CLINICAL STUDY PROTOCOL

Protocol Title:	Phase 1-2 Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Various Combinations of BGB-A425 and LBL-007 with Tislelizumab in Patients with Advanced Solid Tumors
Protocol Identifier:	BGB-900-102
Phase:	1-2
Investigational Products:	BGB-A425, LBL-007, and Tislelizumab
Reference Number	NCT03744468 IND: 139200 EU CT Number: 2022-500694-14-00
Indication:	Advanced Solid Tumors
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive, 3rd Floor San Mateo, CA 94404 USA
Sponsor Medical Monitor:	[redacted], PhD BeiGene co, Ltd. [redacted] Email: [redacted]
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FINAL PROTOCOL APPROVAL SHEET

Phase 1-2 Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Various Combinations of BGB-A425 and LBL-007 with Tislelizumab in Patients with Advanced Solid Tumors

BeiGene, Ltd. Approval:

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Sponsor Medical Monitor

Date

INVESTIGATOR SIGNATURE PAGE

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Protocol Identifier: BGB-900-102

This protocol is a confidential communication of BeiGene, Ltd. and its subsidiaries. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. 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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd.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 subsidiaries.

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 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: _____

Printed Name: _____

Name/Address of Center: _____

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STUDY SYNOPSIS

Title of Study:	Phase 1-2 Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Various Combinations of BGB-A425 and LBL-007 with Tislelizumab in Patients with Advanced Solid Tumors
Sponsor:	BeiGene, Ltd.
Amendment Date:	14 December 2022
Study Phase:	1-2
Regulatory Agency Identifier Number(s):	EU CT Number: 2022-500694-14-00 NCT03744468 IND: 139200
Rationale:	Immune surveillance plays a critical role in preventing cancer cell proliferation and tumor metastasis. However, tumors have developed resistance mechanisms to suppress and/or escape the host immune system, thereby enabling tumorigenesis to proceed unchecked. One such resistance mechanism involves upregulation of immune checkpoint receptors expressed on immune cells (eg, effector T-cells), such as programmed cell death protein-1 (PD-1), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), and lymphocyte activation gene-3 (LAG-3). BGB-A425 is a humanized immunoglobulin G1 (IgG1)-variant monoclonal antibody (mAb) against TIM-3 that is being developed for the treatment of human malignancies. Tislelizumab (also known as BGB-A317) is a humanized, IgG4-variant mAb against PD-1 under clinical development for the treatment of several human malignancies. LBL-007 is a fully human anti-LAG-3 monoclonal IgG4/κ isotype antibody that is being developed for the treatment of advanced solid tumors. There is clinical evidence supporting TIM-3's role in tumorigenesis as well as emerging clinical data suggesting that the TIM-3 and PD-1 often overexpress in various cancers and drive immune escape pathways to promote tumor growth. Both LAG-3 and TIM-3 when co-expressed with PD-1 on tumor infiltrating T cells upregulated anti-PD-1 resistance, suggesting co-blockade of PD-1 with LAG-3 or TIM-3 could further enhance antitumor immunity. Thus, clinical efficacy demonstrated by PD-1 blockade via tislelizumab could significantly further improve and/or extend therapeutic benefits when combined with anti-TIM-3 antibody (BGB-A425) and/or anti-LAG-3 antibody (LBL-007). This study will assess the safety and tolerability of BGB-A425 in combination with tislelizumab and LBL-007 and the efficacy of the combined treatment as measured in the objective criteria for tumor response in patients with advanced solid tumors.

Objectives and Endpoints:

Objective	Endpoint
Phase 1 (Dose Escalation)	
Primary: To assess the safety and tolerability of BGB-A425 in combination with tislelizumab in patients with advanced solid tumors	Adverse events (AE) and serious AEs (SAEs) as characterized by type, frequency, severity (as graded by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 5.0), timing, seriousness, and relationship to study therapy; laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI-CTCAE v5.0), and timing; AEs meeting protocol defined dose limiting toxicity (DLT) criteria
Primary: To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and recommended Phase 2 dose (RP2D) of BGB-A425 in combination with tislelizumab	The MTD or MAD, defined as the highest dose at which < 33% of the patients experience a DLT The RP2D of BGB-A425 in combination with tislelizumab will be determined based upon the MTD or MAD, and will also take into consideration the long-term tolerability, PK, efficacy, and any other relevant data as available
Secondary: To assess the preliminary antitumor activity of BGB-A425 in combination with tislelizumab	Objective response rate (ORR), duration of response (DOR), and disease control rate (DCR) will be determined from investigator derived tumor assessments per RECIST v1.1
Secondary: To characterize the pharmacokinetics (PK) of BGB-A425 in combination with tislelizumab	Maximum observed plasma concentration (C_{max}), minimum observed plasma concentration (C_{min}), time to maximum plasma concentration (T_{max}), half-life ($t_{1/2}$), area under the concentration-time curve from zero to 21 days ($AUC_{0\text{-}21d}$), clearance (CL), and apparent volume of distribution (Vz) for BGB-A425 and C_{max}, C_{min} for tislelizumab
Secondary: To assess host immunogenicity to BGB-A425 in combination with tislelizumab	Immunogenic responses to BGB-A425 and tislelizumab will be assessed by summarizing the number and percentage of patients who develop detectable antidrug antibodies
Exploratory: To explore drug exposure and response (safety and efficacy) correlations	Assessments of the correlations between drug exposure and response (efficacy and safety endpoints)
Exploratory: To assess predictive, prognostic, and pharmacodynamic biomarkers including any association with response to study treatment and mechanism(s) of resistance	Evaluation of biomarkers from patient derived tumor tissue(s) and blood (or blood derivatives) samples obtained before, during and/or after the combination treatment. Candidate biomarkers may include, but are not limited to PD-1, TIM-3 receptor occupancy (RO) and immune cell subpopulation in peripheral blood cells, concentrations of cytokine and soluble proteins

	in plasma or serum, circulating tumor DNA (ctDNA) analysis in peripheral blood, programmed cell death ligand-1 (PD-L1), TIM-3 expression, tumor infiltrating lymphocytes (TILs), gene expression profiling and tumor mutation analysis in tumor tissue.
Phase 2 (Safety Lead-in)	
Primary: To assess the safety and tolerability BGB-A425 in combination with LBL-007 and tislelizumab or LBL-007 in combination with tislelizumab in patients with advanced solid tumors	Adverse events (AEs) and SAEs as characterized by type, frequency, severity (as graded by NCI-CTCAE v5.0, timing, seriousness, and relationship to study therapy; laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI-CTCAE v5.0), and timing; AEs meeting protocol defined DLT criteria
Primary: To determine the MTD or MAD and