimental cohorts to receive BGB-A445 plus investigational agent(s).

A safety lead-in with approximately 6 patients enrolled will be initiated in each cohort for confirmation of the safe dosage (Section 3.4). After the dosage is deemed as safe, the randomization will be continued until approximately 20 patients are enrolled into a cohort. Efficacy and safety will be evaluated to determine if the experimental cohort(s) could be selected for further development in Stage 2, as described in Section 9.2.1.1 and Section 9.8, respectively.

Stage 2: Patients will be equally enrolled or randomized into the experimental cohort(s) selected from Stage 1.

See Section 7.2.2 and Section 9.1.1 for details of randomization. Efficacy and safety will be evaluated as described in Section 9.2.1.2 and Section 9.3, respectively.

The study design schematic is presented in Figure 1. In Stage 1, the combination treatments to be administered in this study include the following:

- BGB-A445 + docetaxel
- BGB-A445 + BGB-15025

In Stage 2 of the current protocol, the combination treatments to be administered in this study include the following:

- Experimental cohorts: BGB-A445 + selected investigational agent(s) from Stage 1
- Reference cohort: Docetaxel + ramucirumab

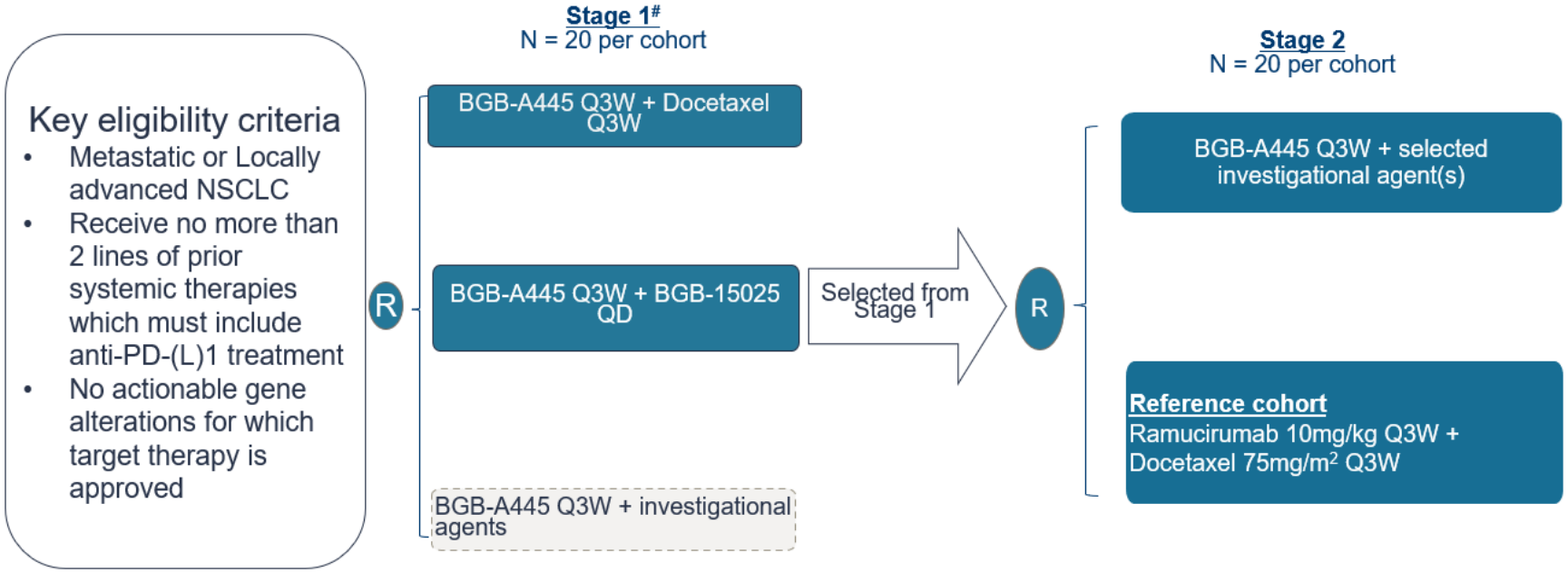
- Dose optimization for selected cohort: Different dose levels of the investigational agents may be explored to more fully characterize exposure-response relationships to enable future development.

In both stages, study treatments in all cohorts will be administered (1 cycle consists of 3 weeks based on the schedule of administration of BGB-A445) until disease progression, intolerable toxicity, withdrawal of informed consent, or another discontinuation criterion is met, whichever occurs first (see Section 3.8).

Patients will be required to sign an informed consent form (ICF) to undergo screening procedures. Patients will also be required to provide tissue samples for retrospective analysis of biomarkers.

For all study procedures, see Section 7 and Appendix 1.

Figure 1: Study Schema



Abbreviations: NSCLC, non-small cell lung cancer; PD-(L)1, programmed cell death protein-1/programmed cell death protein ligand-1; Q3W, once every 3 weeks; QD, once a day; R, randomization.

3.2. Screening Period

Screening evaluations will be performed ≤ 28 days before randomization (see Appendix 1). Patients who agree to participate in this study will sign the ICF before undergoing any screening procedure. Screening evaluations may be repeated as needed within the screening period; the investigator is to assess preliminary patient eligibility according to the latest screening assessment results. For rescreening requirements, see Section 7.1.

During the screening period, patients are required to provide archival tumor tissue (formalin-fixed paraffin-embedded [FFPE] blocks containing tumor [preferred] or approximately 15 [at least 10] freshly cut unstained slides). The most recently collected tissue is preferred. Refer to Section 7.6 for more details.

3.3. Treatment Period

After completing all screening activities, eligible patients will be equally enrolled or randomized into cohorts of Stage 1 and Stage 2 (Section 3.1), where applicable (Figure 1), to receive the study treatment as described in Section 5.

Study treatments in all cohorts will be administered up to 36 cycles (ie, approximately 2 years, every cycle consists of 3 weeks based on the schedule of administration of BGB-A445) until disease progression, intolerable toxicity, withdrawal of informed consent, or another discontinuation criterion is met, whichever occurs first.

Treatment beyond the initial investigator-assessed, Response Evaluation Criteria in Solid Tumors (RECIST) v1.1-defined disease progression is permitted in all cohorts if the criteria below are met:

- Absence of clinical symptoms and signs of progressive disease (including clinically significant worsening of laboratory values)
- Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, spinal cord compression) that requires urgent alternative medical intervention
- The investigator must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that doing so would not be considered standard practice in the treatment of cancer. Patients must be informed that by continuing treatment on this study despite progression, they may be forgoing a treatment option that may be more beneficial for tumor control.
- The decision to continue study drug(s) beyond the initial investigator-assessed progression must be made following discussion with the sponsor's medical monitor.

Patients who receive study treatment beyond initial progression will have tumor assessments performed according to the original schedule until study treatment discontinuation. If the response assessment performed following treatment beyond progression shows continued progression of disease, treatment must be discontinued.

Tumor response will be assessed by investigators using standard RECIST v1.1 criteria. Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held (ie, their schedule should not be adjusted for delays in cycles). See Section 7.4 for details.

Safety will be assessed throughout the study by monitoring AEs, serious AEs (SAEs) (toxicity grades assigned per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 [NCI-CTCAE v5.0]), and laboratory results. Safety assessments are further detailed in Section 7.3.

3.4. Details for Safety Lead-in

This protocol includes a dose-confirmation component for novel combinations where the safety profile of the combination has not been characterized. For such combination, a safety lead-in is planned included to evaluate the safety of the dosage of the combination.

Approximately 6 patients will be randomized into the safety lead-in of each cohort in Stage 1 and treated at the proposed dose deemed safe based on the previous studies. Safety and tolerability data will be reviewed by the Safety Monitoring Committee (SMC).

Additional details including the definition and assessment of DLTs will be provided in Section 3.4.1 and Section 3.4.2.

The information for the safety lead-in planned for specific investigational agents will be provided in the respective appendices.

3.4.1. Assessment of Dose-Limiting Toxicity

For patients enrolled in the safety lead-in, AEs will be assessed per the DLT criteria (Section 3.4.2) during a 21-day DLT assessment window.

Patients will be considered evaluable for DLTs if they 1) received ≥ 80% of each scheduled study drug(s) administration during the DLT assessment window, and had sufficient safety evaluation, and/or 2) experienced a DLT. Patients who are not evaluable for DLT may be replaced.

Clinically important or persistent AEs that are not part of the DLT criteria (Section 3.4.2) may also be considered a DLT following review by the sponsor in consultation with the investigators.

Any patient who experiences a DLT may be withdrawn from treatment or may continue at a lower dose level following discussion with and approval by the sponsor's medical monitor.

3.4.2. Dose-Limiting Toxicity Definition

All toxicities or AEs will be graded according to NCI-CTCAE v5.0. A DLT is defined as one of the following toxicities occurring during the DLT assessment window and considered by the investigator to be related to study drug(s):

Hematologic:

1. Grade 4 neutropenia lasting ≥ 7 days

2. ≥ Grade 3 febrile neutropenia (defined as absolute neutrophil count [ANC] < 1000/mm^3 with a single temperature of 38.3°C or a sustained temperature of 38°C for > 1 hour)
3. Grade 3 neutropenia with clinically significant infection
4. Grade 3 thrombocytopenia with clinically significant bleeding (≥ Grade 2 hemorrhage)
5. Grade 4 thrombocytopenia
6. ≥ Grade 4 anemia

Nonhematologic:

1. Any death not clearly defined because of underlying disease or extraneous causes
2. ≥ Grade 4 toxicity
3. Grade 3 toxicity that is clinically significant and does not resolve to baseline or ≤ Grade 1 within 3 days after initiating optimal supportive care (unless excluded in the listed criteria)
4. Confirmed drug-induced liver injury meeting Hy's law criteria

Note: Some AEs may be considered DLTs based on the mechanism of action and expected toxicity of the compound being studied. The following AEs will not be considered DLTs:

- Grade 3 hypothyroidism that is adequately controlled by hormonal replacement
- Grade 3 tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumors)
- Grade 3 rash
- Grade 3 fatigue ≤ 7 days

Investigational agent-specific DLT criteria or exceptions to the DLT definition above are provided in the investigational agent-specific appendix.

3.4.3. Safety Lead-in Data Review

The proposed dose cohort will be deemed as safe in the case of no more than 1 DLT event out of 6 DLT-evaluable patients, and the randomization/enrollment will be continued until approximately 20 patients are randomized/enrolled into a cohort. In addition to the DLT evaluation, other available relevant data (eg, safety data, available PK analyses) will be reviewed by the SMC with input from other members, as appropriate, to make the final decision. If the proposed dose is deemed not tolerable, the enrollment will be paused or the dose level will be changed for further evaluation. Please refer to the respective appendix for more information.

Only DLTs that occur within the DLT assessment window will be considered for the corresponding dose level for the purpose of data review in the safety lead-in. Additionally, clinically important or persistent AEs (eg, imAEs) that are not part of the DLT criteria and are observed outside of the DLT assessment window may also be considered regarding subsequent decision.

3.4.3.1. BGB-A445 Combined With Docetaxel

A safety lead-in is planned for the combination of BGB-A445 and docetaxel.

If the combination of BGB-A445 and docetaxel is deemed not tolerable, the enrollment will be paused for further evaluation.

3.4.3.2. BGB-A445 Combined With Investigational Agents

For the details of data review during safety lead-in for the combination of BGB-A445 with other investigational agents, please refer to the agent-specific appendix.

3.5. Patient Discontinuation From Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. If necessary, the investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue study treatment for reasons other than disease progression should be followed for assessments of antitumor activity (Section 7.4), safety (Section 7.3), and survival (Section 3.7), if possible. The primary reason for discontinuation from the study treatment should be documented on the appropriate electronic case report form (eCRF). Patients may discontinue study treatment for reasons that include but are not limited to the following:

- Disease progression
- Adverse event(s)
- Patient decision
- Pregnancy
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she were to continue the study treatment
- Use of any concurrent systemic anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other country) herbal medicine and Chinese (or other country) patent medicines] for the treatment of cancer)
- Patient noncompliance
  Investigative site staff should first counsel patients who are significantly noncompliant (eg, missing 2 treatment cycles) on the importance of study drug compliance and drug accountability. The investigator may, in consultation with the medical monitor, discontinue patients from treatment who are consistently noncompliant.

Patients who discontinue study treatment before disease progression will continue to undergo tumor assessments as outlined in Section 7.4.

3.6. End of Treatment and Safety Follow-up

The End-of-Treatment (EOT) Visit will be conducted ≤ 7 days after the investigator determines that study treatment will no longer be administered or the patient discontinues the study treatment. Patients will undergo the Safety Follow-up Visit at approximately 30 days (± 7 days) after the last dose or before initiation of any new anticancer therapy, whichever occurs first.

Patients will be contacted by telephone to assess AEs (serious and nonserious) and relevant concomitant medications (ie, those associated with an AE or any new anticancer therapy). These contacts should be made at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of study drug(s), regardless of whether the patient starts a new anticancer therapy. If a patient reports a suspected new or worsening AE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

All AEs, including SAEs, will be collected as described in Section 8.6.

See Appendix 1 for assessments to be performed at the EOT/Safety Follow-up Visit.

3.7. Survival Follow-up

Overall survival data will be collected via telephone calls approximately every 8 weeks (± 7 days) after the Safety Follow-up Visit or as directed by the sponsor until death, withdrawal of consent, loss to follow-up, or the end of the study (see Section 3.9).

3.8. Patient Discontinuation From Study (End of Study for an Individual Patient)

Patients may discontinue from the study for reasons that include, but are not limited to, the following:

- Patient withdrawal of consent
- Adverse events
- Noncompliance
- Toxicity
- Death
- Loss to follow-up
- Patient completion of all study assessments

3.9. End of Study

The end of the study is defined as the timepoint when the final data point is collected from the last patient in the study. This is when the last patient dies, withdraws consent, completes all study assessments, or is lost to follow-up. Alternatively, the end of the study is when the sponsor decides to terminate the study.

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for an EOT/Safety Follow-up Visit.

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) of the early termination of the study.

The sponsor has the right to close a site at any time. Whenever possible, the site will be notified of the decision in advance. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Good Clinical Practice (GCP) noncompliance
- Study activity is completed (ie, all patients have completed the study and all obligations have been fulfilled).
- The sponsor has the right to terminate any of the experimental cohorts at any time based on the available data.

4. STUDY POPULATION

The specific eligibility criteria for the selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

Each patient eligible to participate in this study must meet all of the following criteria:

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments.
2. Age ≥ 18 years on the day of signing the ICF (or the legal age of consent in the jurisdiction in which the study is taking place).
3. Advanced or metastatic NSCLC (nonsquamous or squamous) that is histologically or cytologically confirmed.

   Note: Tumors of mixed non-small cell histology will be categorized by the predominant cell type.
4. Patients who have received no more than 2 lines of prior systemic therapies which must include anti-PD-(L)1 treatment and a platinum-based chemotherapy administered in combination with, or sequentially before or after the anti-PD-(L)1 treatment. Patients who have received prior neoadjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for nonmetastatic disease must have experienced disease progression within 6 months from the last dose of systemic therapy and/or radiotherapy.

   Note: Systemic treatment line number will be counted on the basis of interval disease progression and not the number of agents or switches in agents (eg, a first-line therapy that consists of several cycles of a platinum doublet and subsequent maintenance therapy that introduces or switches to a new chemotherapy agent without interval disease progression will all be considered one line treatment). Anti-PD(L)-1 maintenance therapy following platinum-based chemotherapy is not considered as a separate line of treatment.
5. Agreement to provide archival tumor tissue (FFPE block containing tumor [preferred] or approximately 15 [at least 10] freshly cut unstained slides).
6. At least 1 measurable lesion as defined per RECIST v1.1.

   Note: A lesion in an area subjected to prior locoregional therapy, including previous radiotherapy, is not considered measurable unless there has been demonstrated progression in the lesion since such therapy as defined by RECIST v1.1.
7. ECOG Performance Status of 0 or 1.
8. Adequate organ function as indicated by the following laboratory values during screening:
   a. Patients must not have required blood transfusion or growth factor support ≤ 14 days before sample collection at screening for the following:

i. Absolute neutrophil count ≥ 1.5 x 10^9/L

ii. Platelets ≥ 100 x 10^9/L

iii. Hemoglobin ≥ 90 g/L

b. Estimated glomerular filtration rate (eGFR) or creatinine clearance ≥ 60 mL/min using the equations described in Appendix 11

c. Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN) (total bilirubin must be < 3 x ULN for patients with Gilbert syndrome)

d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN

9. Women of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study and for at least 120 days after the last dose of study drug(s).

   Note: If receiving docetaxel-containing combination treatment, women of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study and at least 180 days after the last dose of study drug(s).

   They must also have a negative urine or serum pregnancy test result at screening and ≤ 7 days before the first dose of study drug(s). See Appendix 12 for details.

10. Nonsterile male patients must be willing to use a highly effective method of birth control for the duration of the study and for at least 120 days after the last dose of study drug(s)

    Note: If receiving docetaxel-containing combination treatment, nonsterile male patients must be willing to use a highly effective method of birth control for the duration of the study and at least 180 days after the last dose of study drug(s).

    a. A sterile male patient is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.

    b. Male patients with known "low sperm counts" (consistent with "subfertility") are not to be considered sterile for the purposes of this study.

4.2. Exclusion Criteria

Patients who meet any of the following criteria are not eligible to enroll:

1. With mixed small cell lung cancer.
2. With known actionable alterations (including, but not limited to, *EGFR*, *ALK*, *BRAF*, *RET*, and *ROS1* mutations) for which targeted therapy has been approved by the respective local health authority in the current treatment setting at the time of patient enrollment.
3. Has received prior therapy targeting OX40 or any other T-cell agonists including, but not limited to, *4-1BB* and *GITR*.
4. Has received prior therapy containing docetaxel and/or ramucirumab for advanced or metastatic NSCLC.

5. Has received any Chinese herbal medicine or Chinese patent medicines used to control cancer ≤ 14 days before the first dose of study drug(s).
6. Active leptomeningeal disease or uncontrolled and untreated brain metastasis.

   Patients with a history of treated and, at the time of screening, stable central nervous system (CNS) metastases are eligible, provided they meet all of the following:

   a. Brain imaging at screening shows no evidence of interim progression, and there is no evidence of new brain metastases
   b. Patient is clinically stable for ≥ 4 weeks
   c. Brain metastases are not the only site of disease
   d. No ongoing requirement for corticosteroids as therapy for CNS disease; off corticosteroids 4 weeks before the first dose of study drugs; anticonvulsants at a stable dose are allowed
   e. No stereotactic radiation or whole-brain radiation ≤ 14 days before the first dose of study drug(s)
7. Active autoimmune diseases or history of autoimmune diseases that may relapse, or history of life-threatening toxicity related to prior immune therapy (Appendix 6).

   Note: Patients with the following diseases are not excluded and may proceed to further screening:

   a. Controlled type 1 diabetes
   b. Hypothyroidism (managed with hormone replacement therapy only)
   c. Celiac disease controlled by diet alone
   d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia)
   e. Any other disease that is not expected to recur in the absence of external triggering factors
8. Any active malignancy ≤ 2 years before randomization/enrollment except for the specific cancer under investigation in this study, those with a negligible risk of metastasis or death, and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, localized prostate cancer, carcinoma in situ of the cervix or breast).
9. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before the first dose of study drug(s).

   Note: Patients who are currently or have previously been on any of the following corticosteroid regimens are not excluded:

   a. Adrenal replacement corticosteroid (dose ≤ 10 mg daily of prednisone or equivalent)
   b. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption

c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy, premedication before pemetrexed or paclitaxel) or for the treatment of a nonautoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)

10. With uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before the first dose of study drug(s).
11. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence ≤ 14 days after intervention). Patients with symptomatic pleural effusion are excluded unless the patient undergoes a therapeutic thoracentesis or has had pleurodesis (> 14 days before randomization/enrollment) with subsequent stable effusions.
12. History of interstitial lung disease, noninfectious pneumonitis, or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc. All patients must undergo an assessment of pulmonary function at screening.
13. Infection (including tuberculosis infection, etc) requiring systemic (oral or intravenous) antibacterial, antifungal, or antiviral therapy ≤ 14 days before the first dose of study drug(s), or patients with symptomatic COVID-19 infection. Patients that have recovered from symptomatic COVID-19 infection can be rescreened on this study.

    Note: Antiviral therapy is permitted for patients with chronic infection with hepatitis B virus (HBV) or infection with hepatitis C virus (HCV). Patients receiving prophylactic antibiotics (eg, for the prevention of urinary tract infection, chronic obstructive pulmonary disease, or for dental extraction) are eligible.
14. Untreated chronic hepatitis B or chronic HBV carriers with HBV DNA ≥ 500 IU/mL (or ≥ 2500 copies/mL) at screening.

    Note: Inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Patients with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at screening should have been treated for > 2 weeks before randomization/enrollment.
15. With active hepatitis C.

    Note: Patients with a negative HCV antibody test at screening or positive HCV antibody test followed by a negative HCV RNA test at screening are eligible. The HCV RNA test will be performed only for patients testing positive for HCV antibody. Patients receiving antivirals at screening should have been treated for > 2 weeks before randomization/enrollment.
16. Known a history of HIV infection.
17. Any major surgical procedure ≤ 28 days before randomization. Patients must have adequately recovered from the toxicity and/or complications from the intervention before randomization/enrollment.

18. Immunodeficiency as assessed by the investigator not suitable for treatment by immune-modulating anticancer agents (Appendix 6), prior allogeneic stem cell transplantation, or organ transplantation.
19. Any of the following cardiovascular risk factors:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before randomization
    b. Symptomatic pulmonary embolism ≤ 28 days before randomization
    c. Any history of acute myocardial infarction ≤ 6 months before randomization
    d. Any history of heart failure meeting New York Heart Association (NYHA) Classification III or IV (Appendix 7) ≤ 6 months before randomization
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before randomization
    f. Any history of cerebrovascular accident ≤ 6 months before randomization
    g. Patients with inadequately controlled hypertension (defined as average systolic blood pressure [BP] ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg) ≤ 28 days before randomization

       Note: Antihypertensive therapy to achieve these parameters is allowable.
    h. Any prior history of hypertensive crisis
    i. Any episode of syncope or seizure ≤ 28 days before randomization
20. With a history of severe hypersensitivity reactions to other monoclonal antibodies or has experienced a severe imAE with prior immunotherapy.
21. Has received any immunotherapy (eg, interleukin, interferon, thymosin, etc) or any investigational therapies ≤ 14 days or ≤ 5 half-lives (whichever is shorter) before the first dose of study drug.
22. Was administered a live vaccine ≤ 28 days before randomization.

    Note: Seasonal vaccines for influenza or COVID-19 are generally inactivated vaccines and are allowed. Live intranasal vaccines are not allowed.
23. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug, will affect the explanation of drug toxicity or AEs, or will result in insufficient or impaired compliance with study conduct.
24. Women who are pregnant or are breastfeeding.
25. Concurrent participation in another therapeutic clinical study.

    Note: Concurrent participation in observational or noninterventional studies is allowed. In addition, patients who have completed active treatment in a clinical study and are in the follow-up period can be enrolled in this study.

26. Patients with toxicities (as a result of prior anticancer therapy) that have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities).

5. STUDY TREATMENT

The specific stipulations of the study treatment for experimental cohorts including formulation, packaging, handling dosage, administration, dose modification, and overdose are provided in each investigational agent-specific appendix. Only common requirements for study treatment are presented in this section, unless otherwise specified.

5.1. Formulation, Packaging, Labeling, and Handling

5.1.1. BGB-A445

BGB-A445 is provided as a sterile, nonpyrogenic injectable solution for intravenous administration. It is formulated in the [redacted] at pH [redacted], consisting of [redacted] mg/mL BGB-A445, [redacted], [redacted], [redacted], and [redacted].

The drug product is fill-finished in 20 mL glass vials (United States Pharmacopeia Type I 20 mm finishing neutral borosilicate glass) stoppered with ethylene-tetra-fluoro-ethylene-coated butyl rubber stoppers and aluminum flip-off seal caps.

Each single-use vial contains [redacted] mL ([redacted] mg) of BGB-A445 monoclonal antibody at a concentration of [redacted] mg/mL.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature condition specified on the label. Shaking should be avoided.

Refer to the Pharmacy Manual for details regarding intravenous study drug preparation, administration, accountability, and disposal. Refer to the BGB-A445 Investigator's Brochure for other details regarding BGB-A445.

5.1.2. Docetaxel

Docetaxel will be provided in vials for infusion. The contents of the label will be in accordance with all applicable local regulatory requirements.

Docetaxel must be kept at the temperature condition specified on the label.

Refer to the Pharmacy Manual for details regarding administration, accountability, and disposal.

5.1.3. Ramucirumab

Ramucirumab will be provided in vials for infusion. The contents of the label will be in accordance with all applicable local regulatory requirements.

Ramucirumab must be kept at the temperature condition specified on the label.

Refer to the Pharmacy Manual for details regarding administration, accountability, and disposal.

5.1.4. Investigational Agents

Refer to the respective appendices for details.

5.2. Dosage, Administration, and Compliance

The first dose of study drug is to be administered ≤ 2 business days after randomization. All patients will be monitored during the study for AEs.

Accurate records of all study drugs received, dispensed, returned, and disposed of should be maintained in the site's Drug Inventory Log. Refer to the Pharmacy Manual for details of study drug management.

5.2.1. BGB-A445 Administration

BGB-A445 [redacted] will be administered as an intravenous infusion once every 3 weeks (1 cycle) in combination with investigational agents.

The administration of BGB-A445 in different combination treatments is presented in Table 4.

Table 4: Administration of BGB-A445

Cycle	BGB-A445 Infusion Duration
C1D1, C2D1, and C3D1	BGB-A445 [redacted] infusion 60 (± 5) minutes
C4D1 onwards	BGB-A445 [redacted] infusion 30 (± 5) minutes

Abbreviations: C, cycle; D, day.
Note: The infusion rate may be decreased, or the infusion may be stopped in the event of an infusion-related reaction. See Section 8.7.1 for details.

For the administration schedule of combination treatment, the dose, frequency, administration duration, and patient monitoring duration of BGB-A445 and investigational agents are detailed in the respective section and/or appendices:

- Refer to Section 5.2.2 for the administration of BGB-A445 in combination with docetaxel.
- Refer to Appendix 14 for the administration of BGB-A445 in combination with BGB-15025.

BGB-A445 will be administered separately by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2- or 0.22-micron in-line or add-on filter. BGB-A445 must be prepared and administered as separate infusions and may not be infused simultaneously with any other investigational agents.

5.2.2. Docetaxel Administration

Docetaxel 75 mg/m^2 will be administered as an intravenous infusion over 1 hour once every 3 weeks until disease progression, intolerable toxicity, or withdrawal of consent.

Additional premedications should be administered as per standard practice. Please refer to the label of docetaxel for additional information.

Stage 1: BGB-A445 + docetaxel

For the administration of BGB-A445 in combination of docetaxel in Stage 1, the infusion and post-infusion rules are outlined in Table 5.

Table 5: Administration of BGB-A445 and Docetaxel and Monitoring Time

Cycle	BGB-A445 and Docetaxel
C1D1, C2D1, and C3D1 [a]	BGB-A445 [redacted] infusion 60 (± 5) minutes Docetaxel 75 mg/m^2 infusion over 1 hour (refer to the label of docetaxel for details) Patient monitoring for ≥ 120 minutes
C4D1 onwards	BGB-A445 [redacted] infusion 30 (± 5) minutes Docetaxel 75 mg/m^2 infusion over 1 hour (refer to the label of docetaxel for details) Patient monitoring for ≥ 30 minutes

Abbreviations: C, cycle; D, day.
Note: The infusion rate may be decreased, or the infusion may be stopped in the event of an infusion-related reaction. See Section 8.7.1 for details.
[a] Subsequent decrease(s) in study drug infusion time and/or post-infusion monitoring time is contingent upon the tolerability of prior study drug administrations. If a cycle is missed, the equivalent number of study drug infusions must be met before a decrease in time can occur.

Stage 2: Docetaxel + ramucirumab

For the administration of the reference cohort in Stage 2 (ie, docetaxel in combination with ramucirumab), please refer to Section 5.2.3 for more details.

5.2.3. Ramucirumab Administration

Ramucirumab 10 mg/kg will be administered as an intravenous infusion over 1 hour once every 3 weeks until disease progression, intolerable toxicity, or withdrawal of consent. Ramucirumab will be administered before the administration of docetaxel.

Additional premedications should be administered as per standard practice. Please refer to the label of ramucirumab for additional information.

5.2.4. Investigational Agents Administration

For the administration of investigational agents in combination with BGB-A445, refer to the respective appendices for details.

5.3. Overdose

AEs associated with an overdose or incorrect administration of study drug will be recorded in the AE eCRF. Any SAEs associated with an overdose or incorrect administration must be reported ≤ 24 hours after awareness via the SAE reporting process described in Section 8.6.2. Supportive care measures should be administered as appropriate.

Refer to each investigational agent-specific appendix for details.

5.4. Dose Delay and Modification

Every effort should be made to administer the study drugs according to the planned dose and schedule. In the event of significant toxicities, dose modification may be taken. Reasons for

dose modification, the supportive measures taken, and the outcome will be documented in the patient's source documents and recorded in the eCRF.

The dose modification guidelines in the protocol are not intended to be a substitute for clinical judgment. Investigators may delay doses for other reasons (eg, AEs or laboratory findings) as appropriate.

5.4.1. Dose Delay

In general, dose delays for reasons other than management of AEs are prohibited. A dose delay of ≤ 12 weeks after the last dose of study drug(s) is allowed for the combination treatment at the discretion of the investigator after consultation with the medical monitor or designee. If the patient is unable to resume the combination treatment ≤ 12 weeks of total delay duration, then the patient should be discontinued from the combination treatment. If the patient is not able to resume study treatment ≤ 12 weeks of total delay duration for unforeseen nondrug related reasons, continued treatment may be allowed after consultation and approval by the medical monitor.

Study treatment(s) may be temporarily suspended if the patient experiences a toxicity that is suspected to be related to the treatment and requires a dose to be withheld. If study treatment is delayed because of TEAEs, study treatment may resume only after the AEs have returned to baseline or ≤ Grade 1 severity except for alopecia or AEs that, in the opinion of the investigator, are not considered a safety risk to the patient. If a treatment delay is because of worsening of laboratory results, eg, hematologic or biochemical parameters, the frequency of relevant blood tests should be increased, as clinically indicated.

The total durations of dose delay allowed for the management of AEs suspected to be related to each study drug are specified in the following sections and agent-specific appendix. If the patient is unable to resume a certain study drug within the allowed time frame, the treatment of study drug should be discontinued. However, if a patient is benefiting from study treatment(s) while meeting the discontinuation criteria, resumption of study treatment(s) may occur after discussion and agreement with the medical monitor.

When treatment is delayed, the next cycle, including assessments scheduled for that cycle, will be delayed until the treatment commences. The counting of the next cycle (eg, C2D1) for the combination treatment is detailed in each agent-specific appendix.

In cases of prolonged study treatment delays, consult the medical monitor regarding modification (eg, frequency, types of assessments, etc) of the unscheduled assessments. When the patient receives study treatment, all of the scheduled assessments for that cycle (including PK and biomarkers) and each subsequent cycle (assuming no dose delays) should be performed according to the Appendix 1. For example, if a patient's C2D1 was delayed, the patient should continue to undergo safety assessments as outlined for Cycle 1 in the Schedule of Assessments (Appendix 1), which means the patient will undergo weekly assessments. Once a patient resumes study treatment, the Schedule of Assessments for Cycle 2 should be followed.

Tumor assessments should continue as scheduled, which is every 6 weeks (± 7 days) from randomization for the first 9 months, and every 12 weeks (± 7 days) thereafter.

5.4.1.1. Dose Delay for BGB-A445

BGB-A445 treatment may be temporarily suspended if the patient experiences a toxicity that is suspected to be related to BGB-A445 and requires a dose to be withheld. Study treatment of BGB-A445 should resume as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) after the last dose of BGB-A445.

Additional dose modification details for BGB-A445 when administered in combination with investigational agent(s) in experimental cohorts are provided in the investigational agent-specific appendix.

Specific treatment modifications to manage study treatment-related toxicities, such as infusion-related reactions and imAEs, are described in Section 8.7, Appendix 8, and Appendix 9.

5.4.1.2. Dose Delay for Docetaxel

Stage 1: BGB-A445 + docetaxel

Please refer to Section 5.4.1.1 for the details of BGB-A445 dose delay.

Docetaxel treatment may be temporarily suspended if the patient experiences a toxicity that is suspected to be related to docetaxel and requires a dose to be withheld. Study treatment of docetaxel should resume as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) after the last dose of docetaxel.

If a dose delay of either BGB-A445 or docetaxel (because of the causes mentioned above) is ≤ 10 days for a planned dosing cycle (eg, C2D1), the delayed treatment(s) in this cycle (eg, Cycle 2) should be administered, and the combination treatment in the next cycle (eg, C2D1) will not be delayed and will be administered as scheduled.

If the dose delay of either BGB-A445 or docetaxel (because of the causes mentioned above) is > 10 days for a planned dosing cycle (eg, C2D1), then the patient should skip the delayed treatment in the delayed cycle (eg, C2), and the combination treatment should be administered on Day 1 of the next planned cycle (eg, C3D1).

Exceptions may be considered following consultation between the investigator and the medical monitor.

Specific treatment modifications to manage study treatment-related toxicities, such as infusion-related reactions are described in Section 8.7.

Stage 2: Docetaxel + ramucirumab

For the administration of the reference cohort in Stage 2 (ie, docetaxel in combination with ramucirumab), please refer to Section 5.4.1.3 for more details.

5.4.1.3. Dose Delay for Ramucirumab

In Stage 2, ramucirumab is administered in combination with docetaxel as the reference treatment. The guidance of dose delay for ramucirumab and docetaxel is to be followed per the local guideline and the investigator's discretion.

5.4.1.4. Dose Delay for Investigational Agents

Dose delay for the investigational agent(s) is provided in the investigational agent-specific appendix.

5.4.2. Dose Modification

In the event of significant toxicity, dosing may be interrupted and/or dose(s) modified in accordance with Table 6.

Table 6: Management of Nonimmune-Mediated Adverse Events

System	Adverse event	Toxicity management	Study drug management
Hematologic	**Anemia** Grade 3	Treat with appropriate supportive care as medically indicated.	Hold study treatment until resolved to Hgb ≥ 9 g/dL. If resolved ≤ 7 days, then maintain current dosage. If resolved > 7 days, decrease A445 treatment by 1 dose level. If blood transfusion is required, consider decreasing A445 treatment by 1 dose level if clinically indicated.
	Anemia Grade 4	Maximize supportive therapy until Hgb ≥ 9 g/dL.	Hold study treatment until resolved to Hgb ≥ 9 g/dL. After resolution, decrease A445 by 1 dose level.
	Neutropenia (ANC decrease) Grade 3	Treat with appropriate supportive care as medically indicated until ANC ≥ 1000/mm^3.	Hold study treatment until resolved to ANC ≥ 1000/mm^3 or baseline. If resolved in ≤ 7 days, then maintain current dosage. If resolved in > 7 days, then decrease A445 by 1 dose level.
	Neutropenia (ANC decrease) Grade 4	Maximize appropriate supportive therapy until ANC ≥ 1000/mm^3.	Hold study treatment until resolved to ANC ≥ 1000/mm^3 or baseline. After resolution, decrease A445 by 1 dose level.
	Febrile neutropenia ≥ Grade 3	Maximize appropriate supportive therapy. Rule out other etiologies of fever.	Hold study treatment until neutrophil count ≥ 1000/mm^3. After resolution, decrease A445 by 1 dose level. For Grade 4 event, discontinue therapy.

System	Adverse event	Toxicity management	Study drug management
	Thrombocytopenia (platelet count decrease) Grade 2	Monitor and treat with appropriate supportive care as medically indicated.	Maintain current dosage if no concerns of clinically significant risk of bleeding; continue to monitor using additional hematology assessments as required.
	Thrombocytopenia (platelet count decrease) Grade 3	Treat with appropriate supportive care as medically indicated.	Hold study treatment until resolved to ≤ Grade 1 or baseline. After resolution, decrease A445 by 1 dose level.
	Thrombocytopenia (platelet count decrease) Grade 4	Treat with appropriate supportive care as medically indicated.	Hold study treatment until resolved to ≤ Grade 1 or baseline. After resolution, decrease A445 by 1 dose level.
	Other hematologic event Grade 3	Treat with appropriate supportive care as medically indicated.	Hold study treatment. If improved to ≤ Grade 1 or baseline, decrease A445 treatment by 1 dose level. If event recurs at the reduced dose after receiving optimal supportive care, permanently discontinue study treatment.
	First occurrence of other hematologic Grade 4 event	Treat with appropriate supportive care as medically indicated.	Hold study treatment until improved to ≤ Grade 1 or baseline. After resolution, decrease A445 by 1 dose level, or permanently discontinue study treatment.
	Recurrent other hematologic Grade 4 event	Treat with appropriate supportive care as medically indicated.	Permanently discontinue study treatment.
Nonhematologic	**Nonhematologic event** Grade 3	Treat with appropriate supportive care as medically indicated.	Hold study treatment. If improved to ≤ Grade 1 or baseline, decrease A445 treatment by 1 dose level. If event recurs at the reduced dose after receiving optimal supportive care, permanently discontinue study treatment.

System	Adverse event	Toxicity management	Study drug management
	First occurrence of nonhematologic Grade 4 event	Treat with appropriate supportive care as medically indicated.	Hold study treatment until improved to ≤ Grade 1 or baseline. After resolution, decrease A445 by 1 dose level, or permanently discontinue study treatment.
	Recurrent nonhematologic Grade 4 event	Treat with appropriate supportive care as medically indicated.	Permanently discontinue study treatment.

Abbreviations: A445, BGB-A445; ANC, absolute neutrophil count; Hgb, hemoglobin.

5.4.2.1. Dose Modification for BGB-A445

After any interruption because of toxicity, BGB-A445 may be resumed at the same dose or at a reduced dose, depending on the toxicity, grade, prior events, and number of dose reductions.

In general, a dose should be reduced to the next immediate lower dose level that was previously determined to be tolerable (Table 7). A patient must discontinue BGB-A445 if, after BGB-A445 is resumed at a lower dose, the toxicity recurs with the same or worse severity.

A patient may have a maximum of 2 dose reductions. Patients requiring > 2 dose reductions must discontinue study treatment except when, in the opinion of the investigator, the patient is benefiting from treatment. For these patients, treatment may be continued after consultation and approval by the sponsor.

Table 7: BGB-A445 Dose Reduction Levels

	Dose	Frequency of Administration
Initial dose level [a]	[redacted]	Day 1 of each cycle (3 weeks)
Dose Reduction 1	[redacted]	
Dose Reduction 2 [b]	[redacted]	
Dose Reduction 3 [c]	Discontinue BGB-A445	

[a] The initial dose level of BGB-445 should be deemed as safe in the combination treatments during the safety lead-in.

[b] BGB-A445 must be discontinued if, after it is resumed at a lower dose, the toxicity recurs with the same or worse severity.

[c] If > 2 dose reductions are required for a patient, BGB-A445 must be discontinued unless, in the opinion of the investigator, the patient is benefiting from BGB-A445 treatment. In this case, BGB-A445 may be continued after consultation with and approval by the sponsor.

5.4.2.2. Dose Modification for Docetaxel

Guidelines for docetaxel dose modifications presented in the US labeling to manage general toxicities are shown in Table 8.

After any interruption because of toxicity, docetaxel may be resumed at the same dose or at a reduced dose, depending on the toxicity, grade, prior events, and number of dose reductions.

In general, a dose should be reduced to the next immediate lower dose level per the US labeling (Table 8). A patient must discontinue docetaxel if, after docetaxel is resumed at a lower dose, the toxicity recurs with the same or worse severity.

Table 8: Guidelines for Docetaxel Dose Modifications

Adverse Event (Worst Grade in Previous Cycle)	Action to Be Taken
Febrile neutropenia/Grade 4 neutropenia ≥ 7 days Severe or cumulative cutaneous reactions Grade 3 or 4 nonhematologic toxicity	Withhold docetaxel until resolution of toxicity and then resumed at 55 mg/m^2. [a]
Peripheral neuropathy ≥ Grade 3 Recurrence of ≥ Grade 3 toxicity after prior dose reduction	Discontinue docetaxel treatment.

[a] Docetaxel 75 mg/m^2 should be deemed as safe first during the safety lead-in.

Do not treat or discontinue treatment, if started, in patients: 1) with bilirubin above upper limit of normal (ULN), or 2) with AST and/or ALT elevation above 1.5 x ULN concomitant with alkaline phosphatase above 2.5 x ULN.

5.4.2.3. Dose Modification for Ramucirumab

Guidelines for ramucirumab dose modifications presented in the US labeling to manage general toxicities are shown below.

Infusion-Related Reactions (IRR)

- Reduce the infusion rate of ramucirumab by 50% for Grade 1 or 2 IRRs.
- Permanently discontinue ramucirumab for Grade 3 or 4 IRRs.

Hypertension

- Interrupt ramucirumab for severe hypertension until controlled with medical management.
- Permanently discontinue ramucirumab for severe hypertension that cannot be controlled with antihypertensive therapy

Proteinuria

- Interrupt ramucirumab for urine protein levels ≥ 2 g/24 hours. Reinitiate treatment at a reduced dose of 6 mg/kg every 2 weeks once the urine protein level returns to < 2 g/24 hours. If the protein level ≥ 2 g/24 hours reoccurs, interrupt ramucirumab and reduce the dose to 5 mg/kg every 2 weeks once the urine protein level returns to < 2 g/24 hours.
- Permanently discontinue ramucirumab for urine protein level > 3 g/24 hours or in the setting of nephrotic syndrome.

Wound Healing Complications

- Interrupt ramucirumab before scheduled surgery until the wound is fully healed.

Arterial Thromboembolic Events, Gastrointestinal Perforation, or Grade 3 or 4 Bleeding

- Permanently discontinue ramucirumab.

Please refer to the label for additional information of the dose modification for ramucirumab.

5.4.2.4. Dose Modification for Investigational Agents

Dose modification for the investigational agent(s) is provided in the investigational agent-specific appendix.

5.5. Continued Access to Study Drug After the End of the Study

At the end of the study as determined by the sponsor, any patient who is still on treatment and, in the opinion of the investigator, continues to benefit from study treatment will continue treatment via being kept in the study for continuous access to study drugs. Continuous access could be terminated in case of a decision to stop manufacturing investigational agents used in the study.

Patients will still be monitored by assessments as described in Section 7.3 and Section 8. No further data will be collected in EDC system for patients in continuous access to study drugs, SAE reports should be submitted through paper forms per requirements and timelines described in Section 8.6.2. The blood and tissue samples for PK/ADA and biomarker analysis are not required to be collected. The continuous treatment access would be discontinued for reasons listed in Section 3.5 or when the total duration reaches 36 cycles (ie, approximately 2 years) as described in Section 3.3. During the continuous study treatment, patient visits should be dependent on investigator's discretion. Other assessments, including but not limited to tumor assessment and adverse events collection, continue to follow the Appendix 1. These assessment data will be kept in study sites.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

The exclusion criteria specify that patients must not have received prior therapy for current lung cancer targeting OX40 or any other T-cell agonists including, but not limited to, *4-1BB* and *GITR* (Section 4.2). All prior cancer-related treatments, treatments for underlying active medical conditions, and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient ≤ 30 days before randomization must be recorded in the appropriate eCRF.

Information on prior and concomitant therapies that are permitted, prohibited, and/or restricted in relation to a specific investigational agent is provided in each appendix.

6.2. Concomitant Therapy

If applicable, additional requirements with respect to concomitant therapy for a particular experimental cohort will be presented in the investigational agent-specific appendix. In addition to the common stipulations stated this section in the protocol body, investigational agent-specific requirements for concomitant therapy should be met based on patient assignment.

6.2.1. Permitted Concomitant Medications/Procedures

Most concomitant medications and therapies deemed necessary and in keeping with the local standards of medical care at the discretion of the investigator for the supportive care (eg, antiemetics, antidiarrheals, pain medications, and nutritional support) and for a patient's wellbeing are allowed. All concomitant medications will be recorded in the eCRF, including all prescriptions, over-the-counter drugs, herbal supplements, and intravenous medications and fluids. If changes (dose, stop, or start) in concomitant medication occur during the study, documentation of drug dosage, frequency, route, date, and reason for use will be recorded in the eCRF. Medications received ≤ 30 days before the first dose or infusion of study drug and after the last dose or infusion of study drug are considered as concomitant medications and should be recorded.

6.2.1.1. Systemic Corticosteroids

Systemic corticosteroids for management of imAEs must be tapered gradually (see Appendix 8) and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next study treatment administration. The short-term use of steroids as prophylactic treatments (eg, for patients with allergies to diagnostic imaging contrast dyes) is permitted.

6.2.1.2. Hepatitis B Treatment

Management of prophylactic antiviral therapy for patients with inactive, treated, and stable hepatitis B (HBV DNA < 500 IU/mL) is at the discretion of the investigator, as aligned with local guidance. Such medications must be documented in the patient's chart and recorded in the eCRF. Patients receiving antivirals at screening should be treated for > 2 weeks before enrollment. Once initiated, antiviral treatment should continue until 6 months after the last dose of study treatment or as permitted by local guidance.

6.2.1.3. Hepatitis C Treatment

Patients with detectable HCV RNA who are receiving treatment at screening must meet the criterion of negative HCV RNA to be eligible. If the patients are treated and eligible, they should remain on continuous, effective antiviral therapy during the study. Investigators can consider treatment with antivirals following the international or local guidelines as appropriate. Patients who are given antiviral therapy must initiate treatment > 14 days before enrollment and continue treatment during the study and for 6 months after study treatment discontinuation.

6.2.1.4. Radiation Therapy

Palliative (limited-field) radiation therapy is permitted, but only for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline provided the following criteria are met:

- Repeat imaging demonstrates no new sites of bone metastases
- The lesion being considered for palliative radiation is not a target lesion for RECIST v1.1
- The case is discussed with the medical monitor, and the medical monitor agrees that the conditions required to receive palliative radiation are met

Additionally, palliative radiation or other focally ablative therapy for other nontarget sites of the disease is permitted if clinically indicated per investigators' discretion and after consultation with the medical monitor. Whenever possible, these patients should have a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out progression of disease.

It is not required to withhold study treatment during palliative radiotherapy.

6.2.1.5. COVID-19 Vaccines

Vaccines for COVID-19 are allowed except for any live vaccine (ie, live SARS-CoV-2 virus) that may be developed. Attenuated (vector) COVID-19 vaccines are inactivated vaccines and, as such, are permitted. It is recommended to avoid COVID-19 vaccination ≤ 72 hours before or after study drug administration during the first 2 treatment cycles. Vaccinations are considered a concomitant medication and hence should be entered in the eCRF. The specific COVID-19 vaccine should be recorded instead of generic language, eg, mRNA-1273 vaccine (Moderna), BioNTech vaccine (Pfizer), etc.

6.2.2. Prohibited Concomitant Medications/Procedures

The following medications are prohibited from screening to the EOT/Safety Follow-up Visit:

- Except for study treatment(s), any concurrent antineoplastic therapy(ies) (eg, any systemic anticancer therapy including chemotherapy, targeted therapies, hormonal therapy, immunotherapy, standard anticancer agents, and investigational anticancer agents, or any local antineoplastic treatment including radiotherapy, ablation, and other resection surgery for any cancer) are prohibited.
- Live vaccines ≤ 28 days before randomization and ≤ 60 days after the last dose of study treatment(s) are prohibited.

- Herbal remedies for the treatment of cancer or Chinese patent medicines as anticancer treatment (regardless of cancer type) ≤ 14 days before the first dose of study drug(s) and during the treatment and EOT/Safety Follow-up Visit are prohibited (Appendix 13).
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with the liver or other major organ functions (eg, hypericin) are prohibited (Appendix 13).

Patients must notify the investigator of all herbal remedies used during the study.

6.2.3. Restricted Concomitant Medications/Procedures

The following medications/procedures are restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE).
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug-related AE (per protocol) or for short-term use as prophylactic treatment.
- Patients should not abuse alcohol or other drugs during the study.
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored.
- Opiates and other medications required for palliative management of patients are allowed. Patients must notify the investigator of all concurrent medications used during the study.

6.3. Potential Interactions Between the Study Drugs and Concomitant Medications

Information on potential interactions between study drug and concomitant medications are provided in each investigational agent-specific appendix.

7. STUDY ASSESSMENTS AND PROCEDURES

A table of scheduled study assessments for screening is provided in Appendix 1. The assessments required for the treatment period, EOT Visit, Safety Follow-up, and Survival Follow-up are provided. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented in the medical record for each patient.

Dosing will occur only if the clinical assessment and local laboratory test values (which must be available before any dosing) have been reviewed and found to be acceptable per protocol guidelines.

7.1. Screening

Screening evaluations will be performed ≤ 28 days before randomization. Patients who agree to participate will sign the ICF before undergoing any screening procedure. The screening period begins on the date the ICF is signed. Screening evaluations may be repeated as needed within the screening period; the investigator will assess patient eligibility according to the latest screening assessment results.

Results of standard-of-care tests or examinations performed before obtaining informed consent and ≤ 28 days before randomization may be used for the purposes of screening rather than repeating the standard-of-care tests unless otherwise indicated.

For descriptions of assessments conducted during screening, see Section 7.3, Section 7.4, and Section 7.6.

EGFR, *ALK*, *BRAF V600E*, *RET*, and *ROS1* mutational status or other actionable alterations, if known, will be collected at screening. Patients with known actionable alterations for which a targeted therapy has been approved by the local health authority will not be eligible.

Rescreening under limited conditions may be allowed after consultation with the sponsor. For example, rescreening may be considered when a patient narrowly misses a laboratory criterion that is correctable and not because of a rapidly deteriorating condition or disease progression. Rescreening is allowed only once. Rescreened patients must provide new informed consent, as described in Section 7.1.1. A new patient number will be assigned as described in Section 7.1.2.

7.1.1. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before any study-specific procedures are performed. ICFs for enrolled patients and for patients who are screened but not enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization/enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

7.1.2. Patient Numbering

After obtaining informed consent, study site personnel will access the interactive response technology (IRT) system to assign a unique patient number to a potential study participant.

Patients who are rescreened (see Section 7.1) will be assigned a new patient number. Screening numbers that are assigned to the same patient within the IRT system will be linked.

7.2. Enrollment

7.2.1. Confirmation of Eligibility

Prior to enrollment, the investigator is responsible for assessing and confirming that each patient meets all inclusion eligibility criteria for this study and that none of the exclusion criteria apply. All results from the screening procedures and relevant medical history must be available and reviewed by the investigator before eligibility can be determined. No eligibility waivers will be granted.

Sponsor verification of patient eligibility will be managed by way of source data verification in accordance with International Council for Harmonisation (ICH) E6.

The sponsor's medical monitor will support the investigator and/or site staff by answering any queries or questions relating to protocol eligibility criteria.

7.2.2. Enrollment and Randomization

Patients enrolled in the study for safety lead-in will receive treatment for the appropriate experimental cohort. All other patients will be randomized/enrolled to a treatment cohort according to the randomization ratios specified in Section 3.1 and Section 9.1.1 after enrollment.

Site personnel will access the IRT system to enroll patients to perform randomization/enrollment and to enable study drug dispensation.

Study treatment must commence ≤ 2 business days after randomization.

7.3. Safety Assessments

7.3.1. Vital Signs

See Appendix 1 for vital signs to be collected at screening. Vital signs collected during the treatment period and at the EOT Visit are described in the Schedule of Assessments (Appendix 1).

7.3.2. Physical Examinations

During the Screening Visit, a complete physical examination will be conducted, including evaluations of the head, eyes, ears, nose, and throat, as well as the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified during screening will be graded according to NCI-CTCAE v5.0 and recorded on the eCRF with appropriate disease/condition terms.

At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed. New or worsened clinically significant abnormalities are to be recorded as AEs on the eCRF. Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

7.3.3. Ophthalmologic Examination

Because CPIs may be associated with imAEs, an eye exam, including a visual acuity test, captured before obtaining written informed consent and within 28 days of first dose of study drug may be used for the screening evaluation.

Patients should be solicited before obtaining written informed consent and within 28 days of the first dose of study drug during screening for signs of uveitis, such as changes in visual acuity or intraocular inflammation (ex, blurred/distorted vision, blind spots, change in color vision, photophobia, tenderness/pain, and eyelid swelling), and referred to an ophthalmologist where slit lamp biomicroscopy should be considered, if warranted, for further evaluation if visual changes are reported. For patients with symptomatic vision changes, dosing of study drug should be held until uveitis can be ruled out by an ophthalmologist. For further management guidance see Appendix 8.

7.3.4. Pulmonary Function Tests

Pulmonary function tests including spirometry and assessment of oxygenation are required. For the assessment of oxygenation, pulse oximetry at rest and with exercise is required at a minimum. Moreover, the diffusion capacity could be tested alternatively for the assessment of oxygenation. Pulmonary function tests are to be performed for all patients during the screening period to assist the determination of suitability on the study. Respective test results need to be submitted to the sponsor. For test results indicative of significantly impaired pulmonary function (eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, forced expiratory volume [FEV1] < 60% or diffusing capacity of the lungs for carbon monoxide [DLCO] [if performed] < 60% of age- and sex-adjusted predicted performance levels [Pellegrino et al 2005]), the medical monitor needs to be consulted to confirm eligibility.

Tests may be repeated as clinically indicated while on study.

7.3.5. Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status (Appendix 4) will be assessed during the study.

7.3.6. Laboratory Safety Tests

Local and/or central laboratory assessments of serum chemistry, hematology, coagulation, urinalysis, and thyroid function will be conducted as described in Appendix 1.

If clinical chemistry, hematology, and coagulation at screening are not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, these tests should be repeated and reviewed within 48 hours before each study drug administration.

The following tests will also be conducted in this study at the timepoints shown in Appendix 1:

- Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative ≤ 7 days before the randomization. Furthermore, a negative urine or serum pregnancy test must be completed and recorded ≤ 72 hours before the administration of study drug(s) at each cycle. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.
- Thyroid function testing (ie, thyroid stimulating hormone, free triiodothyronine [T3], and free thyroxine [T4]). Note: Total T3 [TT3] is acceptable in case free triiodothyronine analysis is not available).

7.3.6.1. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune checkpoint inhibitors, serum creatine kinase (CK) and CK cardiac isoenzyme (CK-MB) are monitored in all BGB-A445 studies to protect study participants and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 8 for guidelines for the management of suspected immune-mediated myocarditis). Serum troponins may be substituted per local guidelines if used consistently throughout the study.

7.3.7. Electrocardiograms

For safety monitoring purposes, the investigator must review, sign, and date all electrocardiogram (ECG) tracings. Paper or electronic copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

All ECGs are to be obtained predose on Day 1 of every cycle before other assessments scheduled at that same time (eg, vital sign measurements, blood draws, etc) and as clinically indicated. The patient should rest in a semirecumbent supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (eg, television, radio, conversation, etc) before each ECG collection.

On Day 1 of Cycle 1 and Cycle 5, ECGs must be performed predose and between 4 to 6 hours after study drug(s) infusion.

Three consecutive 12-lead ECGs will be performed approximately 2 to 3 minutes apart to determine the mean QT interval corrected for heart rate using the Fridericia formula (QTcF) interval (see Appendix 1 for the schedule of ECG).

7.3.8. Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE v5.0. Characterization of toxicities will include frequency, severity, duration, and time to onset.

All AEs, including SAEs, will be collected as described in Section 8.6.

7.3.9. Hepatitis B and C Testing

Testing will be performed by the local laboratory at screening (and as clinically indicated) and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B

core antibody [HBcAb], and HCV antibody). In the case of active HBV or HCV infection, these tests will be followed by viral load assessment (HBV DNA and HCV RNA). Patients who have detectable HBV DNA at screening regardless of screening results will undergo the respective viral load test every 4 cycles starting at Cycle 5.

7.4. Tumor and Response Evaluations

Tumor imaging will be performed ≤ 28 days before randomization. Radiological images captured as standard of care before obtaining informed consent and ≤ 28 days before randomization may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed every 6 weeks (± 7 days) from randomization for the first 9 months, and every 12 weeks (± 7 days) thereafter based on RECIST v1.1. If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted on the planned schedule.

Screening assessments and each subsequent assessment of the tumor must include computed tomography (CT) scans (with oral and/or intravenous contrast, unless contraindicated) or a magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments.

All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening is required to be used throughout the study (eg, the same contrast protocol for CT scans or MRIs).

- Imaging of the brain (preferably MRI) at baseline is required for all screened patients. Screening evaluations will be performed ≤ 28 days before randomization.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- Bone scans (technetium-99m) or PET should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans, technetium-99m or PET bone scans should be repeated when a complete response (CR) is suspected in the target lesion or when progression in bone is suspected.
  - If bone metastases are visualized on the bone scan or PET scan at screening, a confirmatory CT/MRI scan should be performed. If the metastases are confirmed by CT/MRI, then evaluation by CT/MRI should be given preference for subsequent assessments. If the metastases are not confirmed by CT/MRI, then the use of bone scan or CT/MRI for subsequent assessments is at the investigator's discretion.

  - If an increase in the uptake of existing lesions is seen on a bone scan, or the appearance of new osteoblastic bone lesions is seen on an x-ray, CT, or MRI, this should not automatically be considered evidence of progression in an otherwise stable or responding subject. It may in fact be indicative of response to therapy.
  - New areas of uptake seen on a bone scan should not automatically result in diagnosis of progressive disease but should be correlated with other available imaging (eg, CT, MRI, or x-ray).
- CT scans of the neck or extremities should be performed at screening only if clinically indicated and should be repeated throughout the study if there is evidence of metastatic disease in these regions at screening.
- At the investigator's discretion, other methods of assessing target lesions and nontarget lesions per RECIST v1.1 may be used. However, CT or MRI should be given preference for assessment of target lesions.

Response will be assessed by the investigator using RECIST v1.1 (see Appendix 5). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

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

At the investigator's discretion, patients may continue their assigned treatment after progressive disease has been confirmed by the investigator per RECIST v1.1. To continue treatment, the criteria for treatment beyond disease progression in Section 3.3 must be met.

Tumor assessment should continue as planned in patients receiving study drug(s) beyond initial investigator-assessed progression. Tumor assessment in such patients should continue until study treatment discontinuation.

Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient experiences disease progression, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first.

Tumor assessments are required to be performed on schedule, regardless of whether study treatment has been administered or held. That is, assessments should not be adjusted for delays in cycles.

7.5. Pharmacokinetic and Antidrug Antibody Testing

Blood samples will be collected for PK characterization of BGB-A445 and investigational agents. The serum or plasma (as appropriate) samples will be assayed for BGB-A445 and/or investigational agent concentrations using validated bioanalytical methods. Validated screening and confirmatory assays will be employed to detect ADAs for BGB-A445 and other investigational agents, as appropriate. The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Koren et al 2008; Rosenberg and Worobec 2004a; Rosenberg and Worobec 2004b) to characterize ADA responses to BGB-A445 and investigational agents in support of the clinical development program.

The timing for blood sample collection for PK assessment and ADA testing is specified in Appendix 1.

Shipping, storage, and handling of samples for the assessment of PK and ADA will be managed through the central laboratory. Refer to the laboratory manual for instructions.

7.6. Biomarkers

Blood and tumor tissue samples will be collected at specified times as described in Appendix 2 for the evaluation of biomarkers, including, but not limited to, soluble OX40 levels, concentrations of cytokine and soluble proteins in serum, circulating tumor DNA mutation analysis, investigational agent-specific protein expression, gene expression profiling, tumor infiltrating immune cells in tumor tissue, genomic alterations, and tumor mutation burden/microsatellite instability/genetic mutation and profiles. Other assessments may be conducted as indicated and as allowed by local regulations.

During the screening period, patients are required to provide archival tumor tissues (FFPE blocks containing tumor [preferred] or approximately 15 [at least 10] freshly cut unstained slides). The most recently collected tissue is preferred.

Optional biopsy after 2 cycles of treatment is recommended if the patient is medically fit and it is clinically feasible (within 3-day window before Cycle 3 Day 1 is recommended).

Optional biopsies are also recommended from patients who have confirmed disease progression and at the EOT or Safety Follow-up Visit for evaluation of pharmacodynamic effects and resistance mechanism(s). If feasible, post treatment biopsy samples should be taken from the same tumor lesion as the baseline biopsy or archival tissue.

Tumor tissues will be sent to the designated laboratory for evaluation of the expression level of PD-L1, OX40, and other investigational agent-specific proteins. In addition, other tumor tissue-based exploratory biomarkers, such as, but not limited to, tumor-infiltrating lymphocytes assessment, tumor mutation analysis, and gene expression profiling, may be tested and studied retrospectively in correlation with clinical response/benefit to treatments.

Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

Shipping, storage, and handling of blood as well as archival tumor and/or fresh tumor tissue samples for the assessment of biomarkers will be managed through a central laboratory. Refer to the laboratory manual for details of sample handling and Appendix 2 for timepoints.

8. SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an AE or SAE as provided in this protocol.

8.1. Risks Associated With Study Drug

8.1.1. Risks Associated With BGB-A445

BGB-A445 is an investigational agent currently in clinical development. Limited clinical information is available for BGB-A445. OX40 is an immune costimulatory receptor involved in innate and adaptive immune tolerance and therefore imAEs are a potential risk for BGB-A445. Although most imAEs observed with CPIs have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested evaluation and management guidelines for suspected imAEs are provided in Appendix 8.

BGB-A445 is a monoclonal antibody drug formulated for intravenous infusion and, therefore, infusion-related reactions are a potential risk. Symptoms of infusion-related reactions include angioedema, bronchospasm, chills/rigor, dizziness, fever, headache, hypertension, hypotension, myalgia, nausea, pruritus, rash, urticaria, and vomiting. Severe reactions may include acute respiratory distress syndrome, cardiogenic shock, myocardial infarction, and ventricular fibrillation. Patients should be closely monitored for such reactions. The management for infusion-related reactions is outlined in Section 8.7.1.

No animal reproductive and developmental toxicity studies have been conducted at this time. However, there were no gross lesions or histopathological changes noted in male or female reproductive organs of cynomolgus monkeys following 13 weeks of repeated doses.

Refer to the BGB-A445 Investigator's Brochure for more details.

8.1.2. Risks Associated With Docetaxel

Please refer to the Table 9 for the reported toxicity for docetaxel. Because of the ethanol content in the docetaxel formulation, some patients may experience intoxication during and after treatment that should be monitored (and infusion rate decreased if appropriate).

The investigator should refer to the package insert for a complete list of potential side effects.

Table 9: A Summary of the Commonly Reported Toxicities of Docetaxel

Most Common Side Effects	Less Common Side Effects (but May Be Severe or Life Threatening)
Myelosuppression ± infection or bleeding (may be severe) Hypersensitivity (may be severe) Fluid retention (may be severe) Neuropathy (may be severe) Cutaneous effects (including nails, may be severe) Alopecia	Secondary malignancy/leukemia Cardiotoxicity, arrhythmia Pneumonitis Gastrointestinal obstruction, perforation, hemorrhage Venous thromboembolism Arterial thromboembolism

Gastrointestinal (anorexia, nausea, vomiting, stomatitis, diarrhea, constipation) Asthenia (may be severe)	Disseminated intravascular coagulation Seizures Hepatotoxicity

8.1.3. Risks Associated With Ramucirumab

Please refer to the Table 10 for the reported adverse drug reactions (ADRs) for ramucirumab when given in combination with chemotherapies in some Phase 3 studies.

Besides the ADRs mentioned in Table 10, serious and occasionally fatal arterial thromboembolic events occur when ramucirumab is given as a single agent. Additionally, impaired wound healing is also likely to occur as ramucirumab is an antiangiogenic therapy with the potential to adversely affect wound healing.

The investigator should refer to the package insert for a complete list of potential side effects.

Table 10: A Summary of Adverse Drug Reactions Reported in Patients Treated With Ramucirumab in Combination With Chemotherapy or Erlotinib In Phase 3 Clinical Trials

Very Common Adverse Drug Reactions	Common Adverse Drug Reactions
Infections	Sepsis
Neutropenia	Febrile neutropenia
Leukopenia	Hypoalbuminemia
Thrombocytopenia	Hyponatremia
Anemia	Pulmonary hemorrhage
Headache	Gastrointestinal hemorrhage events
Hypertension	Gastrointestinal perforation
Epistaxis	Gingival bleeding
Stomatitis	Palmar-plantar erythyrodysesthesia syndrome
Diarrhea	
Alopecia	
Proteinuria	
Fatigue	
Mucosal inflammation	
Peripheral edema	

8.1.4. Risks Associated With Investigational Agent

The information on the risks associated with the investigational agent(s) is provided in the respective appendix.

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies and clinical data with BGB-A445, as well as the nonclinical/clinical data from other OX40 inhibitors, were considered. Specifically, patients at risk for developing study-emergent active autoimmune diseases or who have a history of autoimmune diseases that may relapse, patients who have undergone allogeneic stem cell or organ transplantation, and patients who have received a live vaccine ≤ 28 days before randomization are excluded from the study.

8.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE v5.0 (except as noted in Section 8.6.4). All enrolled patients will be evaluated clinically and with standard laboratory tests at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, physical examinations, vital signs, laboratory measurements (hematology, chemistry, etc), imaging, consultations (as needed), and other assessments including those listed in Appendix 1. In addition, patients will be closely monitored for the development of any signs or symptoms of infections or autoimmune conditions.

At the start of each cycle, study drug(s) will only be administered after clinical laboratory results have been reviewed. Administration of study drug(s) will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available.

Investigators are instructed to report all AEs (including pregnancy-related AEs).

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in Section 8.7.

8.3. Adverse Events

8.3.1. Definitions and Reporting

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drug or not.

Examples of AEs include:

- Worsening of a chronic or intermittent preexisting condition, including an increase in severity, frequency, or duration, and/or an association with a significantly worse outcome
- Detection or diagnosis of a new condition after study drug administration, even though the condition may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE)

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers must be blinded or redacted on the copies of the medical records before submission to the sponsor.

8.3.2. Assessment of Severity

The investigator will assess the severity of each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon NCI-CTCAE v5.0.

Toxicities that are not specified in NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (eg, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.6.2.

8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE, using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the administration of study drug should be considered and investigated. The investigator should consult the investigator’s brochure of BGB-A445, investigator’s brochure of each investigational agent, and prescribing information of the marketed study drug in making his or her assessment.

There may be situations when an SAE has occurred and the investigator has only limited information to include in the initial report to the sponsor. However, it is very important that the investigator always assess causality for every SAE before transmitting the SAE report to the sponsor, because the causality assessment is one of the criteria used in determining regulatory

reporting requirements. After considering follow-up information, the investigator may subsequently change his or her opinion of causality and may amend the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related" based on all information available at the time of reporting. An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including the following:

- Temporal relationship of the AE to the administration of study treatment or study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility
- An AE should be considered "related" to study drug if any of the following criteria are met. Otherwise, the event should be assessed as "not related":
  - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
  - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
  - There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

8.3.4. Follow-up of Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide the sponsor with further information on the patient's condition.

All AEs and SAEs that were documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes, or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultations with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in Section 8.6.2.

8.3.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count [CBC], coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, x-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator. In general, these are the laboratory test abnormalities or other abnormal assessments that meet the following criteria:

- are associated with clinical signs or symptoms, or
- require active medical intervention, or
- lead to dose interruption or discontinuation, or
- require close observation, more frequent follow-up assessments, or further diagnostic investigation.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 x ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the Adverse Event eCRF. Clinically associated events can be reported as a single event (eg, simultaneous occurrence of anemia, thrombocytopenia, and leukopenia may be reported as myelosuppression). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L (or mmol/L) should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF unless the etiology or grade changes. The initial grade of the event should be recorded, and the grade and seriousness should be updated any time the event changes.

8.4. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose, meet any of the following criteria:

- Results in death
- Is life-threatening
  Note: The term “life-threatening” in the definition of “serious” refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE that hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization
  Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency department for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting.

- Results in disability/incapacity
  Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator or the sponsor based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are not considered to be SAEs:

- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

8.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information [RSI]) and meets the definition of a serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the investigator's brochure of BGB-A445, investigator's brochure of each investigational agent, and prescribing information of the marketed study drug.

The assessment of SUSARs will be performed by the sponsor.

8.6. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

8.6.1. Adverse Event Recording Period

After informed consent has been signed but before the administration of the study drug, only SAEs associated with protocol-defined procedures should be reported to the sponsor.

After the initiation of study drug, all AEs and SAEs, regardless of their relationship to the study drug, will be reported until either 30 days after the last dose of study drug(s) or the initiation of a new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious but not treatment-related or nonserious regardless of relationship to study drug[s]) should be recorded until 90 days after the last dose of study drugs (whichever occurs later), regardless of the initiation of a new anticancer therapy. SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

AEs and SAEs should be recorded according to the details in Table 11. For the follow-up period for AEs, see Section 8.3.4. For the definition of TEAEs, see Section 9.3.2.

Table 11: Guidance for Duration of Recording New or Worsening Adverse Events in All Treatment Cohorts

Event type	Record new or worsening events that occur during this period	
	Begin	End
SAEs associated with protocol-defined procedure	Signing of informed consent	First dose of study drug
Non-serious AEs, AESIs, and SAEs [a]	First dose of study drug	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Immune-mediated AEs	First dose of study drug	Up to 90 days after last dose of BGB-A445 or investigational agent(s) (whichever occurs later, regardless of initiation of new anticancer therapy), death, withdrawal of consent, or loss to follow-up, whichever occurs first

Abbreviations: AE, adverse event; AESI, adverse event of special interest; SAE, serious adverse event.
a All SAEs considered related to the study treatment(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

8.6.2. Reporting Serious Adverse Events

8.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (≤ 24 hours after determination) to the sponsor or designee as described in Table 12.

Table 12: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for sending initial/follow-up report [a]	Documentation method	Reporting method
All SAEs	≤ 24 hours after first knowledge of the SAE	SAE report	Electronic submission of SAE form to safety database [b]

Abbreviations: SAE, serious adverse event.
[a] Report follow-up information that is clinically relevant and pertains to the SAE, which includes but is not limited to the following: update to the SAE, new additional SAE, outcome, seriousness criteria, investigator causality, event start date/date of onset, date of death, and relationship to each study drug. Follow-up information will also be reported as per the discretion of the investigator if the new or updated information changes the medical assessment of the case.
[b] SAE reports should be submitted to the sponsor safety database electronically from within the electronic data capture system. If the electronic submission is not available for any reason, a paper SAE form should be submitted by email or fax.

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, the investigator is to report the information to the sponsor within 24 hours as outlined above in Section 8.6.2.1. The SAE report will always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding an SAE, the investigator must not wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality for each SAE as described in Section 8.3.3.

The sponsor will provide contact information for SAE receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

The investigator, or person responsible according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

All SUSARs (as defined in Section 8.5) will be submitted to all applicable regulatory authorities and investigators for BGB-A445 and investigational agent studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated responsible person is required to promptly notify his or her IRB/IEC. The investigator should place copies of Safety Reports from the sponsor in the Investigator Site File.

8.6.3. Eliciting Adverse Events

The investigator or designee will ask patients about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

8.6.4. Progressive Disease

Progression of an underlying malignancy and related symptoms (including fatal outcomes) are not reported as an AE if it is clearly consistent with the expected pattern of progression of the underlying cancer. In most cases, the expected pattern of progression will be based on RECIST criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through the use of

objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE during the AE recording period on the Adverse Event eCRF, and immediately reported to the sponsor if assessed as a SAE.

8.6.5. Deaths

For this study, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified AE reporting period (see Section 8.6.1) that are attributed by the investigator solely to progression of underlying disease should be recorded on the end of study (EOS)/Death eCRF only.

For all other deaths which occurred during the study safety reporting period (refer to Section 8.6.1), regardless of relationship to the study drug, the primary cause of death must be recorded as a fatal SAE on the Adverse Event eCRF and be immediately reported to the sponsor.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown or if it is a sudden death, then the death could be recorded as an AE as "unknown cause of death" or "sudden death."

8.6.6. Adverse Events of Special Interest

An AE of special interest (serious or nonserious) is an AE of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation to characterize and understand it. Depending on the nature of the event, rapid communication by the study sponsor to other parties (eg, regulators) might also be warranted.

AEs of special interest may warrant collection of additional information across the entire study population to better characterize these events (eg, particular laboratory parameters, vital signs, risk factors, concomitant therapies, and/or concomitant illnesses).

AEs of special interest (no matter nonserious or serious) are required to be reported by the investigator to the sponsor immediately (ie, no more than 24 hours after learning of the event). AEs of special interest for this study are as follows:

- The finding of a concurrent elevated ALT or AST (> 3 x ULN or > 3 x baseline if baseline was abnormal) in combination with an elevated bilirubin (> 2 x ULN or > 2 x baseline if baseline was abnormal). The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the eCRF.
- Potential imAE
  - Grade ≥ 2 Immune-mediated hepatitis.
  - Grade ≥ 2 Immune-mediated pneumonitis.
  - Grade ≥ 2 Immune-mediated colitis.

- Grade ≥ 2 Immune-mediated myositis/rhabdomyolysis.
- Grade ≥ 2 Immune-mediated myocarditis/pericarditis.
- Grade ≥ 2 Immune-mediated reactions (ocular).
- Grade ≥ 2 Immune-mediated reactions (CNS).
- Grade ≥ 3 Immune-mediated skin adverse reaction.

- Grade ≥ 3 Infusion-related Reaction.

8.6.7. Pregnancies

If a female patient or the female partner of a male patient becomes pregnant within 120 days after the last dose of study drug(s), a pregnancy report form must be submitted to the sponsor.

If the patient receives docetaxel-containing combination treatment, a pregnancy report form must be submitted to the sponsor when the female patient or the female partner of the male patient becomes pregnant within 180 days after the last dose of study drug(s).

The pregnancy report is a type of SAE report and must follow the same prompt reporting guidelines described in Section 8.6.2.1. The outcome of the pregnancy, including any premature termination of the pregnancy, will also be reported to the sponsor.

While pregnancy itself is not considered an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. An abortion, whether accidental, therapeutic, or spontaneous, should always be reported as an SAE. Similarly, any congenital anomaly or birth defect in a child born to a patient exposed to the study drug should be recorded and reported as an SAE.

Patients who become pregnant must immediately discontinue treatment (see Section 3.5). For patients who are no longer pregnant, resumption of treatment may be discussed with the medical monitor.

8.6.8. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent Ethics Committees

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the RSI documents in the investigator's brochure of BGB-A445, investigator's brochure of each investigational agent, and prescribing information of the marketed study drug.

8.6.9. Assessing and Recording Immune-Mediated Adverse Events

Treatment with anti-OX40 therapy or immune checkpoint inhibitors can cause autoimmune disorders. All AEs considered by the investigator to be immune mediated (see Section 8.7.2) should be classified as imAEs and identified as such on the eCRF AE page.

8.6.10. Recording Infusion-Related Reactions

Most anticancer treatments carry a risk for infusion reactions; the incidence may increase when different agents are administered concomitantly. The majority of infusion-related reactions are characterized by nonspecific symptoms including headache, nausea, fever or chills, dizziness, flush, pruritus, and chest or back pain. These may occur more frequently on initial exposure with less frequent, or less severe reactions observed on re-exposure. Severe reactions are uncommon but may be fatal without appropriate intervention. Any signs or symptoms experienced by patients during the infusion of pharmacologic or biologic agents or any event occurring on the first day of drug administration should be evaluated accordingly.

Any event occurring during or within 24 hours of study drug administration and considered related to the infusion of study treatment should be recorded as a diagnosis (infusion-related reaction) on the Adverse Event eCRF. Associated signs and symptoms, associated drug cycles, onset time, duration, etc should be recorded in the case narrative if the event meets the criteria of AESIs or SAEs.

8.6.11. Recording Anaphylaxis

Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. It is characterized by the rapid development of airway and/or breathing and/or circulation problems. Intramuscular adrenaline is the most important treatment. Rechallenge is contraindicated. The definition currently accepted by the EMA relies on clinical diagnostic criteria and does not specify a particular immunologic mechanism (Sampson et al 2006).

It is acknowledged that the distinction between an infusion reaction and anaphylaxis (refer to Section 8.6.10) can be challenging, but nevertheless such distinction is necessary due to the different clinical consequences and the potential option of being rechallenged.

To capture all potential AEs, it is recommended to report all cases meeting the clinical diagnostic criteria of anaphylaxis as a diagnosis of "Anaphylaxis" with appropriate NCI-CTCAE grading (only Grade 3 through 5 is applicable).

8.7. Management of Events to be Monitored

Infusion-related reactions, anaphylaxis, and imAEs according to the NCI-CTCAE criteria are outlined below. In addition to the common statements with respect to AEs of special interest presented in this section, additional requirements regarding AEs of special interest for each agent are provided in the investigational agent-specific appendix, if applicable.

8.7.1. Infusion-Related Reactions

As a routine precaution after infusion of the study treatments, patients must be monitored. Refer to Section 5.2 for the administration of the study treatments and monitoring time.

Patients should be closely monitored during and after study drug administration for infusion-related reactions and anaphylaxis. Immediate access to an intensive care unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions and anaphylaxis.

See Appendix 8 and Appendix 10 for management of infusion-related reactions and anaphylaxis as well as treatment modifications.

8.7.2. Immune-Mediated Adverse Events

In this study, imAEs are of special interest. Potential imAEs are listed in Table 13 below. All AEs similar to those listed in the table should be evaluated in patients receiving BGB-A445 with investigational agent(s) to determine whether the AE is immune mediated. The investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic causes, toxins, disease progression, or other neoplastic causes) with appropriate diagnostic tests that may include, but are not limited to, serologic, immunologic, and histologic (biopsy) data (see Appendix 8). If alternative causes have been ruled out and the AE required the use of systemic corticosteroids, other immunosuppressants, or endocrine therapy, and it is consistent with an immune-mediated mechanism of action, the imAE indicator in the eCRF AE page should be checked.

The recommendations for diagnostic evaluation and management of imAEs are based on European Society for Medical Oncology and American Society of Clinical Oncology guidelines (Haanen et al 2017; Brahmer et al 2018), and common immune-mediated toxicities are detailed in Appendix 8. For any AEs not included in Appendix 8, please refer to the American Society of Clinical Oncology Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Recommendations for managing imAEs are detailed in Appendix 8.

Table 13: Examples of Immune-Mediated Adverse Events

Body System Affected	Events
Skin	rash; vitiligo; follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet syndrome; full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis
Endocrine	thyroiditis; hypothyroidism; hyperthyroidism; hypophysitis with features of hypopituitarism; insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	pneumonitis/diffuse alveolitis
Eye	episcleritis; conjunctivitis; iritis/uveitis
Musculoskeletal	arthritis; arthralgia; myalgia; myasthenic syndrome/myasthenia gravis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis
Cardiac	pericarditis; myocarditis
Neurologic	encephalitis; meningitis; meningoradiculitis; meningoencephalitis; Guillain-Barré syndrome; neuropathy

Recommendations for managing imAEs are detailed in Appendix 8.

If a toxicity does not resolve to ≤ Grade 1 within 12 weeks, study drug(s) should be discontinued after consultation with the sponsor. Patients who experience a recurrence of any event at the same or higher severity grade after restart of the study drug should permanently discontinue treatment.

8.7.3. Hepatic Function Abnormalities

When liver function laboratory abnormalities are observed, the investigator must evaluate for reactivation of viral hepatitis, consider other drug-related toxicities, and exclude progressive disease involving the liver. Findings of an elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia are indicators of severe liver injury (potential Hy's law case). Investigators must report the occurrence as an SAE to the sponsor. For diagnosis and management of patients with abnormal ALT or AST, please see Section 8.6.6 and refer to Appendix 8.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

9.1. Statistical Analysis

9.1.1. Randomization

As discussed in Section 7.2.2, once eligibility is determined, patients will be randomly assigned to a cohort using the IRT system. For either stage, an equal randomization is initially applied to each cohort, and approximately 20 patients per cohort may be enrolled or randomized.

9.1.2. Analysis Sets

The Intent-to-Treat (ITT) Analysis Set consists of all the patients who were enrolled or randomized to a treatment cohort.

The Safety Analysis Set consists of all the patients who were enrolled or randomized and received any dose of any study drug.

The Efficacy Evaluable Analysis Set consists of all patients who were enrolled or randomized and received any dose of any study drug, have evaluable disease at baseline, and have ≥ 1 evaluable postbaseline tumor response assessment unless any clinical progressive disease or death occurred before the first postbaseline tumor assessment.

The PK Analysis Set consists of all the patients who received any dose of the study drug and for whom the valid study drug PK parameters can be estimated.

The Biomarker Analysis Set consists of all the patients who received any dose of study drug(s) and have ≥ 1 derivable biomarker parameter.

9.1.3. Patient Disposition

The number of patients enrolled, randomized, treated, and discontinued from the study drug(s) and/or the study will be counted. The primary reason for study drug(s) and/or study discontinuation will be summarized according to the categories in the eCRF.

Important protocol deviations will be summarized and listed by each category.

9.1.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics.

9.1.5. Prior and Concomitant Medications

Prior medications will be defined as medications that stopped before the day of the first dose of any study drug. Concomitant medications will be defined as medications that 1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or 2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose (as of the EOT/Safety Follow-up Visit). In addition, concomitant medication associated with an imAE or a new anticancer therapy at 60 and 90 days (± 14 days) after the last dose of

study drug(s), regardless of whether the patient starts a new anticancer therapy, may also be included as part of the analysis, where applicable.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary drug codes and will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the clinical study report for this study.

9.2. Efficacy Analyses

The efficacy endpoints will be based upon investigators' tumor assessments per RECIST v1.1 and will be summarized as follows to evaluate the anticancer activities of BGB-A445 combined with investigational agent(s):

- ORR is defined as the proportion of patients with best overall response (BOR) of a CR or PR.
- Duration of response (DOR) is defined as the time from the first determination of an objective response per RECIST v1.1 until the first documentation of progression or death, whichever comes first.
- Disease control rate (DCR) is defined as the proportion of patients with BOR of a CR, PR, or stable disease.
- Clinical benefit rate (CBR) is defined as the proportion of patients with BOR of a CR, PR, or stable disease lasting ≥ 24 weeks.
- PFS is defined as the time from the date of randomization to the date of the first documentation of progressive disease or death due to any cause, whichever occurs first.
- OS is defined as the time from the date of randomization to the date of death due to any cause.

9.2.1. Primary Efficacy Analysis

ORR assessed by the investigator will be reported. The corresponding 95% CIs will be reported using the Clopper-Pearson method (Clopper and Pearson 1934).

9.2.1.1. Stage 1 Primary Efficacy Analysis

Confirmed ORR assessed by the investigator will be reported for each cohort. The corresponding 95% CIs will be reported using the Clopper-Pearson method (Clopper and Pearson 1934).

9.2.1.2. Stage 2 Primary Efficacy Analysis

In Stage 2, the ORR difference between any experimental cohort and the concurrent reference cohort (ΔORR) and the corresponding 95% CIs will be reported. For investigational agents evaluated in both stages, an analysis by combing the data from two stages will be conducted if deemed necessary.

9.2.2. Secondary Efficacy Analysis

The DOR, CBR, and DCR will be summarized. The DOR will be estimated using the Kaplan-Meier method in the responders. The CBR and DCR will be analyzed similarly to ORR. In addition, the difference between any experimental cohort and the reference cohort will be reported in Stage 2.

Waterfall plots of maximum tumor shrinkage per patient will be presented.

9.2.3. Exploratory Efficacy Analysis

The PFS will be estimated using the Kaplan-Meier method. The median PFS and the cumulative probability of PFS at every 3 months will be calculated for each cohort and presented with 2-sided 95% CIs. The PFS censoring rule will follow United States Food and Drug Administration Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (US FDA 2018).

OS will be analyzed similarly to PFS.

9.3. Safety Analyses

The safety profile will be determined by the AEs observed and by laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and ECG findings will also be used in determining the safety profile. The severity of AEs will be graded according to NCI-CTCAE v5.0. The incidence of DLT events and TEAEs will be reported as the number (percentage) of patients with TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs. Safety data will be summarized using the Safety Analysis Set.

9.3.1. Extent of Exposure

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

The number (percentage) of patients requiring dose reduction, interruption, dose delay, and drug discontinuation because of AEs will be summarized for each study drug. Reasons for dose modifications will be summarized as well.

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

9.3.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA by the Lowest Level Term, Preferred Term, and primary System Organ Class.

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 TEAEs.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by System Organ Class and Preferred Term. 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 TEAE within a specific System Organ Class and Preferred Term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug(s).

Treatment-related TEAEs include those events considered by the investigator to be related to a study drug or with a missing assessment of the causal relationship. SAEs, deaths, TEAEs ≥ Grade 3, imAEs, treatment-related TEAEs, and TEAEs that led to treatment discontinuation, dose interruption, dose reduction, or dose delay will be summarized.

Immune-mediated AEs will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of BGB-A445 and/or the investigational agent(s) and up to 90 days after the last dose of BGB-A445 or the investigational agent(s) (whichever occurs later), regardless of whether the patient starts a new anticancer therapy. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

9.3.3. Laboratory Analyses

Clinical laboratory (eg, hematology, serum chemistry, 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. Reference (normal) ranges for laboratory parameters will be provided. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline visit.

Laboratory parameters that are graded by NCI-CTCAE v5.0 will be summarized by NCI-CTCAE grade. In the summary of laboratory parameters by NCI-CTCAE grade, parameters with NCI-CTCAE grading in both high and low directions (eg, glucose, potassium, and sodium) will be summarized separately.

9.3.4. Vital Signs

Descriptive statistics for vital sign parameters (body temperature, pulse rate, and systolic and diastolic blood pressure) and changes from baseline will be presented by visit for all visits. Vital signs will be listed by patient and visit.

9.4. Pharmacokinetic Analysis

Serum/plasma concentration data will be tabulated and summarized by the visit/cycle at which these samples are collected. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate. Additional PK analyses, such as population PK, may be conducted as appropriate. Exposure-response (efficacy or safety endpoints) analysis may be

conducted if supported by data. The results from these analyses will be reported separately from the main study report.

9.5. Immunogenicity Analyses

ADA samples will be collected for BGB-A445 and relevant investigational agents in this study as outlined in Appendix 1. The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs. The incidence of positive ADAs and neutralizing ADAs will be reported for evaluable patients. The effect of immunogenicity on PK, efficacy, and safety may be evaluated if data allow and reported separately from the main clinical study report.

9.6. Other Exploratory Analyses

Summary statistics will be provided for pharmacodynamic biomarkers. An exploratory analysis on a potential correlation of these pharmacodynamic biomarkers with the dose, safety, and preliminary anticancer activity will be performed as appropriate.

Exploratory predictive biomarker analyses will be performed in an effort to understand the association of these markers with study drug(s) response, such as efficacy.

9.7. Sample Size Consideration

This study is designed to obtain efficacy, safety, PK, and immunogenicity data on BGB-A445 in combination with novel agents. No formal hypothesis testing will be performed in the efficacy evaluation because the study is not designed to make explicit power and Type I error considerations for a hypothesis test. In both Stage 1 and Stage 2, approximately 20 patients will be enrolled or randomized into each treatment cohort; approximately 6 patients will be enrolled first if a safety lead-in is planned.

9.8. Interim Monitoring

A futility analysis will be conducted when approximately 20 patients are enrolled or randomized in any of the experimental cohorts at the end of Stage 1 and when these patients have been followed up for ≥ 2 postbaseline tumor assessments. Bayesian posterior probability will be used to evaluate clinical antitumor activity in Stage 1 for BGB-A445 in combination with investigational agents in each cohort. An experimental cohort will be considered futile and not proceed to Stage 2 if the ORR in this group is unlikely to exceed a historical benchmark (eg, Posterior Probability [true ORR ≥ 23%] ≤ 20%). The historical benchmark will be assessed periodically and may be updated based on the emergent data during the cause of the study.

This section also provides the safety monitoring process with safety stopping rules that will be performed during the course of the study to evaluate the safety of any treatment cohort.

To control the number of patients at risk in the event of a major safety concern, a pause in enrollment will be triggered by unacceptable conditions such as any death because of reasons other than disease progression and at least possibly related to the study treatment.

The safety stopping boundaries for TR-Deaths (deaths possibly related to the study treatment) are listed in Table 14, which is derived based on the Bayesian posterior probability that the

number of patients with deaths possibly related to the study treatment is > 5% with 90% confidence and a weak prior distribution Beta (0.005, 0.095).

Following the stopping boundaries, if the accumulating data in a cohort suggest that the incidence rate of TR-Deaths is likely to exceed 5% with 90% probability, the enrollment to that specific cohort will be paused, and a comprehensive evaluation of the safety data will be performed by the SMC and the sponsor. Based on the totality of the data, recommendations from the SMC, and benefit-risk evaluation, the sponsor will take appropriate safety actions to continue or terminate enrollment in the relevant treatment cohort(s).

Table 14: Safety Stopping Boundaries for Number of Patients With TR-Deaths

Number of Patients in a Cohort	Number of Patients With TR-Deaths That Will Trigger Pause in Enrollment
1-2	≥ 1
3-11	≥ 2
12-23	≥ 3
24-36	≥ 4
37-40	≥ 5

Abbreviation: TR-Deaths, deaths possibly related to the study treatment.

10. STUDY COMMITTEES AND COMMUNICATION

An SMC will be established to review safety data for patients enrolled in the safety lead-in and for regular safety monitoring during the randomization phase. The SMC will include both investigators and the sponsor (including the medical monitor and study team members from Pharmacovigilance/Drug Safety, Clinical Pharmacology, and Biostatistics, with other members, as appropriate). The SMC will review available safety and other relevant data as appropriate to make recommendations regarding dose selection, modification, and further enrollment. The SMC may also be called upon by the sponsor to advise on the conduct of the study on an ad hoc basis where applicable. The detailed scope and meeting frequency of the SMC is defined in the SMC charter.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The investigator must maintain adequate and accurate records to ensure that the conduct of the study can be fully documented. Such records include, but are not limited to, the protocol, protocol amendments, ICFs, and documentation of IRB/IEC and governmental approvals. In addition, at the end of the study, the investigator will receive patient data, which will include an audit trail containing a complete record of all changes to such data.

11.1. Access to Information for Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

11.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide the representatives of a regulatory agency or representatives of the sponsor with access to records, facilities, and personnel for the effective conduct of any inspection or audit.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements. Alternatively, the sponsor will file the protocol to the appropriate regulatory agency before the study is initiated at a study center in that country.

12.2. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his or her time and the time of his or her personnel to the auditor/inspector to discuss findings and any relevant issues.

12.3. Study Site Inspections

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits may be performed periodically by the sponsor's or the contract research organization's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

Site visits will be conducted by the sponsor or an authorized representative to inspect study data, patients' medical records, and eCRFs. The investigator is to permit national and local health authorities; sponsor study monitors, representatives, and collaborators; and IRB/IEC members to inspect all facilities and records relevant to this study.

12.4. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug(s). This includes acknowledging receipt of each shipment of study product (quantity and condition), patient drug dispensation records, and returned or destroyed study product. Dispensation records will document quantities received from the sponsor's designated depot or its designee and quantities dispensed to patients, including batch/lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with the sponsor's requirements specified in the Pharmacy Manual. At appropriate times during the conduct of the study or at the end of the study after final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements specified in the Pharmacy Manual for disposal, arrangements will be made between the site and the sponsor or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be reviewed periodically and verified by the study monitor over the course of the study.

13. ETHICS/PROTECTION OF HUMAN PATIENTS

13.1. Ethical Standard

This study will be conducted by the investigator and the study center in full conformance with the guidelines for Good Clinical Practice (ICH E6) and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the patient. The study will also comply with the Definitions and Standards for Expedited Reporting (ICH E2A).

13.2. Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted, reviewed, and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC. Copies of the IRB/IEC correspondence and approval of the amended ICF or other information and the approved amended ICF or other information must be forwarded to the sponsor promptly.

The investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments. In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and the IRB/IEC. Investigators may receive written investigational new drug (IND) safety reports or other safety-related communications from the sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC and archived in the site's study file.

13.2.1. Protocol Amendments

Any protocol amendments will be prepared by the sponsor. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in medical monitor or contact information).

Information on any change in risk and/or change in scope must be provided to patients already actively participating in the study, and they must read, understand, and sign each revised ICF confirming their willingness to remain in the study.

13.3. Informed Consent

The sponsor's sample ICF will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The final IRB/IEC-approved ICFs must be provided to the sponsor for health authority submission purposes according to local requirements.

The ICFs must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained before participation in the study.

The ICFs will be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB-/IEC-approved consent forms must be provided to the sponsor for health authority submission purposes.

Patients must reconsent to the most current version of the ICFs (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. For any updated or revised ICFs, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

13.4. Patient and Data Confidentiality

The principal investigator, institution, sponsor, and site will maintain confidentiality and privacy standards for the collection, storage, transmission, and processing of patients' personal and medical information by following applicable laws and regulations related to the confidentiality, use, and protection of such information, including the ICH Good Clinical Practice Guideline, as implemented locally. Such laws may be more stringent than the requirements in this protocol.

The principal investigator and site shall code the personal and medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Unless required to be provided by laws or regulations or specifically requested in exceptional circumstances by the sponsor or its representatives, the principal investigator and site must ensure that any personal and medical information transmitted to the sponsor or its service providers is: 1) required by the protocol, and 2) appropriately de-identified (eg, via redaction and/or coding with the patient identification number) to ensure the following information about patients are NOT shared:

- names or initials (full or partial);
- full dates of birth;
- contact information (such as phone numbers or home or email addresses);
- numerical identifiers (eg, hospital or medical record, government, health insurance, or financial account numbers) other than patient identification numbers assigned as part of this study;
- geographic identifiers smaller than a state, province, or local equivalent (such as city, county, zip code, or other equivalent geographic identifiers); or

- information about marital status, family, or household members; employment, sex life, sexual preference, or other sensitive data that is not relevant to the study.

Patient personal and medical information obtained during this study is confidential and may only be disclosed to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law. In limited circumstances, such as in connection with insurance purposes or patient support services ancillary to certain study sites (eg, for patient travel or reimbursement), the principal investigator and site may provide certain of this personal or medical information to the sponsor or its representatives. Such personal or medical information may not be provided as part of the protocol (eg, as part of the eCRF, or on samples or reports submitted to the central laboratory).

Investigator and site personnel must use only the specific forms and clinical trial systems, (eg, the electronic data capture [EDC] system and any secure file transfer platforms [SFTPs]) designated by the sponsor for sharing and transferal of personal and medical information.

In the event of a breach of the confidentiality of a patient's personal or medical information, the principal investigator, site personnel, and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable laws. If the sponsor identifies personal or medical information that was not properly de-identified, it may be required to report the disclosure under local applicable laws.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes where allowed by local law or the patient's signed ICF.

Information generated during this study must be available for inspection upon request by representatives of the US FDA, the China NMPA, and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator agrees that all information received from the sponsor, including, but not limited to, the Investigator's Brochure, this protocol, eCRFs, the investigational drugs, and any other study information, are confidential and remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

If a written contract for the conduct of the study that includes confidentiality or privacy provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

13.5. Financial Disclosure

Investigators (including any sub-investigators and coinvestigators) are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest

of the clinical investigators, and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure financial interests and arrangements of the clinical investigators with the sponsor that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Entry in the Electronic Case Report Form

All study-related data collected or received by the investigator or study team shall be promptly entered into the eCRFs. In no event should the entry of the study data into the eCRF be later than what is stipulated in the site contract after the data are collected or received by the investigator or study team without prior communication with and approval by the sponsor.

14.1.2. Data Collection

Data required by the protocol will be entered into an EDC system.

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The e-signature of the investigator or designee must be provided in the EDC system to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of the sponsor and should not be made available in any form to third parties without written permission from the sponsor, except for authorized representatives of the sponsor or appropriate regulatory authorities.

14.1.3. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol will be stored by the sponsor at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file that includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

During the study, a study monitor (clinical research associate) will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

The eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross-checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits and will be carried out with due consideration given to data protection and medical confidentiality.

The AE verbatim descriptions (the investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA by the Lowest Level Term, Preferred Term, and primary System Organ Class. Concomitant medications will be coded using the WHO Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

14.2. Data Integrity and In-House Blinding

Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings or summaries that may introduce unwanted bias or to share such outputs from the EDC system with other functions or persons who do not have access to the EDC. Although the study is open-label, analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented.

14.3. Study Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least 1 of the following categories: 1) investigator's study file, and/or 2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC and governmental approval with correspondence, ICFs, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include documents such as (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECGs, electroencephalograms, x-rays, pathology and special assessment reports, consultant letters, screening and enrollment logs, etc.

After closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval when needed (eg, audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, or electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure that there is an acceptable backup of these reproductions and that an acceptable quality control process exists for making these reproductions.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements, local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to ≥ 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, or transfer of ownership of or responsibility for the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers away from the site so that they can be returned sealed to the

investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage away from the site.

Subject to patient consent, or as otherwise allowed under applicable law, biological samples at the conclusion of this study may be retained for ≤ 10 years or as allowed by your IRB/IEC, whichever is shorter.

14.4. Protocol Deviations

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert that they will apply due diligence to avoid protocol deviations and shall report all protocol deviations to the sponsor.

The investigator is to document and explain any deviations from the approved protocol. Any major deviations that might impact patient safety and/or data integrity must be promptly reported by the investigator to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

14.5. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). The sponsor will ensure that the report meets the standards set out in the Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of the sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. As this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors 2018).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor for review before submission or presentation in accordance with the clinical study agreement. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The process of reviewing manuscripts and presentations that are based on the data from this study is detailed in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

14.6. Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return of all study data to the sponsor
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Collection of all study documents for the trial master file filing according to GCP and local regulation
- Shipment of samples (including but not limited to those for PK, ADA, and biomarkers) to the assay laboratory for central laboratory analysis according to protocol and laboratory manual requirements

In addition, the sponsor reserves the right to suspend the enrollment or prematurely discontinue this study either at a single study center or at all study centers at any time for any reason. Potential reasons for suspension or discontinuation include, but are not limited to, safety or ethical issues or noncompliance with this protocol, GCP, the sponsor's written instructions, the clinical study agreement, or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before it takes effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons. The sponsor will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IRB/IEC promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must still be provided to the sponsor. In addition, arrangements will be made for the return of all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to the investigators and/or institutions will be in accordance with the clinical study agreement established between the investigator and/or institutions and the sponsor.

14.7. Information Disclosure and Inventions

All rights, title, and interests in any inventions, know-how, or other intellectual or industrial property rights that are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor and are hereby assigned to the sponsor.

If a written contract for the conduct of the study, which includes ownership provisions inconsistent with this statement, is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) are the sole property of the sponsor and will be kept confidential by the investigator and other study center personnel.

This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the sponsor.

These restrictions do not apply to the following:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IRB/IEC solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results that may be published as described in Section 14.5

If a written contract for the conduct of the study is executed and it includes provisions inconsistent with this statement, that contract's provisions shall apply rather than this statement.

15. REFERENCES

Al-Farsi A, Ellis PM. Treatment paradigms for patients with metastatic non-small cell lung cancer, squamous lung cancer: first, second, and third-line. Front Oncol. 2014;4:157.

American Cancer Society 2020. Accessed February 14, 2023. https://www.cancer.org/cancer/lung-cancer.html.

Aspeslagh S, Postel-Vinay S, Rusakiewicz S, et al. Rationale for anti-OX40 cancer immunotherapy. Eur J Cancer. 2016;52:50-66.

Barnfield PC, Ellis PM. Second-line treatment of non-small cell lung cancer: new developments for tumours not harbouring targetable oncogenic driver mutations. Drugs. 2016;76:1321-36.

Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373:1627–39.

Brahmer J, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714-68.

Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373:123–35.

Clinical Trials Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 21, 2020. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4): 404-13.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

Di Liello R, Cimmino F, Simón S, et al. Role of liquid biopsy for thoracic cancers immunotherapy. Explor Targeted Anti-tumor Ther. 2020;1(3):183.

Dolgin M, Association NYH, Fox AC, Gorlin R, et al. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Lippincott Williams and Wilkins; 1994.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Furuya N, Nishino M, Wakuda K, et al. Real-world efficacy of atezolizumab in non-small cell lung cancer: a multicenter cohort study focused on performance status and retreatment after failure of anti-PD-1 antibody. Thorac Cancer. 2021;12(5):613-18.

Gao SG, Li N, Wang SH, et al. Lung cancer in People's Republic of China. J Thorac Oncol. 2020;15(10):1567-76.

Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. The Lancet. 2014;384(9944):665-73.

Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. J Thorac Oncol. 2016;11(1):39-51.

Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2017:28(suppl 4):iv119-42.

Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Onco. 2004;22(9):1589-97.

Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387:1540–50.

Insa A, Martín-Martorell P, Di Liello R, et al. Which treatment after first line therapy in NSCLC patients without genetic alterations in the era of immunotherapy?. Crit Rev Oncol/Hematol. 2022;169:103538.

International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. 2018. Accessed 17 March 2022. http://www.icmje.org/icmje-recommendations.pdf

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Clinical safety data management: definitions and standards for expedited reporting. E2A. 1994. https://database.ich.org/sites/default/files/E2A_Guideline.pdf

International Council for Harmonisation of Technical Requirements For Pharmaceuticals for Human Use. Structure and content of clinical study reports. E3. 1995. https://database.ich.org/sites/default/files/E3_Guideline.pdf

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Integrated addendum to ICH E6(R1): guideline for good clinical practice. E6(R2). 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

Ito T, Wang YH, Duramad O, et al. OX40 ligand shuts down IL-10-producing regulatory T cells. Proc Natl Acad Sci U S A. 2006;103(35):13138-43.

Jenkins RW, Barbie DA, Flaherty K T. Mechanisms of resistance to immune checkpoint inhibitors. Br J Cancer . 2018;118(1):9-16.

Jensen SM, Maston LD, Gough MJ, et al. Signaling through OX40 enhances antitumor immunity. Semin Oncol. 2010;37(5):524-32.

Koren E, Smith HW, Shores E, et al. Recommendations on risk-based strategies for detection and characterization of antibodies against biotechnology products. J Immunol Methods. 2008;333(1-2):1-9.

Ladanyi A, Somlai B, Gilde K, et al. T-cell activation marker expression on tumor-infiltrating lymphocytes as prognostic factor in cutaneous malignant melanoma. Clin Cancer Res. 2004;10(2):521-30.

National Cancer Institute (NCI). Common Toxicity Criteria Version 5.0. Cancer Therapy Evaluation Program. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. 27 November 2017

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 1.2023.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

Petty JK, He K, Corless CL, et al. Survival in human colorectal cancer correlates with expression of the T-cell costimulatory molecule OX-40 (CD134). Am J Surg. 2002;183(5):512-8.

Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;25(5):948-68.

Piconese S, Valzasina B, Colombo MP. OX40 triggering blocks suppression by regulatory T cells and facilitates tumor rejection. J Exp Med. 2008;205(4):825-39.

Planchard D, Popat ST, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29:iv192-237.

Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer cell. 2015;27(4):450-61.

Reck M, Kaiser R, Mellemgaard A, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. The lancet oncology, 2014;15(2):143-55.

Redmond WL, Weinberg AD. Targeting OX40 and OX40L for the treatment of autoimmunity and cancer. Crit Rev Immunol. 2007;27(5):415-36

Ricciuti B, Jones G, Severgnini M, et al. Early plasma circulating tumor DNA (ctDNA) changes predict response to first-line pembrolizumab-based therapy in non-small cell lung cancer (NSCLC). J Immunothera Cancer. 2021;9(3).

Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389:255–65.

Rosello S, Blasco I, Garcia Fabregat L, et al. Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines. Annals of Oncology. 2017;28 (suppl_4): iv100-iv118.

Rosenberg AS, Worobec A. A risk-based approach to immunogenicity concerns of therapeutic protein products, part 1: considering consequences of the immune response to a protein. BioPharm Intl. 2004a;17(11).

Rosenberg AS, Worobec A. A risk-based approach to immunogenicity concerns of therapeutic protein products, part 2: considering host-specific and product-specific factors impacting immunogenicity. BioPharm Intl. 2004b;17(12).

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol, 2006;117(2):391-7.

Sarff M, Edwards D, Dhungel B, et al. OX40 (CD134) expression in sentinel lymph nodes correlates with prognostic features of primary melanomas. Am J Surg. 2008;195(5):621-5.

Shah DK, Betts AM. Antibody biodistribution coefficients: inferring tissue concentrations of monoclonal antibodies based on the plasma concentrations in several preclinical species and human. MAbs. 2013;5(2):297-305.

Sharma P, Hu-Lieskovan S, Wargo J A, et al. Primary, adaptive, and acquired resistance to cancer immunotherapy. Cell. 2017;168(4):707-23.

Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Onco. 2000;18(10):2095-103.

Soar J, Pumphrey R, Cant A, et al. Emergency treatment of anaphylactic reactions--guidelines for healthcare providers. Resuscitation. 2008;77(2):157-69.

St Rose MC, Taylor RA, Bandyopadhyay S, et al. CD134/CD137 dual costimulation-elicited IFN-gamma maximizes effector T-cell function but limits Treg expansion. Immunol Cell Biol. 2013;91(2):173-83.

Stinchcombe TE, Socinski MA. Considerations for second-line therapy of non-small cell lung cancer. Oncologist. 2008;13(S1):28-36.

Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209-49.

Takahara Y, Tanaka T, Ishige Y, et al. Efficacy and predictors of rechallenge with immune checkpoint inhibitors in non-small cell lung cancer. Thorac Cancer. 2022;13(4):624-30.

United States Food and Drug Administration Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. December 2018. Accessed February 20, 2023. https://www.fda.gov/media/71195/download

Voo KS, Bover L, Harline ML, et al. Antibodies targeting human OX40 expand effector T cells and block inducible and natural regulatory T cell function. J Immunol. 2013;191(7):3641-50.

Walsh RJ, Soo RA. Resistance to immune checkpoint inhibitors in non-small cell lung cancer: biomarkers and therapeutic strategies. Ther Adv Med Oncol. 2020, 12: 1758835920937902.

Wang R, Yan F, Hilt E, et al. Exploring OX40 receptor modulation in Phase 1/2a study of OX40 costimulatory agonist BMS-986178+/- Nivo or IPI in patients with advanced solid tumors [AACR Abstract LB-127]. Cancer Res. 2018;78(13 Suppl):LB-127-LB-127.

Willoughby J, Griffiths J, Tews I, et al. OX40: Structure and function - What questions remain? Mol Immunol. 2017;83:13-22.

APPENDIX 1. SCHEDULE OF ASSESSMENTS

	Screening [a]	Treatment cycles							Follow-up				
		Cycle 1 (21 days)			Cycle 2 (21 days)			≥ Cycle 3 (every 21 days)	EOT/SFU Visit [b] 60/90 Day SFU [c]			Efficacy Follow-up Visit [d]	Survival Follow-up Visit [d]
Visit day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**+ 30 days (EOT/SFU Visit)**	**+ 60 days (phone call SFU)**	**+ 90 days (phone call SFU)**		
Visit window	**-28 to -1**		**± 1**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**	**± 7**	**± 14**	**± 14**		
Informed consent	X												
Inclusion/exclusion criteria	X												
Demographics/medical history [e]	X												
Prior medications/procedures	X												
Vital signs/height [f]	X	X	X	X	X	X	X	X	X				
Physical examination [g]	X	X	X	X	X	X	X	X	X				
ECOG PS	X	X			X			X	X				
12-lead ECG [h]	X	X			X			X	X				
Ophthalmologic examination [i]	X												
Adverse events [j]	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications/ procedures	X	X	X	X	X	X	X	X	X	X	X		
Hematology [k]	X	X	X	X	X	X	X	X	X				

	Screening [a]	**Treatment cycles**							**Follow-up**				
		Cycle 1 (21 days)			**Cycle 2 (21 days)**			**≥ Cycle 3 (every 21 days)**	**EOT/SFU Visit** [b] **60/90 Day SFU** [c]			**Efficacy Follow-up Visit** [d]	**Survival Follow-up Visit** [d]
Visit day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**+ 30 days (EOT/SFU Visit)**	**+ 60 days (phone call SFU)**	**+ 90 days (phone call SFU)**		
Visit window	**-28 to -1**		**± 1**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**	**± 7**	**± 14**	**± 14**		
Clinical chemistry [k]	X	X	X	X	X	X	X	X	X				
Coagulation parameters [k]	X	X	As clinically indicated						X				
Urinalysis [k]	X	As clinically indicated											
Cardiac enzyme monitoring [l]	X	X	X	X	X	X	X	X	X				
Pregnancy test [m]	X	X			X			X	X				
Thyroid function [n]	X				X			Even-numbered cycles	X				
If applicable: HBV/HCV tests [o]	X	Every 4 cycles starting at Cycle 5 in patients with detectable HBV DNA or HCV RNA at screening or as clinically indicated in all patients											
If applicable: Pulmonary function tests [p]	X	As clinically indicated											
Blood biomarkers [q]		See Appendix 2											
Tumor assessment [r]	X	Every 6 weeks (± 7 days) for the first 9 months after randomization, then every 12 weeks (± 7 days) thereafter							X			X	

	Screening [a]	Treatment cycles							Follow-up				
		Cycle 1 (21 days)			Cycle 2 (21 days)			≥ Cycle 3 (every 21 days)	EOT/SFU Visit [b] 60/90 Day SFU [c]			Efficacy Follow-up Visit [d]	Survival Follow-up Visit [d]
Visit day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**+ 30 days (EOT/SFU Visit)**	**+ 60 days (phone call SFU)**	**+ 90 days (phone call SFU)**		
Visit window	**-28 to -1**		**± 1**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**	**± 7**	**± 14**	**± 14**		
Archival or fresh tumor tissue [s]	X	See Appendix 2											
BGB-A445 administration [t]		X			X			X					
Investigational agents administration [u]		Refer to Section 5.2 and respective appendix											
PK sampling of BGB-A445 [v]		X			X			X	X				
PK sampling of BGB-15025 and BGB-21958 [w]		X	X	X	X			X					
Sampling of Anti-BGB-A445 [x]		X			X			X	X				
Survival status													X

Abbreviations: AE, adverse event; CK, creatine kinase; CK-MB, creatine kinase-myocardial band; CT, computed tomography; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOT, End-of-Treatment (Visit); FFPE, formalin-fixed paraffin-embedded; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IEC, Independent Ethics Committee; IRB, Institutional Review Board; imAE, immune-mediated AE; MRI, magnetic resonance imaging; MUGA, multigated acquisition; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; PK, Pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; SFU, Safety Follow-up; T3, triiodothyronine; T4, thyroxine; TT3, total T3.

Note: Timepoints containing numbers represent timepoints with special considerations for that respective assessment.

[a] Written informed consent is required before performing any study-specific procedure. Results of standard-of-care tests or examinations performed before obtaining informed consent and ≤ 28 days before randomization may be used for screening assessments rather than repeating such tests, unless otherwise indicated.

[b] The EOT Visit will be conducted ≤ 7 days after the investigator determines that study treatment will no longer be administered or the patient discontinues the study treatment. Patients will undergo the Safety Follow-up Visit at approximately 30 days [± 7 days] after the last dose or before the initiation of a new anticancer treatment, whichever occurs first. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT or Safety Follow-up Visit, these tests need not be repeated. Tumor assessment is not required at the EOT or Safety Follow-up Visit if < 6 weeks have passed since the last assessment.

[c] Sixty- and 90-day Telephone Safety Follow-up: Contacts with patients should be conducted to assess adverse events (AEs; serious or nonserious) and related concomitant medications, if appropriate, at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of study drug(s) regardless of whether or not the patient starts a new anticancer therapy. If a patient reports a suspected new or worsening AE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if a further assessment is indicated.

[d] Efficacy Follow-up Period: Patients who discontinue study drug(s) for reasons other than progressive disease will continue to undergo tumor assessments per the original plan until the patient experiences progressive disease, starts subsequent anticancer therapy, or for any other reason listed in Section 3.8, whichever occurs first; Survival Follow-up Period: Overall survival data will be collected via telephone calls approximately every 8 weeks (± 7 days) after the Safety Follow-up Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or the end of the study.

[e] Includes age or year of birth, gender, and self-reported race/ethnicity.

[f] Height assessment is required only at screening. Vital signs will include measurements of weight, temperature (˚C), pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. If coinciding with study drug infusions, the patient's vital signs (temperature [˚C], pulse rate, and blood pressure [systolic and diastolic]) are required to be recorded within 60 minutes before, during, and 30 (± 10) minutes after the first infusion of study drug(s). For subsequent infusions, vital signs (temperature [˚C], pulse rate, and blood pressure [systolic and diastolic]) will be collected within 60 minutes before infusion of each study drug(s), and if clinically indicated, during and 30 (± 10) minutes after each study drug(s) infusion.

[g] Complete physical examination is required at screening while subsequent visits entail limited, symptom-directed physical examinations (as detailed in Section 7.3.2). In addition, investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during study treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.

[h] The ECG recording will be performed predose on Day 1 of each cycle at the same time and when clinically indicated. On Day 1 of Cycle 1 and Cycle 5, ECGs must be performed predose and between 4 to 6 hours after study drug(s) infusion. During screening and at EOT Visit, 3 consecutive ECGs will be performed approximately 2 to 3 minutes apart. All ECGs are to be obtained before other assessments scheduled at that same time (vital sign measurements, blood draws, etc). The patient should rest in a semirecumbent or supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (television, radio, conversation, etc) before each ECG collection.

[i] Eye examinations, including a visual acuity test captured before obtaining written informed consent and within 28 days of the first dose of study drug, may be used for the screening evaluation rather than repeating tests. Eye examinations, including a visual acuity test, will be assessed by an appropriate specialist at the Screening Visit.

[j] AEs and laboratory abnormalities will be graded per NCI-CTCAE Version 5.0.

[k] Local and/or central laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted. If clinical chemistry, hematology, cardiac enzyme, and coagulation at screening are not performed ≤ 7 days before study drug(s) administration on Day 1 of Cycle 1, these tests should be repeated and reviewed within 48 hours before study drug administration. After Day 1 of Cycle 1, results are to be reviewed within 48 hours before study drug administration. See Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[l] CK and CK-MB levels will be evaluated at the timepoints specified within the table and when clinically indicated. All patients will have creatine kinase and CK-MB testing at screening, and testing is to be repeated at all scheduled visits during the first 3 treatment cycles, all predose assessments from Cycle 4 onwards, and at the End-of -Treatment/Safety Follow-up visit. If CK-MB fractionation is not available, assess troponin I and/or troponin T instead. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[m] A serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative ≤ 7 days before the randomization. A negative urine or serum pregnancy test must be completed and recorded ≤ 72 hours before the administration of study drug(s) at each cycle. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

[n] Analysis of T3, T4, and thyroid stimulating hormone will be performed by the local study site laboratory at screening and even numbered cycles. TT3 is acceptable in case T3 analysis is not available.

[o] Testing will be performed (local laboratory) at screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody). In the case of active HBV or HCV infection, these tests will be followed by viral load assessment (HBV DNA and HCV RNA). Patients who have detectable HBV DNA or HCV RNA at screening regardless of screening results will undergo the respective viral load test every 4 cycles starting at Cycle 5. Patients who do not have active HBV/HCV infection or detectable HBV DNA or HCV RNA at screening will not be required to undergo the HBV/HCV tests at the EOT or Safety Follow-up Visit.

[p] Pulmonary function tests including spirometry and assessment of oxygenation are required. For the assessment of oxygenation, pulse oximetry at rest and with exercise is required at a minimum. Moreover, the diffusion capacity could be tested alternatively for the assessment of oxygenation. Pulmonary function tests are to be performed for all patients during the screening period to assist the determination of suitability on the study. Respective test results need to be submitted to the sponsor. Refer to Section 7.3.4 for more details.

[q] Blood biomarkers: See Appendix 2.

[r] Tumor imaging will be performed ≤ 28 days before randomization. Results of standard-of-care tests or examinations performed before obtaining informed consent and ≤ 28 days before randomization may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) from randomization for the first 9 months, and every 12 weeks (± 7 days) thereafter, based on RECIST Version 1.1. Tumor assessments must include CT scans (with oral and/or intravenous contrast, unless contraindicated) or MRI, with preference for CT, of the chest, abdomen, and pelvis. All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening must be used throughout the study (eg, the same contrast protocol for CT scans).

[s] Archival or fresh tumor tissue: During the screening period, patients are required to provide archival tumor tissue (FFPE blocks containing tumor [preferred] or approximately 15 [at least 10] freshly cut unstained slides). The most recently collected tissue is preferred. See Appendix 2.

[t] BGB-A445 will be given intravenously on Day 1 of each 21-day cycle (once every 3 weeks) (see Section 5.2 5.2.1 for details). Note: BGB-A445 must always be prepared and administered separately from any other systemic medication including investigational agents.

[u] Investigational agents including docetaxel will be given intravenously on Day 1 of each 21-day cycle (every 3 weeks), while investigational agents including BGB-15025 will be received orally on a daily basis for each 21-day cycle (every 3 weeks) before the infusion. Refer to the respective appendix for details.

[v] Predose serum samples for BGB-A445 (≤ 60 minutes before starting infusion) are required to be collected on Day 1 of Cycles 1, 2, 5, 9, and 17. Postdose serum samples (≤ approximately 30 minutes after completing study drug infusion) are required to be collected on Day 1 of Cycles 1 and 5. An additional PK sample is required to be collected at the Safety Follow-up Visit. Should a patient present with any ≥ Grade 3 immune-mediated adverse event (imAE), an additional blood PK sample may be taken. These tests are required when it is allowed by local regulations/Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs).

[w] Predose blood samples for BGB-15025 and its metabolite BGB-21958 (≤ 30 minutes before dose) are required to be collected on Day 1 of Cycles 1, 2, and 3, and Days 8 and 15 of Cycle 1. Postdose blood samples at 2 hours (± 10 minutes) and 4-6 hours (± 20 minutes) after dosing are required to be collected on Day 1 of Cycles 1 and 2. Should a patient present with any ≥ Grade 3 imAE, an additional blood PK sample may be taken. These tests are required when it is allowed by local regulations/IRBs/IECs.

[x] Blood samples to test for anti-BGB-A445 antibody will be collected ≤ 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 5, 9, and 17 and at the Safety Follow-up Visit. All samples should be drawn at the same time as blood collection for the predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/IECs.

APPENDIX 2. BLOOD AND TUMOR TISSUE BIOMARKER ANALYSIS

	Screening	Treatment cycles							Follow-up				
		Cycle 1 (21 days)			Cycle 2 (21 days)			≥ Cycle 3 (every 21 days)	EOT/SFU Visit 60/90 Day SFU			Efficacy Follow-up Visit	Survival Follow-up Visit
Visit day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**+ 30 days (EOT/SFU Visit)**	**+ 60 days (phone call SFU)**	**+ 90 days (phone call SFU)**		
Visit window			**± 1**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**	**± 7**	**± 14**	**± 14**		
Archival or fresh tumor tissue [a]	X							X (Cycle 3 only)	X				
Blood collection for biomarker analysis (Soluble OX40) [b]		X (predose)	X		X (predose)								
Blood collection for biomarker analysis (cytokine/chemokine or soluble proteins) [c]		X (predose)	X		X (predose)								
Blood collection for biomarker analysis (ctDNA/TMB/ mutation profiling) [d]		X (predose)						X (predose, same visit as every tumor assessment until progressive disease)	X (confirmed progressive disease)				

Abbreviations: ctDNA, circulating tumor DNA; EOT, End-of-Treatment (Visit); FFPE, formalin-fixed paraffin-embedded; MSI, microsatellite instability; SFU, Safety Follow-up; TMB, tumor mutation burden.

[a] Patients are required to provide an archived FFPE tumor tissue sample (block or approximately 15 [at least 10] freshly unstained FFPE slides). The most recently collected tissue is preferred. Optional biopsy after 2 cycles of treatment is recommended if the patient is medically fit and it is clinically feasible (within 3-day window before Day 1 of Cycle 3 is recommended). Patients who have progressive disease will be asked to provide an optional biopsy sample at the EOT Visit (or at a clinically feasible visit and as deemed appropriate by the treating physician) for the assessment of mechanisms of resistance.

[b] Blood collection for biomarker analysis (Soluble OX40): Blood will be collected at Day 1 of Cycle 1 (predose), Day 8 of Cycle 1, and Day 1 of Cycle 2 (predose).

[c] Blood collection for biomarker analysis (cytokine/chemokine or soluble proteins): Blood samples for cytokine and soluble protein analysis will be collected at Day 1 of Cycle 1 (predose), Day 8 of Cycle 1, and Day 1 of Cycle 2 (predose).

[d] Blood collection for biomarker analysis (ctDNA/TMB/mutation profiling): Blood samples will be taken predose on Day 1 of Cycle 1, then at every tumor assessment schedule until progressive disease, and at the EOT Visit after disease progression to evaluate TMB, MSI, mutational profiles, as well as other biomarkers in blood.

APPENDIX 3. CLINICAL LABORATORY ASSESSMENTS

Serum chemistry	Hematology	Coagulation	Urinalysis	Thyroid function
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Total bilirubin Direct bilirubin Blood urea nitrogen or urea Potassium Sodium Calcium [a] Creatinine Glucose Lactate dehydrogenase Total protein Lipase Amylase	Red blood cell count Hematocrit Hemoglobin Platelet counts WBC count Lymphocyte count Neutrophil count	Prothrombin time Partial thromboplastin time or activated partial thromboplastin time International normalized ratio	Glucose Protein Blood Ketones 24-hour protein	Free triiodothyronine Free thyroxine Thyroid stimulating hormone

Abbreviations: WBC, white blood cell.
[a] Calcium values will be corrected for patients with hypoproteinemia.

APPENDIX 4. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: Oken et al 1982. Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.

APPENDIX 5. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

Source: Eisenhauer et al 2009

Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (v1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria.

Note: Lesions are either measurable or nonmeasurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) and magnetic resonance imaging (MRI) (no less than double the slice thickness and a minimum of 10 mm). Assumes a scan slice thickness no greater than 5 mm.
- 10 mm caliper measurement by clinical exam (when superficial)

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered nonmeasurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all nonmeasurable.

Bone lesions:

- Bone scan, positron-emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- The concept of cystic metastases also applies to metastatic lesions with a necrotic component. Hence, measurable lesions with a necrotic component may be selected as target lesions. However, if non-necrotic lesions are present, these are preferred for selection as target lesions.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. A maximum of 2 measurable lymph nodes, inclusive of all lymphatic chains involved, may be chosen as target lesions (ie, the lymphatic system is considered one organ). Target lesions should be selected based on size (lesions with the longest diameter), how representative they are of all involved organs, and whether they lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures, which may be visible by imaging even if not involved by tumor. Pathological nodes, which are defined as measurable and may be identified as target lesions, must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 perpendicular dimensions in the plane in which the image is obtained (for a CT scan, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal, but the axial plane is recommended for measurements). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm by 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with a short axis ≥ 10 mm but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Nontarget Lesions

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required, and

these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases"). If a nontarget lymph node normalizes (< 10 mm in short axis) after baseline, the respective evaluation should be "absent."

Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. An imaging-based evaluation should always be done rather than a clinical examination, unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.
- Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: Target lesion measurements should be performed in the axial plane. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have a slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans). If there is a change from CT to MRI or the reverse, target lesions should continue to be measured provided the imaging parameters do not render measurements incomparable.
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date, and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence after complete response (CR) or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.
- Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Response Criteria

Evaluation of Target Lesions

- CR: Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease : At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of 1 or more new lesions is also considered progression).
- Stable Disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.
- Both PR and progressive disease: If the change in sum of diameters is consistent with both PR and progressive disease at a tumor assessment visit, progressive disease should take precedence.
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. The case report form may be designed to have target nodal lesions recorded in a separate section where, to qualify for CR, each node must achieve a short axis < 10 mm. For PR, stable disease, and progressive disease, the

actual short axis measurement of the nodes is to be included in the sum of target lesions.

- Target lesions that become "too small to measure": While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure." When this occurs, it is important that a value be recorded on the electronic case report form (eCRF). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially nonreproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that measurement should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Evaluation of Nontarget Lesions

While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (< 10 mm short axis).
- Non-CR/Non-progressive disease: Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive disease: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: The appearance of 1 or more new lesions is also considered progression.)
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of stable

disease or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of stable disease or PR of target disease will therefore be extremely rare.

- When the patient has only nonmeasurable disease: This circumstance arises in some Phase 3 studies when it is not a criterion of study entry to have measurable disease. The same general concept applies here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare progressive disease for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).
- Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread, or it may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the patient should be considered to have had overall progressive disease at that point. While it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is a patient who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered that reveals metastases. The patient's brain metastases are considered evidence of progressive disease even if he or she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents a truly new disease. If repeat scans confirm

there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in the assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of progressive disease based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is progressive disease. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of progressive disease will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not progressive disease.
- Timepoint Response: It is assumed that at each protocol-specified timepoint, a response assessment occurs. The following table provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline:

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-progressive disease	No	PR
CR	Not evaluated	No	PR
PR	Non-progressive disease or not all evaluated	No	PR
Stable disease	Non-progressive disease or not all evaluated	No	Stable disease
Not all evaluated	Non-progressive disease	No	NE
Progressive disease	Any	Yes or No	Progressive disease
Any	progressive disease	Yes or No	Progressive disease
Any	Any	Yes	Progressive disease

Abbreviations: CR, complete response; NE, not evaluable; PR, partial response.

When patients have nonmeasurable (therefore nontarget) disease only, the following table is to be used:

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-progressive disease	No	Stable disease (Non-CR/non-progressive disease)
Not all evaluated	No	NE
Unequivocal progressive disease	Yes or No	Progressive disease
Any	Yes	Progressive disease

Abbreviations: CR, complete response; NE, not evaluable.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study drug treatment until the end of treatment considering any requirement for confirmation. On occasion, a response may not be documented until after the end of therapy, so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response."

The best overall response is determined once all the data for the patient are known.

Best response determination in studies where confirmation of complete or partial response IS NOT required: Best response in these studies is defined as the best response across all timepoints (for example, a patient who has stable disease at first assessment, PR at second assessment, and progressive disease on last assessment has a best overall response of PR). When stable disease is believed to be the best response, it must also meet the protocol-specified minimum time from baseline. If the minimum time is not met when stable disease is otherwise the best timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has stable disease at first assessment, progressive disease at second, and does not meet minimum duration for stable disease, will have a best response of progressive disease. The same patient lost to follow-up after the first stable disease assessment would be considered inevaluable.

Best response determination in studies where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent timepoint as specified in the protocol (generally 4 weeks later).

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order to not to overstate progression should it be based on increase in the size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero."

In studies where confirmation of response is required, repeated "NE" (not evaluable) timepoint assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be addressed in determination of the response and progression. For example, in most studies it is reasonable to consider a patient with timepoint responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy.

Conditions that define "early progression, early death, and inevaluability" are study specific and should be clearly described in each protocol (depending on treatment duration, and treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to a false positive CR because of limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions. cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If progression is confirmed at the next scheduled assessment, the date of progression should be the earlier date when progression was suspected.

Confirmation of Measurement/Duration of Response

Confirmation

In nonrandomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies. However, in all other circumstances, ie, in randomized studies (Phase 2 or 3) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies that are not blinded.

In the case of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than 6 weeks).

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are the first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for the calculation of progressive disease).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between 2 measurements for the determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

APPENDIX 6. PREEXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

Prospective patients should be carefully questioned to determine whether they have any history of an acquired or congenital immune deficiency or autoimmune disease.

Contact the medical monitor regarding any uncertainty about immune deficiency/autoimmune disease exclusions.

Acute disseminated encephalomyelitis	Addison disease
Ankylosing spondylitis	Antiphospholipid antibody syndrome
Aplastic anemia	Autoimmune hemolytic anemia
Autoimmune hepatitis	Autoimmune hypoparathyroidism
Autoimmune hypophysitis	Autoimmune myocarditis
Autoimmune oophoritis	Autoimmune orchitis
Autoimmune thrombocytopenic purpura	Behcet disease
Bullous pemphigoid	Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome	Crohn disease
Dermatomyositis	Dysautonomia
Epidermolysis bullosa acquisita	Gestational pemphigoid
Giant cell arteritis	Goodpasture syndrome
Granulomatosis with polyangiitis	Graves disease
Guillain-Barre syndrome	Hashimoto disease
Immunoglobulin A (IgA) neuropathy	Inflammatory bowel disease
Interstitial cystitis	Kawasaki disease
Lambert-Eaton myasthenic syndrome	Lupus erythematosus
Lyme disease (chronic)	Mooren ulcer
Morphea	Multiple sclerosis
Myasthenia gravis	Neuromyotonia
Opsoclonus myoclonus syndrome	Optic neuritis
Ord thyroiditis	Pemphigus
Pernicious anemia	Polyarteritis nodosa
Polyarthritis	Polyglandular autoimmune syndrome
Primary biliary cirrhosis	Psoriasis
Reiter syndrome	Rheumatoid arthritis
Sarcoidosis	Sjögren syndrome

Stiff person syndrome	Takayasu arteritis
Ulcerative colitis	Vogt-Koyanagi-Harada disease

APPENDIX 7. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Adapted from Dolgin et al 1994.
Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

APPENDIX 8. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any immune-mediated adverse event (imAE) are intended as guidance. This document should be used in conjunction with expert clinical judgement (by specialist physicians experienced in the treatment of cancer using immunological agents), and individual institutional guidelines or policies.

The recommendations for diagnostic evaluation and management of imAEs are based on European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines (Haanen et al 2017; Brahmer et al 2018). For any adverse events (AEs) not included in the tables below, refer to the ASCO Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Criteria used to diagnose imAEs include blood tests, diagnostic imaging, histopathology, and microbiology assessments to exclude alternative causes such as infection, disease progression, and adverse effects of concomitant drugs. In addition to the results of these tests, the following factors should be considered when making an imAE diagnosis:

- What was the temporal relationship between initiation of study treatment and the AE?
- How did the patient respond to withdrawal of study treatment?
- Did the event recur when study treatment was reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is disease progression or an alternative diagnosis a more likely explanation?

When alternative explanations to autoimmune toxicity have been excluded, the imAE field associated with the AE in the electronic case report form (eCRF) should be checked. If further diagnostic evaluations change the assessment, the eCRF should be updated accordingly.

Recommended Diagnostic Tests in the Management of Possible Immune-Mediated Adverse Events

Immune-mediated Toxicity	Diagnostic Evaluation Guideline
Thyroid disorders	Scheduled and repeated thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss, and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.

Immune-mediated Toxicity	Diagnostic Evaluation Guideline
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath, or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including DLCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.
Neurological toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, *Clostridium difficile* toxin, and cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging (eg, x-ray, CT scan). If a patient experiences bleeding, pain, or distension, consider colonoscopy with biopsy and surgical intervention as appropriate.
Eye disorders	If a patient experiences acute, new onset, or worsening of eye inflammation; blurred vision; or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3 to 4; every 2 to 3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging (eg, ultrasound scan for metastases or thromboembolism). Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment, or phase-contrast microscopy. Refer to a nephrologist for further management assistance.
Dermatology	Consider other causes by conducting a physical examination. Consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint x-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to a rheumatologist for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include CK, ESR, CRP, troponin, and consider a muscle biopsy.

Immune-mediated Toxicity	Diagnostic Evaluation Guideline
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; D_{LCO}, diffusing capacity for carbon monoxide; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FBC, full blood count; HIV, human immunodeficiency virus; INR, international normalized ratio; LCI, liver cytosolic antigen; LFT, liver function test; LKM, liver kidney microsomal antibody; LP, liver pancreas antigen; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SLA, soluble liver antigen; SMA, smooth muscle antibody; T4, thyroxine; TFT, thyroid function tests; TSH, thyroid-stimulating hormone; UEC, urea electrolytes and creatinine.

Management of Immune-Mediated Adverse Events

Immune-mediated AEs can escalate quickly. Study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention as appropriate are required. Immune-mediated AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice, and contact the study medical monitor.

If a toxicity does not resolve to ≤ Grade 1 within 12 weeks, study drug(s) should be discontinued after consultation with the sponsor. Patients who experience a recurrence of any event at the same or higher severity grade after the restart of study drug should permanently discontinue treatment.

For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study medical monitor.

Corticosteroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory imAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil [MMF]). Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy.

Management of Immune-Mediated Adverse Events

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker, and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with comorbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1.
Hypophysitis	**1-2** Mild-moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse intravenous methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinologist's advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to ≤ Grade 2. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider *Pneumocystis* infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe or life-threatening symptoms: breathless at rest	Admit to a hospital and initiate treatment with intravenous methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for *Pneumocystis* infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological toxicity	**1** Mild symptoms	N/A	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening symptoms	Initiate treatment with oral prednisolone or intravenous methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/Diarrhea	**1** Mild symptoms: ≤ 4 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days, manage as a Grade 2 event.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper corticosteroids over 2-4 weeks. Consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: ≥ 7 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.
	4 Life-threatening symptoms	If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA Class III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Discontinue study treatment.
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical corticosteroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral corticosteroids.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate corticosteroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: intravenous methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3 x ULN	Check LFTs within 1 week and before the next dose to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST > 3 x to 5 x ULN	Recheck LFTs every 48-72 hours. For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days, then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline grade and prednisolone tapered to ≤ 10 mg.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 ALT or AST > 5 x to 20 x ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate intravenous (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	If ALT and AST ≤ 10 x ULN: Hold study treatment until improved to baseline grade; reintroduce only after discussion with the medical monitor. If ALT or AST > 10 x ULN: Discontinue study treatment.
	4 ALT or AST > 20 x ULN	Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite corticosteroids: If on oral prednisolone, change to pulsed intravenous methylprednisolone. If on intravenous methylprednisolone, add mycophenolate mofetil (MMF) 500 to 1000 mg twice a day. If worsens on MMF, consider addition of tacrolimus. Duration and dose of corticosteroid required will depend on severity of event.		
Nephritis	**1** Creatinine 1.5 x baseline or > ULN to 1.5 x ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5-3 x baseline or > 1.5-3 x ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Creatinine > 3 x base line or > 3-6 x ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate intravenous (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6 x UL N	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Ocular toxicity	**1** Asymptomatic eye examination/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral corticosteroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate intravenous (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment, manage as a Grade 3 event.	Continue treatment or, if symptoms continue to worsen, hold study treatment until symptoms improve to baseline or Grade 0-1.
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ Stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improve to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider intravenous corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral corticosteroids and treat as Grade 2.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 Moderate weakness with/without pain	If CK is 3 x ULN or worse, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus intravenous (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve, add immunosuppressant therapy. Taper oral corticosteroids over at least 4 weeks.	For Grade 3: Hold study treatment until improved to Grade 0-1. Discontinue upon any evidence of myocardial involvement.
Myocarditis[a]	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing and including ECG, cardiac echo/MUGA, and/or other interventions per institutional guidelines; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2.	Hold study treatment. If a diagnosis of myocarditis is confirmed and considered immune mediated, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart study treatment unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or intravenous (methyl)prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response, change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab, or anti-thymocyte globulin.	
	3 Severe symptoms with mild exertion		
	4 Life-threatening		
	≤ 2		Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Other immune-mediated adverse events	**3**	Clinical management per local guideline based on adverse event type and severity.	Hold study treatment until improved to Grade 0-1. For recurrent Grade 3: Discontinue study treatment.
	4		Discontinue study treatment.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; ECG, electrocardiogram; INR, international normalized ratio; LFT, liver function test; MMF, mycophenolate mofetil; MUGA, multigated acquisition scan; N/A, not applicable; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.

[a] If clinically significant cardiac enzyme abnormalities are detected during laboratory assessment and serial cardiac enzyme assessments pose logistical hardship for the patient, then patient hospitalization should strongly be considered until immune-mediated myocarditis has been ruled out.

APPENDIX 9. MANAGEMENT OF INFUSION-RELATED REACTIONS

Patients should be closely monitored during and after study drug administration for infusion-related reactions and anaphylaxis. See Section 5.2.1 for the monitoring periods required. Immediate access to an intensive care unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Management of infusion-related reactions is provided in the table below (Rosello et al 2017).

NCI-CTCAE Grade v5.0	Management
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	Decrease infusion rate by 50%. Closely monitor for worsening signs or symptoms. Medical management as needed. Subsequent infusions should be given after appropriate premedication and at the reduced infusion rate.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDS], narcotics, intravenous [IV] fluids); prophylactic medications indicated for ≤ 24 hours	Temporarily stop infusion. Treatment may include but is not limited to H1/H2 antagonists or corticosteroids. Restart infusion at 50% rate once infusion-related reaction has resolved or decreased to Grade 1 in severity and titrate to tolerance Closely monitor for worsening signs or symptoms. Appropriate medical management should be instituted. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for clinical sequelae	Immediately stop the infusion. Treatment includes but not limited to H1/H2 antagonists or corticosteroids. The patient should be withdrawn from study drug(s) treatment.
Grade 4 Life-threatening consequences; urgent intervention indicated	Immediately stop the infusion. Treatment includes but not limited to H1/H2 antagonists or corticosteroids. Proper medical management should be instituted. The patient should be withdrawn from study drug(s) treatment. Hospitalization is recommended.

For the prophylaxis of mild events (eg, nasal congestion or flu-like symptoms), a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (eg, 600 mg ibuprofen or 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of study drugs(s) infusion. Alternative treatments for fever (eg, paracetamol) may be given to patients at the discretion of the investigator.

If the patient has a second infusion-related reaction (≥ Grade 2) on the slower infusion rate, infusion should be discontinued, and the patient should be withdrawn from the treatment.

APPENDIX 10. MANAGEMENT OF ANAPHYLAXIS

If anaphylaxis occurs, the patient must be managed according to the best available medical practice, as described in the guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (UK) (Soar et al 2008). Patients should be instructed to report any delayed reactions to the investigator immediately.

The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading of anaphylaxis starts from Grade 3.

Management and treatment modifications for symptoms of anaphylaxis associated with study drug(s) administration are provided in the table below.

NCI-CTCAE Grade v5.0	Management
Grade 3 Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension **Grade 4** Life-threatening consequences; urgent intervention indicated	Immediately stop the infusion. Proper medical management should be instituted. Treatment may include but is not limited to oral or intravenous antihistamines, antipyretics, glucocorticoids, epinephrine, bronchodilators, and oxygen. The patient should be withdrawn from study drug(s) treatment. Rechallenge is prohibited.

Abbreviations: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Event.

APPENDIX 11. FORMULAE FOR ESTIMATING RENAL FUNCTION

The Cockcroft-Gault Formula:

FOR SERUM CREATININE CONCENTRATION (SCr) IN MG/DL[a]

Cl_{cr} for males (mL/min) $\quad \frac{(140\text{-age})(\text{weight}^{b})}{(72)(SCr)}$

CL_{cr} for females (mL/min) $\quad \frac{(0.85)(140\text{-age})(\text{weight}^{b})}{(72)(SCr)}$

FOR SERUM CREATININE CONCENTRATION (SCr) IN µMOL/L[a]

Cl_{cr} for males (mL/min) $\quad \frac{(140\text{-age})(\text{weight}^{b})}{(0.81)(SCr)}$

CL_{cr} for females (mL/min) $\quad \frac{(0.85)(140\text{-age})(\text{weight}^{b})}{(0.81)(SCr)}$

a Age in years and weight in kilograms.

b If the subject is obese (>30% over ideal body weight), use ideal body weight in calculation of estimated CL_{cr}.

Source: Cockcroft and Gault 1976
Abbreviation: Clcr/CLcr, creatinine clearance; SC_r, serum creatinine.
Note: The ideal body weight is determined by the local practice and/or guideline.

APPENDIX 12. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group recommendations related to contraception and pregnancy testing in clinical studies include the use of highly effective forms of birth control (Clinical Trials Facilitation Group 2020). These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation
  - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation
  - Oral, injectable, implantable
    Note: Oral birth control pills are not considered a highly effective form of birth control, and if they are selected, they must be used with a second, barrier method of contraception such as condoms with or without spermicide.
- An intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
  Note: This is only considered a highly effective form of birth control when the vasectomized partner is the sole partner of the study participant and there has been a medical assessment confirming surgical success.
  - A sterile male is one for whom azoospermia, in a semen sample, has been demonstrated as definitive evidence of infertility.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment)
  Note: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception, and if used, this method must be used in combination with one of the highly effective forms of birth control listed above.

Definitions of "Women of Childbearing Potential" AND "Women of No Childbearing Potential"

As defined in this protocol, "women of childbearing potential" are female patients who are physiologically capable of becoming pregnant.

Conversely, "women of no childbearing potential" are defined as female patients meeting any of the following criteria:

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
  - < 55 years of age with no spontaneous menses for ≥ 12 months AND with postmenopausal follicle-stimulating hormone (FSH) concentration > 30 mIU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If an FSH measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

Adapted from Clinical Trials Facilitation Group (CTFG) 2014.

APPENDIX 13. LIST OF PROHIBITED CHINESE HERBAL AND PATENT MEDICINES

The following table provides examples of Chinese herbal and patent medications that may be used to treat cancer or that have immune-stimulating properties. **This list is not intended to be all-inclusive.** These medications require a 14-day washout period and should be prohibited during the study.

Drug Name (Chinese)	**Drug Name (English)**
Rg3 参一胶囊	Ginsenoside-Rg3 capsule
养正消积胶囊	Yangzheng Xiaoji Jiaonang
化癥回生口服液	Huazheng Huisheng Koufuye
十全大补汤	Juzentaihoto
华蟾素注射液	Cinobufacini/Huachansu injection
华蟾素片/胶囊	Cinobufacini/Huachansu Pian/Capsules
博尔宁胶囊	Boerning capsule
去甲斑蝥素片	Norcantharidin Pian
参丹散结胶囊	Shendan Sanjie Jiaonang
参芪扶正注射液	Shengqi Fuzheng Zhusheye
参莲胶囊/颗粒	Shen Lian Jiao Nang/Ke Li
吗特灵注射液	Ma Te Ling injection
回生口服液	Hui Sheng Kou Fu Ye
复方斑蝥胶囊	Fufang Banmao Jiaonang
复方红豆杉胶囊	Fufang Hongdoushan Jiaonang
复方苦参注射液	Fufang Kushen Zhusheye
天仙胶囊	Tian Xian capsule
奇宁注射液	Qining injection
威麦宁胶囊	Weimaining Jiao Nang
安尔欣注射液	Anerxin/Ginseng polysaccharide injection
安康欣胶囊	Ankangxin Jiaonang
安替可胶囊	Antike capsule
岩舒注射液	Yanshu injection
平消片/胶囊	Ping Xiao Pian/Jiao Nang
康力欣胶囊	Kanglixin Jiaonang
康艾注射液	Kang’ai Zhusheye
康莱特注射液	Kanglaite Injection

Drug Name (Chinese)	Drug Name (English)
康莱特软胶囊	Kanglaite Soft Capsules
慈丹胶囊	CIDAN Capsule
槐耳颗粒	Huaer Keli
海生素注射液	Haishengsu injection
消癌平丸/片/胶囊/颗粒	Xiaoaiping Wan/Pian/Jiao Nang/Ke Li
消癌平注射液	Xiaoaiping Zhusheye
牛黄醒消丸	Niuhuang Xingxiao pill
猪苓多糖注射液	Polyporus polysaccharide injection
白花蛇舌草注射液	Hedyotis Dissusa wild injection
紫龙金片	Zi Long jin pian
肝复乐片/胶囊	Ganfule Jiaonang/GFL tablet
肿节风片	Zhongjiefeng tablet
胃复春片	Weifuchun pill
艾迪注射液	Ai Di Zhu She Ye
芪珍胶囊	Qizhen Jiaonang
莪术油注射液	Zedoary turmeric oil injection
金复康口服液	Kanglixin Jiaonang
金蒲胶囊	Jinpu capsule
金龙胶囊	Jinlong Capsules
香菇多糖	Lentinan
鸦胆子油乳注射液	Yadanzi/Brucea javanica Youru Zhusheye
鸦胆子油软胶囊/口服乳液	Yadanziyou Ruan jiao nang/Kou Fu Ru Ye

Terminology list: Jiao Nang/Jiaonang, capsule; Ke Li/Keli, granules; Kou Fu Ye/koufuye, oral liquid; Pian, tablet; Wan, pill/bolus; Zhue She ye/Zhusheye, injections

APPENDIX 14. BGB-15025

1. INTRODUCTION - BGB-15025

BGB-15025 is developed as a potent and selective inhibitor of hematopoietic progenitor kinase 1 (HPK1), a hematopoietic cell-restricted serine/threonine protein kinase, which has been reported to serve as a critical negative feedback regulator of T lymphocytes and dendritic cells (DC) activation (Alzabin et al 2009; Shui et al 2007) and appears to be a potential target for immune-oncology therapy. HPK1 is prominently expressed in immune cells such as T cells, B cells, and DC (The Human Protein Atlas). Notably, HPK1 is involved in the progression of a variety of malignant tumorigenesis and disease progression (Yang et al 2006; Alzabin et al 2010).

Furthermore, it has been recently demonstrated that the kinase activity of HPK1 is essential for antitumor immune surveillance and HPK1 blockade as a potential combination with the immune checkpoint inhibitor therapy for effective cancer treatment (Hernandez et al 2018; Liu et al 2019). HPK1 kinase-dead (KD) mice enhanced T-cell receptor (TCR) signaling and effector cytokine secretion with TCR stimulation. Therapeutic co-blockade of HPK1 kinase and programmed death ligand 1 (PD-L1) enhanced T effector cell function, resulting in antiviral responses and tumor growth suppression. Therefore, the kinase activity of HPK1 played a key role in the antitumor immune response and small molecule HPK1 inhibitors can be potentially combined with the immune checkpoint inhibitor therapy for effective cancer treatment.

Refer to the BGB-15025 Investigator's Brochure for additional background on BGB-15025.

1.1. Background Information on BGB-15025

1.1.1 Pharmacology

BGB-15025 potently inhibited HPK1 kinase in biochemical assay, with 50% inhibitory concentration (IC_{50}) of 1.04 nM under Km (Michaelis constant) concentration of adenosine triphosphate. Consistently, BGB-15025 potently inhibited HPK1-mediated SH2 domain-containing leukocyte protein of 76 kDa (SLP76) phosphorylation and increased downstream extracellular signal-regulated kinases (ERK) phosphorylation in Jurkat cells. In consequence, BGB-15025 dose-dependently increased interleukin-2 (IL-2) production in both activated Jurkat cells and peripheral blood mononuclear cells (PBMCs). BGB-15025 was screened against a panel of 57 human kinases in biochemical assays and a SafetyScreen87 panel (Eurofins Panlabs Discovery Services Taiwan, Ltd.) for 87 primary molecular targets including G protein-coupled receptors, transporters, ion channels, nuclear receptors, and other nonkinase enzymes. BGB-15025 was identified as a selective inhibitor of HPK1.

In in vivo pharmacodynamic studies, oral administration of BGB-15025 demonstrated a dose-dependent phosphorylated SLP76 (pSLP76) inhibition in splenic T cells and serum IL-2 level increase. In vivo efficacy studies demonstrated that BGB-15025, in combination with an anti-programmed cell death protein-1 (anti-PD-1) antibody, induced potent antitumor effects against the syngeneic CT26 wild type (WT) tumors in mice at as low as 1 mg/kg. In addition, BGB-15025 demonstrated dose-dependent antitumor effects in the syngeneic GL261 tumor model.

The inhibition of BGB-15025 on the human ether-à-go-go-related gene (hERG) channel appeared to be moderate with an IC_{50} of 8.9 μM. No BGB-15025-related effects on the central nervous system or respiratory system were noted in Sprague Dawley rats following single oral doses up to 100 mg/kg. No BGB-15025-related effects on blood pressure, heart rate, electrocardiogram (ECG) parameters, or qualitative ECG waveforms were noted in cynomolgus monkeys at doses up to 100 mg/kg via telemetry. Moreover, no BGB-15025-related changes in ECG were noted in monkeys at repeated oral doses up to 100 mg/kg/day for 28 days. Based on the ECG data from single and repeated-dose studies in monkeys, and the hERG assay result, the risk of corrected QT interval (QTc) prolongation is considered low.

1.1.2. Toxicology

Based on International Council for Harmonisation (ICH) S9, all the available toxicological studies and data are considered adequate to support the in-patient dosing and the clinical development of BGB-15025 for treatment of patients with advanced cancer. All pivotal toxicology studies were conducted in compliance with Good Laboratory Practices (GLP) regulations/principles.

In the single-dose studies in rats and in monkeys orally administered BGB-15025 at doses of 1000 mg/kg, no test article-related adverse effects or apparent treatment-related toxicity were noted. The maximum tolerance dose (MTD) was considered to be 1000 mg/kg.

In the 14-day repeat-dose studies in rats and in monkeys orally administered BGB-15025 at doses of 30, 100, or 300/200 mg/kg/day, no test article-related adverse effects were noted at doses of ≤ 100 mg/kg/day. The no observed adverse effect level (NOAEL)/MTD was considered to be 100 mg/kg/day.

In the 28-day repeat-dose studies in rats and in monkeys orally administered BGB-15025 at doses of 10, 30, or 100 mg/kg/day, no mortality in rats was noted and one moribundity in monkeys was noted at the dose of 100 mg/kg/day. The MTD was considered to be 100 mg/kg/day and NOAEL was considered to be 30 mg/kg/day in rats, while the NOAEL/MTD was considered to be 30 mg/kg/day in monkeys.

Because BGB-15025 absorbed wavelengths between 290 and 382 nm with a molar extinction coefficient (MEC) greater than 1000 L/mol/cm, according to the ICH S10 photosafety evaluation guideline, an in vitro phototoxicity study was conducted in 3T3 cells using the neutral red uptake phototoxicity test and demonstrated a positive result for BGB-15025. A follow-up in a preclinical in vivo phototoxicity study is planned to verify the phototoxicity potential of BGB-15025 in vivo and its relevance to humans.

In the human PBMC-based cytokine release assay, compared with the negative control (0.01% DMSO), 10 nM of BGB-15025 did not induce any increase of tested cytokines or chemokines, while 100 nM of BGB-15025 only slightly increased IL-8 production (1.6 fold). The results suggested that BGB-15025 had a low risk for causing cytokine release syndrome because of peripheral immune stimulation.

The systemic exposure ($AUC_{0\text{-}24h}$ and C_{max}) increased slightly less than dose proportionally in rats and monkeys. No marked sex differences or drug accumulation was noted.

Refer to the BGB-15025 Investigator's Brochure for detailed information regarding toxicology studies.

1.1.3 Clinical Pharmacology

BGB-15025 is being studied in Study BGB-A317-15025-101 (referred to as Study 101 hereafter). This clinical study is being conducted in compliance with Good Clinical Practice. BGB-15025 was administered using capsule formulation containing free base drug substance in global ex-China cohorts 1A to 6A and 1B to 3B, and in China cohorts 3A to 5A. BGB-15025 was administered using tablet formulation containing citrate drug substance in global ex-China cohorts 7A and 4B. The exposures of BGB-15025 tablets [redacted] are generally comparable to those of BGB-15025 capsules [redacted], respectively.

As of the data cutoff date of 10 January 2023, the preliminary pharmacokinetic (PK) data have shown that BGB-15025 (capsule formulation) is absorbed after oral administration with C_{max} reaching approximately 4 hours after dosing. Both the C_{max} and AUC_{0-24} during BGB-15025 monotherapy increased in an approximately dose-proportional manner [redacted] once daily and in a less than dose proportional manner [redacted] once daily in global ex-China cohorts. In contrast, BGB-15025 PK exposures increased approximately dose proportionally [redacted] after single doses in China cohorts. These differences are likely because of PK variability and the small cohort sizes. Preliminary population PK analysis indicated no significant PK differences between the global ex-China and China cohorts. The mean elimination half-life ($t_{1/2}$) across the doses evaluated was approximately 13 hours. Consistent with its $t_{1/2}$, minimal accumulation of plasma exposure was observed after repeated dosing once daily compared to that after a single dose. In comparison, the steady-state AUC_{0-24hr} following [redacted] is approximately 2.6-fold of that after a single dose. The active metabolite BGB-21958 showed similar $t_{1/2}$ to BGB-15025 with its mean exposure ranging from 18% to 40% of BGB-15025 across cohorts. In addition, BGB-15025 exposure and elimination half-life values across the China cohorts after single and multiple doses in general are comparable to those in the global ex-China cohorts, indicating that race may not impact BGB-15025 plasma exposure.

Refer to the BGB-15025 Investigator's Brochure for detailed information regarding clinical pharmacology studies.

1.1.4. Prior Clinical Experience with BGB-15025

Study 101 is an open-label, multicenter, and nonrandomized Phase 1a/1b clinical study to investigate the safety, tolerability, PK, and preliminary antitumor activity of BGB-15025 alone and in combination with tislelizumab in patients with advanced solid tumors.

The study is designed to include 2 phases:

- Phase 1a, a dose-escalation phase to assess the safety and tolerability and determine the MTD or maximum administered dose (MAD) and recommended dose(s) for expansion (RDFE[s]) of BGB-15025 alone and in combination with tislelizumab in patients with advanced solid tumors.

- Phase 1b, a dose-expansion phase to assess the overall response rate (ORR) per Response Evaluation Criteria in Solid Tumor Version 1.1 (RECIST v1.1) for BGB-15025 alone and in combination with tislelizumab with or without chemotherapy in patients with advanced solid tumors.

1.1.4.1. Safety Assessment of BGB-15025

As of 14 January 2023, 81 patients have been dosed in Australia, New Zealand, the United States of America, and China. Fifty-five patients were dosed with BGB-15025 monotherapy and 26 patients were dosed with BGB-15025 plus tislelizumab at enrollment. Among the 55 patients who received BGB-15025 monotherapy, 14 patients switched to tislelizumab, 2 patients switched to BGB-15025 [redacted] in combination with tislelizumab, and 4 patients switched to BGB-15025 [redacted] in combination with tislelizumab.

BGB-15025 monotherapy

Of the 55 patients with BGB-15025 monotherapy, treatment-emergent adverse events (TEAEs) were reported in 53 patients (96.4%). TEAEs identified in 37 patients (67.3%) were considered to be treatment related. Grade 3 or higher TEAEs were reported in 23 patients (41.8%) and 4 patients (7.3%) experienced a ≥ Grade 3 TEAE considered treatment related. Serious TEAEs were reported in 24 patients (43.6%), and 4 patients (7.3%) experienced ≥ 1 serious TEAE considered treatment related.

The Grade 3 or higher TEAEs occurring in ≥ 2 patients with BGB-15025 monotherapy by PT were Anaemia (4 patients, 7.3%), Abdominal pain (3 patients, 5.5%), Dyspnoea (2 patients, 3.6%), Pleural effusion (2 patients, 3.6%), and Pneumonia (2 patients, 3.6%).

Treatment-emergent immune-mediated AEs (imAEs) were reported in 9 patients (16.4%). All 9 treatment-emergent imAEs were considered to be treatment related. As of the data cutoff date, 1 Grade 3 or higher treatment-emergent imAE (1.8%) was observed and considered treatment related. No serious treatment-emergent imAE was observed. Two treatment-emergent imAEs (3.6%) were reported leading to treatment modification. No treatment-emergent imAEs leading to death or treatment discontinuation were reported. The reported treatment-emergent imAE occurring in ≥ 2 patients by PT was Pruritus (3 patients, 5.5%).

TEAEs leading to death were reported in 4 patients (7.3%), but no treatment-related TEAE leading to death was reported. TEAEs leading to treatment modification were reported in 23 patients (41.8%). No TEAE leading to treatment discontinuation was reported. No dose-limiting toxicity (DLT) was observed as of the data cutoff date.

BGB-15025 in combination with tislelizumab

Of the 26 patients with BGB-15025 plus tislelizumab combination therapy, TEAEs were reported in 25 patients (96.2%). TEAEs identified in 20 patients (76.9%) were considered to be treatment related. Grade 3 or higher TEAEs were reported in 14 patients (53.8%), and 7 patients (26.9%) experienced a ≥ Grade 3 TEAE considered treatment related. Serious TEAEs were reported in 13 patients (50.0%), and 6 patients (23.1%) experienced ≥ 1 serious TEAE considered treatment related.

The Grade 3 or higher TEAEs occurring in ≥ 2 patients by PT were Alanine aminotransferase increased (3 patients, 11.5%), Aspartate aminotransferase increased (3 patients, 11.5%),

Diarrhoea (2 patients, 7.7%), Blood bilirubin increased (2 patients, 7.7%), Dyspnoea (2 patients, 7.7%), and Rash (2 patients, 7.7%).

Treatment-emergent imAEs were reported in 12 patients (46.2%). All 12 treatment-emergent imAEs were considered to be treatment related. As of the data cutoff date, 5 Grade 3 or higher treatment-emergent imAEs were observed and considered treatment related. Five serious treatment-emergent imAEs were observed and considered treatment related. Three patients experienced DLTs as of the data cutoff date. No treatment-emergent imAEs were reported leading to death. The reported treatment-emergent imAEs occurring in ≥ 2 patients by PT were Alanine aminotransferase increased (4 patients, 15.4%), Aspartate aminotransferase increased (3 patients, 11.5%), Uveitis (2 patients, 7.7%), Diarrhoea (2 patients, 7.7%), and Rash (2 patients, 7.7%).

TEAEs leading to death were reported in 4 patients (15.4%), but no treatment-related TEAE leading to death was reported. TEAEs leading to treatment discontinuation were reported in 5 patients (19.2%). TEAEs leading to treatment modification were reported in 17 patients (65.4%). Four patients experienced DLTs as of the data cutoff date. One infusion-related reaction was reported.

1.2. BGB-15025 Rationales

1.2.1. Rationale for BGB-15025 in Combination With BGB-A445

Half of the non-small cell lung cancer (NSCLC) patients receive primary or secondary checkpoint inhibitor (CPI)-based therapies and almost all of them inevitably develop disease progression or relapse after CPI-based therapies. Two main mechanisms have been revealed for the CPI resistance in NSCLC, which include: 1) the lack of sufficient T-cell proliferation and activation, and 2) an immunosuppressive tumor microenvironment (TME) that is characterized by high levels of immune-suppressing cytokines and/or metabolites with high levels of immune-suppressive cells.

The kinase activity of HPK1 has been recently demonstrated to play an important role in antitumor immune surveillance, and the HPK1 blockade could be a potential modality in combination with CPI including anti-PD-(L)1 therapy for effective cancer treatment (Hernandez et al 2018; Liu et al 2019). BGB-15025, as a highly potent and selective HPK1 kinase inhibitor, is hypothesized to modulate the TME by activating the CD4+ and CD8+ T cells; in vitro, BGB-A445 in combination with BGB-15025 has demonstrated a dual combo effect in human peripheral blood mononuclear cells activation assay in preclinical studies.

Therefore, BGB-15025 may be potentially effective for anti-PD-(L)1-pretreated NSCLC in combination with BGB-A445, which can also modulate the TME by targeting the different signal pathway.

1.2.2. Rationale for Selection of BGB-15025 Dose

BGB-15025 will be administered at a dose no higher than the highest confirmed safe dose in the Phase 1 Study BGB-A317-15025-101. The dose [redacted] was selected based on the acceptable safety and tolerability observed in patients in the ongoing Phase 1 Study 101. Additional dose levels may be explored in Stage 2 if indicated based on emerging clinical data from the ongoing Study 101.

1.2.3. Rationale for Biomarker Strategy

Biomarker analyses will be performed to study the following aspects of BGB-A445 in combination with BGB-15025: 1) treatment effects induced in patients, and 2) biomarkers predictive of or correlated with response or resistance (exploratory). HPK1 inhibitors have been shown to enhance immune cell activation and increase pro-inflammatory cytokines secretion. Cytokines secreted by these immune cell subsets may be evaluated through cytokine analysis in blood. Treatment effects may be evaluated by comparing cytokines, circulating tumor DNA (ctDNA), tumor mutation burden (TMB), microsatellite instability (MSI), and gene alterations in peripheral blood before, during, and post treatment. Cluster of differentiation 8 (CD8), PD-L1, HPK1, and OX40 expression level at baseline and/or changed levels upon treatment in tumor tissue by immunohistochemistry may serve as predictive biomarkers. TMB, MSI, gene alterations, gene expression profiles, and tumor infiltrating lymphocytes may be explored in these tissues as possible predictive biomarkers.

1.3. Benefit-Risk Assessment of BGB-15025

Nonclinical experience with BGB-15025 suggests that patients may experience gastrointestinal toxicity, potential abnormal liver function based on minimal to mild multifocal centrilobular hepatocellular degeneration/necrosis, and potential skin phototoxicity. Patients who are enrolled in this study must be closely monitored for these potential adverse events (AEs). As of the data cutoff date (14 January 2023) for the most recent BGB-15025 Investigator's Brochure, available clinical safety and tolerability data suggest that risks observed in patients treated with BGB-15025 as monotherapy or in combination with tislelizumab are manageable.

Based upon the mechanism(s) of action, preclinical efficacy data suggest that BGB-15025 could inhibit the growth of solid tumors in combination with the anti-OX40 antibody. BGB-15025 administered in combination with BGB-A445 is unlikely to result in clinically relevant drug-drug interactions (DDI) based on absorption, metabolism, elimination, or protein binding. The GLP toxicity studies demonstrated sufficient safety margins by comparing the exposures of tolerable doses in toxicity studies and the predicted human efficacious dose in solid tumors. In summary, given the unmet medical need and limited treatment options for these patients, the anticipated benefit/risk of BGB-15025 in combination with BGB-A445 is considered favorable.

2. STUDY OBJECTIVES AND ENDPOINTS

No BGB-15025-specific content.

3. STUDY DESIGN

A safety lead-in is planned for the combination of BGB-A445 and BGB-15025. The details can be found in Section 3.4.

During the safety lead-in, please refer to §Section 5.2 for the detailed schedule of administration.

If the combination of BGB-A445 and BGB-15025 is deemed not tolerable, the dose of BGB-15025 will be reduced to [redacted] combined with [redacted] BGB-A445 for further evaluation. The stopping rules described in Section 9.8 will be applied in the further evaluation.

4. STUDY POPULATION

No BGB-15025-specific content.

5. STUDY TREATMENT – BGB-15025

5.1. Formulation, Packaging, Labeling, and Handling

BGB-15025 will be provided as [redacted]. BGB-15025 tablets are packaged in high-density polyethylene bottles with induction-seals and child-resistant caps.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drugs must be stored at the condition specified on the label.

Refer to the Pharmacy Manual for details regarding administration, accountability, and disposal. Please also refer to the BGB-15025 Investigator's Brochure for other details regarding BGB-15025.

5.2. Dosage, Administration, and Compliance

BGB-15025 will be self-administered orally at the recommended dose [redacted] once a day.

In this study, BGB-15025 will be self-administered in combination with BGB-A445. The dosing selection and timing for BGB-15025 in combination with BGB-A445 are provided in §Table 1.

§Table 1: Selection and Timing of Dose for Study Drug

Study Drug	Dose	Frequency and Sequence of Administration	Route of Administration
BGB-A445	[redacted]	Day 1 of each cycle (3 weeks)	Intravenous infusion
BGB-15025	[redacted]	Once daily in each cycle (3 weeks) Administer before BGB-A445	Orally

Specific instructions for product preparation, storage, and administration are provided in the Pharmacy Manual.

On the day when the administration of BGB-A445 is scheduled, the patient will take the daily dose of BGB-15025 before receiving BGB-A445. Dosing administration and monitoring times are provided in §Table 2.

Monitoring must occur in an area where emergency medical equipment and appropriately trained staff are available. If the infusion of BGB-A445 is well tolerated in the first cycle, duration of infusion and monitoring time can be decreased in subsequent cycles, as outlined in §Table 2.

§Table 2: Administration of BGB-15025 and BGB-A445 and Monitoring Time

Cycle	BGB-15025 and BGB-A445 Combination
Cycle 1, Cycle 2, and Cycle 3 Day 1	BGB-15025 oral administration BGB-A445 infusion 60 (± 5) minutes Patient monitoring for ≥ 120 minutes
Cycle 4 Day 1 Onwards	BGB-15025 oral administration BGB-A445 infusion 30 (± 5) minutes Patient monitoring for ≥ 30 minutes

Note: The infusion rate of BGB-A445 may be decreased or the infusion may be stopped in the event of an infusion-related reaction.

5.3. Overdose

No BGB-15025-specific content.

5.4. Dose Delay and Modification for BGB-15025

Dose Delay for BGB-15025

BGB-15025 is administered in combination with BGB-A445.

Please refer to Section 5.4.1.1 for the details of BGB-A445 dose delay.

BGB-15025 may be temporarily suspended if the patient experiences a toxicity that requires a dose to be withheld for toxicity deemed solely related to BGB-15025. BGB-15025 should resume as soon as possible after AEs recover to baseline or Grade 1 (whichever is more severe) after the last dose of BGB-15025. BGB-15025 may be resumed at the same dose or at a reduced dose, depending on the toxicity, grade, prior events, and number of dose reductions.

If a dose delay for BGB-A445 is required, the treatment of BGB-15025 may continue. Resumption of BGB-A445 after dose interruption because of BGB-A445-related toxicity requires consultation with the medical monitor. Study drug(s) may be resumed only after discussion with the medical monitor and approval by the sponsor.

If a dose delay for BGB-15025 is required, BGB-A445 and tislelizumab treatment may continue.

If, in the opinion of the investigator, the toxicity may be related to both study drugs (BGB-A445 and BGB-15025), then the most conservative guidance should be followed until the toxicity is resolved to baseline level or Grade 1 (whichever is more severe).

Exceptions may be considered following consultation between the investigator and the medical monitor.

When treatment is delayed, the next cycle, including assessments scheduled for that cycle, will be delayed until the patient receives study treatment of BGB-A445. For example, if a patient comes in for C2D1 but treatment of BGB-A445 is delayed, the counting of C2D1 will not commence until the patient resumes study treatment of BGB-A445. Accordingly, the day study treatment of BGB-A445 is given will be considered C2D1. In such cases, patients should continue with safety assessments (Appendix 1) according to the most recent cycle in which they received study treatment. Such assessments should be entered into the electronic data capture system as unscheduled assessments.

5.4.1. Dose Delay for BGB-15025

In the event of significant toxicities, dosing may be modified based on the guidelines described in §Table 3.

§Table 3: Management of Non-Immune-Mediated Adverse Events

System	Adverse event	Toxicity management	Study treatment management
Hematologic	**Anemia** Grade 3	Treat with appropriate supportive care as medically indicated.	Hold study treatment until resolved to Hgb ≥ 9 g/dL. If resolved ≤ 7 days, then maintain current dosage. If resolved > 7 days, decrease BGB-15025 treatment by 1 dose level.
	Anemia Grade 4	Maximize supportive therapy until Hgb ≥ 9 g/dL.	Hold study treatment until resolved to Hgb ≥ 9 g/dL. After resolution, decrease BGB-15025 by 1 dose level.
	Neutropenia (ANC decrease) Grade 3	Treat with appropriate supportive care as medically indicated until ANC ≥ 1000/mm^3.	Hold study treatment until resolved to ANC ≥ 1000/mm^3 or baseline. If resolved in ≤ 7 days, then maintain current dosage. If resolved in > 7 days, then decrease BGB-15025 by 1 dose level.
	Neutropenia (ANC decrease) Grade 4	Maximize appropriate supportive therapy until ANC ≥ 1000/mm^3.	Hold study treatment until resolved to ANC ≥ 1000/mm^3 or baseline. After resolution, decrease BGB-15025 by 1 dose level.
	Febrile neutropenia ≥ Grade 3	Maximize appropriate supportive therapy. Rule out other etiologies of fever.	Hold study treatment until neutrophil count ≥ 1000/mm^3. After resolution, decrease BGB-15025 by 1 dose level. For Grade 4 event, discontinue treatment.
	Thrombocytopenia (platelet count decrease) Grade 2	Monitor and treat with appropriate supportive care as medically indicated.	Maintain current dosage if no concerns of clinically significant risk of bleeding; continue to monitor using additional hematology assessments as required.
	Thrombocytopenia (platelet count decrease) Grade 3	Treat with appropriate supportive care as medically indicated.	Hold study treatment until resolved to ≤ Grade 1 or baseline. After resolution, decrease BGB-15025 by 1 dose level.
	Thrombocytopenia (platelet count decrease) Grade 4	Treat with appropriate supportive care as medically indicated.	Hold study treatment until resolved to ≤ Grade 1 or baseline. After resolution, decrease BGB-15025 by 1 dose level.

System	Adverse event	Toxicity management	Study treatment management
	Other hematologic event Grade 3	Treat with appropriate supportive care as medically indicated.	Hold study treatment. If improved to ≤ Grade 1 or baseline, decrease BGB-15025 treatment by 1 dose level. If event recurs at the reduced dose after receiving optimal supportive care, permanently discontinue study treatment.
	First occurrence of other hematologic Grade 4 event	Treat with appropriate supportive care as medically indicated.	Hold study treatment until improved to ≤ Grade 1 or baseline. After resolution, decrease BGB-15025 by 1 dose level, or permanently discontinue study treatment.
	Other recurrent hematologic Grade 4 event	Treat with appropriate supportive care as medically indicated.	Permanently discontinue study treatment.
Nonhematologic	**Non-hematologic event** Grade 3	Treat with appropriate supportive care as medically indicated.	Hold study treatment. If improved to ≤ Grade 1 or baseline, decrease BGB-15025 treatment by 1 dose level. If event recurs at the reduced dose after receiving optimal supportive care, permanently discontinue study treatment.
	First occurrence of non-hematologic Grade 4 event	Treat with appropriate supportive care as medically indicated.	Hold study treatment until improved to ≤ Grade 1 or baseline. After resolution, decrease BGB-15025 by 1 dose level, or permanently discontinue study treatment.
	Recurrent non-hematologic Grade 4 event	Treat with appropriate supportive care as medically indicated.	Permanently discontinue study treatment.

Abbreviations: ANC, absolute neutrophil count; Hgb, hemoglobin.

After any interruption, BGB-15025 may be resumed at the same dose or at a reduced dose, depending on the toxicity, grade, prior events, and number of dose reductions.

In general, a dose should be reduced to the next immediate lower dose level that was previously determined to be tolerable (§Table 4). A patient must discontinue BGB-15025 if the toxicity recurs with the same or worse severity after BGB-15025 is resumed at a lower dose.

A patient may have a maximum of 1 dose reduction for BGB-15025. For these patients, treatment with BGB-15025 may be continued after consultation and approval by the sponsor.

§Table 4: BGB-15025 Dose Reduction Levels

	Dose		Frequency of Administration
Initial dose level [a]	[redacted]	[redacted] [b]	Once daily every 3 weeks
Dose Reduction 1	[redacted] [b]	Discontinue BGB-15025	
Dose Reduction 2	Discontinue BGB-15025	N/A	N/A

Abbreviations: N/A, not applicable.
[a] The initial dose level of BGB-15025 depends on the evaluation in the safety lead-in.
[b] BGB-15025 must be discontinued if, after it is resumed at a lower dose, the toxicity recurs with the same or worse severity.

6. PRIOR AND CONCOMITANT THERAPY – BGB-15025

6.1. Permitted Concomitant Medications, Prohibited Concomitant Medications, and Restricted Concomitant Medications

Medications/Procedures Prohibited to be Used With BGB-15025

- Any herbal or prescription medications known to be strong inhibitors or inducers of CYP3A enzymes should be avoided during the study (see §Appendix 1)
- Any herbal or prescription medications known to be strong inhibitors of P-gp should be avoided during the study (see §Appendix 2)
- Drugs known to prolong QT/QTc interval should be avoided in the study (see §Appendix 3).

Medication to be Used with Caution

- Any herbal or prescription medications known to be moderate inhibitors or inducers of CYP3A enzymes (see §Appendix 1)
- Any herbal or prescription medications known to be moderate P-gp inhibitors (see §Appendix 2)

6.2. Potential Interactions Between the Study Drugs and Concomitant Medications

The potential for drug-drug interaction between BGB-A445 and BGB-15025 is very low, given BGB-A445 is a therapeutic monoclonal antibody. BGB-A445 is unlikely to have an effect on drug metabolizing enzymes or transporters because it is expected to be degraded into amino acids and recycled into other proteins.

7. STUDY ASSESSMENTS AND PROCEDURES

No BGB-15025-specific content.

8. SAFETY MONITORING AND REPORTING - BGB-15025

8.1. Risks Associated With BGB-15025

BGB-15025 is being evaluated in the first-in-human study. According to the nonclinical data, gastrointestinal toxicity is the major finding. Gastrointestinal toxicities (including vomitus, diarrhea, depressed foci [focal erosion] in mucosa of the stomach, dilated cecum/colon, and mucosal single cell necrosis of cecum/colon/rectum) were noted in both species of rats and monkeys. Gastrointestinal toxicities should be closely monitored in clinical trials. Initial findings of gastrointestinal toxicity observed in the clinical trial have been mostly of low grade.

Increases in liver weights and minimal to mild multifocal centrilobular hepatocellular degeneration/necrosis were noted in rats at 100 mg/kg/day, which had a 15- to 17-fold margin of predicted human exposure at the first-in-human starting dose of 20 mg. Although no obvious alterations in liver functional serum chemistry parameters were noted, close monitoring of changes in serum chemistry values and other liver toxicity signs in clinical studies is highly recommended. Initial findings of liver toxicity observed in the clinical trial have been mostly of low grade.

BGB-15025 phototoxicity was evaluated in accordance with ICH S10. The initial evaluation was based on the photochemical properties of this product. The molar extinction coefficient of BGB-15025 was greater than 1000 $L \cdot moL^{-1} \cdot cm^{-1}$ between 290 nm and 382 nm; a potential phototoxicity risk in skin is considered based on ICH S10. Patients should be advised to minimize exposure to the sun and use sunscreen. Patients should be monitored for potential skin phototoxicity.

8.2. Pregnancies – BGB-15025

No BGB-15025-specific content.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

No BGB-15025-specific content.

10. STUDY COMMITTEES AND COMMUNICATION

No BGB-15025-specific content.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

No BGB-15025-specific content.

12. QUALITY ASSURANCE AND QUALITY CONTROL

No BGB-15025-specific content.

13. ETHICS/PROTECTION OF HUMAN PATIENTS

No BGB-15025-specific content.

14. DATA HANDLING AND RECORD KEEPING

No BGB-15025-specific content.

15. REFERENCES

Alzabin S, Bhardwaj N, Kiefer F, et al. Hematopoietic progenitor kinase 1 is a negative regulator of dendritic cell activation. J Immunol. 2009;182(10):6187-94.

Alzabin S, Pyarajan S, Yee H, et al. Hematopoietic progenitor kinase 1 is a critical component of prostaglandin E2-mediated suppression of the anti-tumor immune response. Cancer Immunol Immunother. 2010;59(3):419-29.

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. 2007. http://medicine.iupui.edu/clinpharm/ddis/main-table/. Accessed 02 May 2022.

Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Drug Development and Drug Interactions and Inducers. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed 02 May 2022.

Hernandez S, Qing J, Thibodeau RH, et al. The kinase activity of hematopoietic progenitor kinase 1 is essential for the regulation of T cell function. Cell Rep. 2018;25(1):80-94.

Liu J, Curtin J, You D, et al. Critical role of kinase activity of hematopoietic progenitor kinase 1 in anti-tumor immune surveillance. PLoS One. 2019;14(3):e0212670.

Shui JW, Boomer JS, Han J, et al. Hematopoietic progenitor kinase 1 negatively regulates T cell receptor signaling and T cell-mediated immune responses. Nat Immunol. 2007;8(1):84-91.

Woosley RL, Heise CW, Gallo T, et al. QTdrugs List. 2013. www.CredibleMeds.org. Accessed 01 December 2020.

Yang HS, Matthews CP, Clair T, et al. Tumorigenesis suppressor Pdcd4 down-regulates mitogen-activated protein kinase kinase kinase kinase 1 expression to suppress colon carcinoma cell invasion. Mol Cell Biol. 2006;26(4):1297-306.

16. Appendices

16.1. §Appendix 1: CYP3A Inhibitors and Inducers

Strong CYP3A Inhibitors (To Be Avoided)
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat [a], conivaptan, elvitegravir, idelalisib, nefazodone
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir [a], saquinavir, tipranavir
Moderate CYP3A Inhibitors (To Be Used With Caution)
Antibiotics: ciprofloxacin, erythromycin [b]
Antifungals: fluconazole, clotrimazole
Protease inhibitors: amprenavir, atazanavir, fosamprenavir
Calcium channel blockers: diltiazem, verapamil [b]
Tyrosine kinase inhibitors (anticancer): imatinib, crizotinib
Others: amiodarone [b], aprepitant, casopitant, cimetidine, cyclosporine, dronedarone [b], tofisopam
Food products: grapefruit juice, Seville oranges or their juices
Strong CYP3A Inducers (To Be Avoided)
Carbamazepine, oxcarbazepine, enzalutamide, mitotane, phenytoin, phenobarbital, rifampin (rifampicin), St. John's wort (*Hypericum perforatum*)
Moderate CYP3A Inducers (To Be Used With Caution)
Avasimibe, bosentan, efavirenz, etravirine, modafinil, rifabutin

Source: FDA Drug Development and Drug Interactions.

Abbreviations: CYP3A, cytochrome P450 family 3 subfamily A; P-gp, p-glycoprotein

Note: For a more complete list, please refer to the Flockhart Table (Flockhart 2007).
The list of drugs in this table is not exhaustive. Please refer to the prescribing information and Summary of Product Characteristics to check for CYP3A inhibition or induction risks or contact the medical monitor.

[a] Ritonavir and cobicistat are usually given in combination with other antiviral drugs in clinical practice.

[b] The drugs will be avoided due to the strong inhibition of P-gp during coadministration with BGB-15025.

16.2. §Appendix 2: P-glycoprotein Inhibitors

Strong P-gp Inhibitors (To Be Avoided)
Antibiotics: clarithromycin, tetracycline, gentamicin, erythromycin
Antifungals: itraconazole, posaconazole
Antivirals: telaprevir and cobicistat [a]
Cardiovascular drugs: amiodarone, dronedarone, carvedilol, verapamil, captopril, quinidine, propafenone, ranolazine
Protease inhibitors: ritonavir [a], lopinavir and ritonavir, saquinavir and ritonavir, tipranavir and ritonavir
Other: lapatinib, vemurafenib, flibanserin
Moderate P-gp Inhibitors (To Be Used With Caution)
Antibiotics: trimethoprim, telithromycin
Antivirals: saquinavir, velpatasvir
Cardiovascular drugs: diltiazem, tolvaptan, conivaptan, ticagrelor, atorvastatin
Blood pressure: spironolactone, telmisartan, nifedipine
Proton-pump inhibitor: rabeprazole
Other: indomethacin, nefazodone, quinine, propantheline, mirabegron

Source: University of Washington, drug-drug interaction database and FDA Drug Development and Drug Interactions.
Abbreviation: P-gp, P-glycoprotein.
Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information and Summary of Product Characteristics to check for P-gp inhibition risks or contact the medical monitor.
[a] Ritonavir and cobicistat are usually given in combination with other antiviral drugs in clinical practice.

16.3. §Appendix 3: Drugs With a Known Risk of QT Prolongation/Torsades de Pointes

The text below was obtained from sources as follows: Woosley et al 2013 and Flockhart 2007.

Bold font indicates medications or substances that might be relatively commonly used.

- amiodarone
- anagrelide
- arsenic trioxide
- astemizole (off United States [US] market)
- azithromycin
- bepridil (off US market)
- chloroquine
- chlorpromazine
- cilostazol
- ciprofloxacin
- cisapride (off US market)
- citalopram
- clarithromycin
- cocaine
- disopyramide
- dofetilide
- domperidone (not on US market)
- donepezil
- dronedarone
- droperidol
- erythromycin
- escitalopram
- flecainide
- fluconazole
- gatifloxacin (off US market)
- grepafloxacin (not on US market)
- halofantrine (not on US market)
- ibutilide
- levofloxacin
- levomepromazine/ methotrimeprazine (not on US market)
- levomethadyl (off US market)
- levosulpiride (not on US market)
- mesoridazine (off US market)
- **methadone**
- moxifloxacin
- **ondansetron**
- oxaliplatin
- pentamidine
- pimozide
- probucol (off US market)
- procainamide
- propofol
- quinidine
- roxithromycin (not on US market)
- sevoflurane
- sotalol
- sparfloxacin (off US market)
- sulpiride (not on US market)
- sultopride (non on US market)
- terfenadine (off US market)
- terlipressin (not on US market)
- terodiline (not on US market)

- haloperidol
- ibogaine (not on US market)
- thioridazine
- vandetanib

Signature Page for VV-CLIN-112506 v4.0

Approval with eSignature	[redacted] Clinical Development 30-Sep-2024 15:33:23 GMT+0000

Signature Page for VV-CLIN-112506 v4.0

BGB-LC-203
PROTOCOL AMENDMENT 1.0
SUMMARY OF CHANGES

Study Title: A Phase 2, Open-label, Randomized, Multi-arm Study of BGB-A445 in Combination With Investigational Agents in Non-Small Cell Lung Cancer Patients Previously Treated With Anti-PD-(L)1 Antibody

BeiGene, Ltd., has updated the BGB-LC-203 protocol from Original Protocol 0.0 (30 March 2023) to Protocol Amendment 1.0 (15 May 2023). The primary purposes for this update are as follows:

- To revise the starting dose of sitravatinib in combination with BGB-A445 and tislelizumab
- To specify the inclusion criteria and exclusion criteria related to sitravatinib
- To clarify the details of some assessments

Overall, editorial and format changes have been made throughout to enhance clarity and readability.

Key changes made are summarized by protocol section in the table below. Additions are in **bold text** and deletions are designated by ~~strike through text.~~

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Cover Page	Changed protocol version and dates	To update the protocol version	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Appendix 13 SITRAVATINIB: Section 1.2.2 Rationale for Selection of Sitravatinib Dose Section 5.2 Dosage, Administration, and Compliance §Table 3 Section 5.4.2 Dose Modification for Sitravatinib §Table 5	Updated the starting dose of sitravatinib in combination with BGB-A445 and tislelizumab from 100 mg to 70 mg	To update the starting dose of sitravatinib in combination with BGB-A445 and tislelizumab for improved tolerability of the combination.	Y	Potential impact on the study conduct and on patient safety
Appendix 13 SITRAVATINIB: Section 1.2.2 Rationale for Selection of Sitravatinib Dose	Given the low potential of pharmacokinetic and pharmacodynamic drug-drug interactions among sitravatinib, tislelizumab, and BGB-A445, ~~and no critical safety findings observed in clinical studies where tislelizumab is combined with sitravatinib or BGB-A445,~~ these doses will be adopted for the combination of three study drugs in this study.	To update the rationale for selection of starting doses based on the latest information from ongoing studies	N	N/A
Section 4.1 Inclusion Criteria #8	**c. Urinary protein < 2+ by urine dipstick. If dipstick is ≥ 2+, then 24-hour urinary protein must be < 1 g per 24 hours**	To update the inclusion criteria based on the proteinuria risk associated with sitravatinib	Y	Potential impact on the study conduct and on patient safety

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Section 4.2 Exclusion Criteria #19	g. **Patients with inadequately controlled** ~~Uncontrolled~~ hypertension **(defined as average systolic blood pressure [BP] ≥ 150 mmHg and/or diastolic BP ≥ 100 mmHg)** ~~that cannot be managed by standard antihypertension medications~~ ≤ 28 days before randomization **Note: Antihypertensive therapy to achieve these parameters is allowable.**	To provide more specific eligibility requirements for blood pressure condition	Y	Potential impact on the study conduct and on patient safety
	h. Any prior history of hypertensive crisis	To provide more specific eligibility requirements for blood pressure condition	Y	Potential impact on the study conduct and on patient safety
	j. QT interval corrected by Fridericia's method (QTcF) > ~~470~~ **450** msec Note: If a patient has QTcF interval > ~~470~~ **450** msec on an initial ECG, a follow-up ECG will be performed to confirm the result.	To update for consistency with CTCAE	Y	Potential impact on the study conduct and on patient safety
Section 5.4.1 Dose Delay	Tumor assessments should continue as scheduled, which is every 6 weeks **(± 7 days)** from randomization for the first 9 months, and every 12 weeks (± 7 days) thereafter.	To keep the contents consistent throughout the protocol	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Section 7.3.7 Electrocardiograms	~~At each timepoint (see Appendix 1), 3~~ **Three** consecutive 12-lead ECGs will be performed approximately 2 to 3 minutes apart to determine the mean QT interval corrected for heart rate using the Fridericia formula (QTcF) interval **(see Appendix 1 for the schedule of ECG)**.	To update for consistency with Appendix 1	N	N/A
Section 8.1.3 Risks Associated With Ramucirumab	**Besides the ADRs mentioned in Table 10, serious and occasionally fatal arterial thromboembolic events occur when ramucirumab is given as a single agent. Additionally, impaired wound healing is likely to occur as ramucirumab is an antiangiogenic therapy with the potential to adversely affect wound healing.**	To update the risks of ramucirumab per the prescribing information of ramucirumab	N	N/A
Section 8.4 Definition of a Serious Adverse Event	An SAE is any untoward medical occurrence that, at any dose, meet any of the following criteria: Is considered a significant medical AE by the investigator **or the sponsor** based on medical judgement…	To comply with US FDA regulation (final rule)	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Section 8.6.1 Adverse Event Recording Period	Immune-mediated AEs (~~serious or nonserious~~ **serious but not treatment-related or nonserious regardless of relationship to study drug[s]**) should be recorded until 90 days…	To maintain consistency with the changes in table 11	N	N/A
Table 11	(First row) SAEs (not treatment-related) **other than those due to progressive disease**	For clarity	N	N/A
	(Third row) Beginning of Treatment-related SAEs: ~~First dose of study drug~~ **Signing of informed consent**	To align with sponsor's template language	N	N/A
	(Forth row) ~~Nonserious~~ **All** AEs due to progressive disease	To maintain consistency with the changes in section 8.6.4	N	N/A
	(Sixth row) Immune-mediated AEs (~~serious or nonserious~~ **serious but not treatment-related or nonserious regardless of relationship to study drug[s]**)	To align with sponsor's template language	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Section 8.6.4 Disease Progression	Similarly, ~~nonserious~~ AEs that are clearly consistent with the pattern of progression of the underlying disease and are considered unequivocally because of disease progression should not be recorded. However, if there is any uncertainty as to whether an ~~nonserious~~ AE is because of disease progression, it should be recorded as an AE. ~~All SAEs and deaths, regardless of relatedness to disease progression, should be recorded and reported (see Section 8.6.2).~~	To maintain consistency with sponsor's internal alignment	N	N/A
Appendix 1 SCHEDULE OF ASSESSMENTS Row	Visit window for Visit day 1 of Cycle 2 (21 days): **± 2**	To clarify the visit window for Cycle 2 Day 1 for the clinical practice	N	N/A
	12-lead ~~triplicate~~ ECG	To clarify the ECG performance requirement for clinical practice	N	N/A
	Tumor assessment Under Treatment Cycles column: Every 6 weeks (± 7 days) for the first 9 months **after randomization**, then every 12 weeks (± 7 days) thereafter	To clarify the start of tumor assessment	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	Tumor assessment Under Efficacy Follow-up Visit column: **X**	To add tumor assessment at Efficacy Follow-up Visit	N	NA
	Archival or fresh tumor tissue Under Efficacy Follow-up Visit column: ~~X~~	To remove the collection of archival or fresh tumor tissue during Efficacy Follow-up Visit	N	N/A
	PK sampling of BGB-15025 and BGB-21958 Under + 30 days (EOT/SFU Visit) Column: ~~X~~	To remove PK sampling point at EOT/SFU Visit	N	N/A
	PK sampling of sitravatinib and M10 Under + 30 days (EOT/SFU Visit) Column: ~~X~~	To remove PK sampling point at EOT/SFU Visit	N	N/A
	Echocardiogram (preferred) or MUGA	To add a test for left ventricular ejection fraction	Y	Potential impact on the study conduct and on patient safety
	Survival status	To maintain consistency with content of protocol body	N	N/A
Appendix 1 SCHEDULE OF ASSESSMENTS Column	**Survival Follow-up Visit**	To add a new column to maintain consistency with content of protocol body	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Appendix 1 SCHEDULE OF ASSESSMENTS footnote	Footnote d: Survival Follow-up Period: Overall survival data will be collected via telephone calls approximately every 8 weeks (± 7 days) after the Safety Follow-up Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or the end of the study.	To provide additional detail regarding the new column to maintain consistency with content of protocol body	N	N/A
	Footnote h: The ~~triplicate~~ ECG recordings will be performed predose on Day 1 of each cycle at the same time and when clinically indicated. … **During screening and at EOT Visit, 3 consecutive ECGs will be performed approximately 2 to 3 minutes apart.**	To clarify the ECG performance requirement for clinical practice	N	N/A
	Footnote k: **For patients receiving the combination treatment containing sitravatinib, urinalysis will be performed at each visit; if urine protein is ≥ 2+ by dipstick, then obtain a 24-hour urine sample for total protein analysis.**	To update the urinalysis requirement for patients receiving the combination treatment containing sitravatinib	Y	Potential impact on the study conduct and on patient safety

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	Footnote r: During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) **from randomization** for the first 9 months, and every 12 weeks (± 7 days) thereafter …	To clarify the start of tumor assessment	N	N/A
	Footnote Z: Only applicable for the patients receiving combination containing sitravatinib: Evaluations of cardiac function will be performed at screening and every 12 weeks (± 7 days). Evaluation by echocardiogram is preferred. Evaluation by MUGA scan is an acceptable alternative, if necessary. The method used for individual patients should be consistent throughout study participation.	To add footnote to clarify testing requirements for left ventricular ejection fraction for patients receiving the combination treatment containing sitravatinib.	Y	Potential impact on the study conduct and on patient safety
Appendix 2 BLOOD AND TUMOR TISSUE BIOMARKER ANALYSIS Row	Visit window for Visit day 1 of Cycle 2 (21 days): **± 2**	To clarify the visit window for Cycle 2 Day 1 for the clinical practice	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Appendix 2 BLOOD AND TUMOR TISSUE BIOMARKER ANALYSIS Column	**Survival Follow-up Visit**	To add a new column to maintain consistency with content of protocol body	N	N/A

Abbreviations: ADR, adverse drug reactions; AE, adverse event; BP, blood pressure; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; EOT, End of Treatment; FDA, Food and Drug Administration; MUGA, multigated acquisition; N/A, not applicable; PK, pharmacokinetics; SAE, serious adverse events; SFU, Safety Follow-up; US, United States.

BGB-LC-203
PROTOCOL AMENDMENT 2.0
SUMMARY OF CHANGES

Study Title: A Phase 2, Open-label, Randomized, Multi-arm Study of BGB-A445 in Combination With Investigational Agents in Non-Small Cell Lung Cancer Patients Previously Treated With Anti-PD-(L)1 Antibody

BeiGene, Ltd., has updated the BGB-LC-203 protocol from Protocol Amendment 1.0 (15 May 2023) to Protocol Amendment 2.0 (13 November 2023). The primary purposes for this update are as follows:

- To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort
- To update the inclusion criteria and exclusion criteria related to sitravatinib
- To specify in the inclusion criteria that prior systemic therapy for patients must include platinum-based doublets chemotherapy, per China Center for Drug Evaluation (CDE) recommendation
- To remove investigational agent information of sitravatinib and tislelizumab in the appendices

Overall, editorial and formatting changes have been made throughout to enhance clarity and readability.

Key changes made are summarized by protocol section in the table below. Additions are in **bold text** and deletions are designated by ~~strike through text.~~

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Cover Page	Changed protocol version and date	To update the protocol version.	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Synopsis Study Design	Removed the sitravatinib in combination with BGB-A445 and tislelizumab cohort	Due to sponsor's decision to discontinue development of sitravatinib, relevant cohort will be removed from the protocol. Cohort specific content was deleted.	Y	Potential impact on the study conduct
Synopsis Key Eligibility Criteria	Patients who have received no more than 2 lines of prior systemic therapies which must include anti-PD-(L)1 treatment **and a platinum-based chemotherapy administered in combination with, or sequentially before or after the anti-PD-(L)1 treatment**.	To clarify inclusion criteria for patients who had prior systemic therapies.	Y	Potential impact on the study conduct
Synopsis Statistical Methods	Update statistical analysis and interim monitoring	For clarity.	N	N/A
Section 1.2.3 Clinical Pharmacology	[redacted] of BGB-A317, **which is a BeiGene developed anti-PD-1 monoclonal antibody, namely tislelizumab,**	For clarity.	N	N/A
Section 3.1 Summary of Study Design, including Figure 1	Removed the sitravatinib in combination with BGB-A445 and tislelizumab cohort	Due to sponsor's decision to discontinue development of sitravatinib, relevant cohort will be removed from the protocol. Cohort specific content was deleted.	Y	Potential impact on the study conduct

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Section 3.3 Treatment Period	**Study treatments in all cohorts will be administered up to 36 cycles (approximately 2 years, everyone cycle consists of 3 weeks based on the schedule of administration of BGB-A445)** ~~All patients will receive study drug(s)~~	To clarify maximum treatment period.	N	N/A
Section 3.4.2 Dose-Limiting Toxicity Definition	Removed the sitravatinib specific DLT	To remove sitravatinib from the study.	N	N/A
Section 4.1 Inclusion Criteria #4	Patients who have received no more than 2 lines of prior systemic therapies which must include anti-PD-(L)1 treatment **and a platinum-based chemotherapy administered in combination with, or sequentially before or after the anti-PD-(L)1 treatment**.	To clarify inclusion criteria for patients who had prior systemic therapies.	Y	Potential impact on the study conduct
Section 4.1 Inclusion Criteria #8	~~c. Urinary protein < 2+ by urine dipstick. If dipstick is ≥ 2+, then 24 hour urinary protein must be < 1 g per 24 hours~~	Sitravatinib specific inclusion criteria; to remove sitravatinib from the study.	Y	Potential impact on the study conduct

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Section 4.1 Inclusion Criteria #9	Note: If receiving ~~the sitravatinib or~~ docetaxel-containing combination treatment, women of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study and at least 180 days after the last dose of study drug(s)	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct
Section 4.1 Inclusion Criteria #10	Note: If receiving ~~the sitravatinib or~~ docetaxel-containing combination treatment, nonsterile male patients must be willing to use a highly effective method of birth control for the duration of the study and at least 180 days after the last dose of study drug(s)	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct
Section 4.2 Exclusion Criteria #2	With known actionable alterations (including, but not limited to, EGFR, ALK, BRAF, RET, and ROS1 mutations) for which targeted therapy has been approved ~~in the second- and third line treatment setting by the respective local health authority.~~ **by the respective local health authority in the current treatment setting at the time of patient enrollment**.	To clarify the exclusion criteria.	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Section 4.2 Exclusion Criteria #19	g. Patients with inadequately controlled hypertension (defined as average systolic blood pressure [BP] ≥ ~~150~~ **140** mmHg and/or diastolic BP ≥ ~~100~~ **90** mmHg) ≤ 28 days before randomization	To update the exclusion criteria for patient safety.	Y	Potential impact on the study conduct
	~~j. QT interval corrected by Fridericia's method (QTcF) > 450 msec~~ ~~Note: If a patient has QTcF interval > 450 msec on an initial ECG, a follow-up ECG will be performed to confirm the result.~~	Sitravatinib specific inclusion criteria; to remove sitravatinib from the study.	Y	Potential impact on the study conduct
	~~k. Cardiac left ventricular ejection fraction < 50% or lower limit of normal as assessed by echocardiography or multigated acquisition (MUGA). The same modality used at baseline must be applied for subsequent evaluations.~~	Sitravatinib specific inclusion criteria; to remove sitravatinib from the study.	Y	Potential impact on the study conduct
Section 5.2.1 BGB-A445 Administration Table 4	BGB-A445 [redacted] infusion ~~over~~ 60 (± 5) minutes BGB-A445 [redacted] infusion ~~over~~ 30 (± 5) minutes	For clarity.	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Section 5.2.1 BGB-A445 Administration	~~Refer to Appendix 13 for the administration of BGB-A445 in combination with tislelizumab and sitravatinib.~~	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct
Section 5.2.2 Docetaxel Administration	BGB-A445 [redacted] infusion ~~over~~ 60 (± 5) minutes BGB-A445 [redacted] infusion ~~over~~ 30 (± 5) minutes	For clarity.	N	N/A
Section 8.2.2 Abnormal Liver Function Tests	Removed this section	The content has been updated in Section 8.6.6 and Section 8.7.3.	N	N/A
Section 8.6.1 Adverse Event Recording Period	After informed consent has been signed but before the administration of the study drug, only **serious adverse events associated with protocol-defined procedures should be reported to the sponsor.** ~~SAEs should be reported by the investigator/investigational site to the sponsor.~~	To align with protocol template updates; to improve the reporting process.	N	N/A
Section 8.6.1 Adverse Event Recording Period Table 11	Streamlined Table 11 guidance on recording new or worsening AEs and included the changes in SAE reporting.	To align with protocol template updates; to improve the reporting process.	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Section 8.6.4 Progressive Disease	Updated disease progression-related AE reporting language	To align with protocol template updates; to improve the reporting process; to avoid duplicate reporting.	N	N/A
Section 8.6.5 Deaths	Updated death-related AE reporting language for clarity	To improve clarity.	N	N/A
Section 8.6.6 Adverse Events of Special Interest	Added adverse events of special interest section	To align with protocol template updates; collecting AESI information to allow the sponsor to receive safety information in a timely manner.	N	N/A
Section 8.6.7 Pregnancies	If the patient receives ~~the sitravatinib or~~ docetaxel-containing combination treatment	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct
Section 8.6.10 Recording Infusion-Related Reactions	Updated infusion-related reactions recording language.	To align with protocol template updates; to improve the reporting process.	N	N/A
Section 8.6.11 Recording Anaphylaxis	Added Anaphylaxis recording language.	To align with protocol template updates; to improve the reporting process.	N	N/A
Section 8.7 Management of Events to be Monitored	Changed the section heading from “Adverse Events of Special Interest” to “Management of Events to be Monitored”.	For accuracy.	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	Replace wording "hypersensitivity" by "anaphylaxis"	For accuracy.	N	N/A
Section 8.7.1 Infusion-Related Reactions	Changed the section heading from "Infusion-Related Reactions and Hypersensitivity Reactions" to "Infusion-Related Reactions"	For accuracy.	N	N/A
	Added language for monitoring patients after infusion of the study treatments	For clarity.	N	N/A
	Replaced wording of "hypersensitivity" with "anaphylaxis"	For accuracy.	N	N/A
Section 8.7.2 Immune-Mediated Adverse Events Table 13	Updated Table 13 examples of imAEs.	For clarity.	N	N/A
Section 8.7.2 Immune-Mediated Adverse Events	Added discontinuation rule for patients with imAEs	For clarity.	N	N/A
Section 8.7.3 Hepatic Function Abnormalities	Added a section titled "Hepatic Function Abnormalities" to provide guidance on diagnosis and management of patients with liver function laboratory abnormalities	To align with Section 8.2.2 due to reorganization of sections.	Y	Impact on safety reporting; ensure timely monitoring of patient safety

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Section 9.2.1 Primary Efficacy Analysis	Updated primary efficacy analysis	For clarity.	N	N/A
Section 9.8 Interim Monitoring	Updated analysis method for interim monitoring	For clarity.	N	N/A
Section 15 References	Added reference accordingly	For consistency of content and reference.	N	N/A
Appendix 1 SCHEDULE OF ASSESSMENTS Row	~~PK sampling of tislelizumab~~	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct
	~~PK sampling of sitravatinib and M10~~	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct
	~~Sampling of anti-tislelizumab antibodies~~	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct
	~~Echocardiogram (preferred) or MUGA~~	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Appendix 1 SCHEDULE OF ASSESSMENTS footnote	~~k. For patients receiving the combination treatment containing sitravatinib, urinalysis will be performed at each visit; if urine protein is ≥ 2+ by dipstick, then obtain a 24-hour urine sample for total protein analysis~~	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct
	u. Investigational agents including ~~tislelizumab and~~ docetaxel will be given intravenously on Day 1 of each 21-day cycle (every 3 weeks), while investigational agents including BGB-15025 ~~and sitravatinib~~ will be received orally on a daily basis for each 21-day cycle (every 3 weeks) before the infusion. Refer to the respective appendix for details	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	v. Predose serum samples for ~~tislelizumab and/or~~ BGB-A445 (≤ 60 minutes before starting infusion) are required to be collected on Day 1 of Cycles 1, 2, 5, 9, and 17. Postdose serum samples (≤ approximately 30 minutes after completing study drug infusion) are required to be collected on Day 1 of Cycles 1 and 5. An additional PK sample is required to be collected at the Safety Follow-up Visit. Should a patient present with any ≥ Grade 3 immune-mediated adverse event (imAE), an additional blood PK sample may be taken. These tests are required when it is allowed by local regulations/Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs)	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	w. Predose blood samples for BGB-15025 and its metabolite BGB-21958 (≤ 30 minutes before dose) are required to be collected on Day 1 of Cycles 1, 2, and 3, and Days 8 and 15 of Cycle 1. Postdose blood samples at 2 hours **(± 10 minutes)** and 4-6 hours **(± 20 minutes)** after dosing are required to be collected on Day 1 of Cycles 1 and 2. Should a patient present with any ≥ Grade 3 AE, an additional blood PK sample may be taken. These tests are required when it is allowed by local regulations/IRBs/IECs.	To clarify the window time.	N	N/A
	~~x. Predose blood samples for sitravatinib and its metabolite M10 (≤ 30 minutes before dose) are required to be collected on Day 1 of Cycles 1, 2, and 5. Postdose blood samples at 6 hours (± 1 hour) after dosing are required to be collected on Day 1 of Cycles 1, 2, and 5. Should a patient present with any ≥ Grade 3 AE, an additional blood PK sample may be taken. These tests are required when it is allowed by local regulations/IRBs/IECs~~	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	~~xy~~. Blood samples to test for anti-BGB-A445 ~~and/or anti tislelizumab antibodies~~ antibody will be collected ≤ 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 5, 9, and 17 and at the Safety Follow-up Visit. All samples should be drawn at the same time as blood collection for the predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/IECs	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct
	~~z. Only applicable for the patients receiving combination containing sitravatinib: Evaluations of cardiac function will be performed at screening and every 12 weeks (± 7 days). Evaluation by echocardiogram is preferred. Evaluation by MUGA scan is an acceptable alternative, if necessary. The method used for individual patients should be consistent throughout study participation.~~	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Appendix 3 CLINICAL LABORATORY ASSESSMENTS footnote	[b] ~~On routine urinalysis, if urine protein is ≥ 2+ by dipstick, then obtain a 24-hour urine sample for total protein.~~	Remove sitravatinib in combination with BGB-A445 and tislelizumab cohort; this is sitravatinib specific.	Y	Potential impact on the study conduct
Appendix 8 IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT	Moved infusion-related reactions to Appendix 9 and anaphylaxis to Appendix 10	To align with protocol template updates; to clarify.	N	N/A
Appendix 9 MANAGEMENT OF INFUSION-RELATED REACTIONS	Created new appendix for management of infusion-related reactions	To align with protocol template updates; to clarify.	N	N/A
Appendix 10 MANAGEMENT OF ANAPHYLAXIS	Created new appendix for management of anaphylaxis	To align with protocol template updates; to clarify.	N	N/A
Appendix 12 TISLELIZUMAB	Removed this appendix	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct
Appendix 13 SITRAVATINIB	Removed this appendix	To remove the sitravatinib in combination with BGB-A445 and tislelizumab cohort.	Y	Potential impact on the study conduct

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Appendix 14 BGB-15025: Table 2	BGB-A445 infusion ~~over~~ 60 (± 5) minutes BGB-A445 infusion ~~over~~ 30 (± 5) minutes	For clarity.	N	N/A
Appendix 14 BGB-15025: Section 8.3 Adverse Events of Special Interest – BGB-15025	Removed this section	Information mentioned in Section 8.6.6.	N	N/A

Abbreviations: AE, adverse event; AESI, adverse event of special interest; DLT, dose-limiting toxicity; ECG, electrocardiogram; IEC, Independent Ethics Committee; IRB, Institutional Review Board; imAE, immune-mediated AE; MUGA, multigated acquisition; N/A, not applicable; PD-(L)1, programmed cell death protein (ligand)-1; PK, pharmacokinetics; SAE, serious adverse event.

BGB-LC-203
PROTOCOL AMENDMENT 3.0
SUMMARY OF CHANGES

Study Title: A Phase 2, Open-label, Randomized, Multi-arm Study of BGB-A445 in Combination With Investigational Agents in Non-Small Cell Lung Cancer Patients Previously Treated With Anti-PD-(L)1 Antibody

BeiGene, Ltd., has updated the BGB-LC-203 protocol from Protocol Amendment 2.0 (13 November 2023) to Protocol Amendment 3.0 (30 September 2024). The primary purpose for this update is to add a description of patient continued access to study drug after the end of the study.

Overall, editorial and formatting changes have been made throughout to enhance clarity and readability.

Key changes made are summarized by protocol section in the table below. Additions are in **bold text** and deletions are designated by ~~strike through text.~~

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Cover Page	Changed protocol version and date	To update the protocol version.	N	N/A
Final Protocol Approval Sheet	**Sponsor Development Core Team Lead** ~~Sponsor Medical Monitor~~	Updated to reflect the approver of the protocol	N	N/A

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Section 3.6 End of Treatment and Safety Follow-up;	The End-of-Treatment (EOT) ~~or Safety Follow-up~~ Visit will be conducted **≤ 7 days after** ~~when~~ the investigator determines ~~that BGB-A445 in combination with investigational agents or reference treatments~~ **that study treatment** will no longer be ~~used~~ **administered** or the patient ~~withdraws from~~ **discontinues the study** treatment. Patients will ~~be asked to return to the clinic for~~ **undergo** the ~~EOT/~~Safety Follow-up Visit ~~which should occur~~ **at** approximately 30 days (± 7 days) after the last dose ~~of study drug~~ or ~~the~~ **before** initiation of any new anticancer therapy, whichever occurs first.	Clarified the visit window of EOT and safety follow-up visit	N	N/A
Section 5.2 Dosage, Administration, and Compliance	The first dose of study drug is to be administered ≤ 2 ~~calendar~~ **business** days after randomization.	Corrected typographical error	N	N/A

Section 5.5 Continued Access to Study Drug After the End of the Study	**At the end of the study as determined by the sponsor, any patient who is still on treatment and, in the opinion of the investigator, continues to benefit from study treatment will continue treatment via being kept in the study for continuous access to study drugs. Continuous access could be terminated in case of a decision to stop manufacturing investigational agents used in the study.** **Patients will still be monitored by assessments as described in Section 7.3 and Section 8. No further data will be collected in EDC system for patients in continuous access to study drugs, SAE reports should be submitted through paper forms per requirements and timelines described in Section 8.6.2. The blood and tissue samples for PK/ADA and biomarker analysis are not required to be collected. The continuous treatment access would be discontinued for reasons listed in Section 3.5 or when the total duration**	To provide continuous access of study drugs for patients who still benefit from the ongoing treatments after the end of study.	**N**	**N**

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	reaches 36 cycles (ie, approximately 2 years) as described in Section 3.3. During the continuous study treatment, patient visits should be dependent on investigator's discretion. Other assessments, including but not limited to tumor assessment and adverse events collection, continue to follow the Appendix 1. These assessment data will be kept in study sites.			
Appendix 1 Schedule of Assessments	Corrected typographical errors in the Schedule of Assessments table, footnote #b, footnote #o, footnote #w	Corrected typographical error	**N**	**N/A**

Abbreviations: ADA: antidrug antibody; EDC: electronic data capture (system); N/A, not applicable; PK, pharmacokinetics; SAE, serious adverse event.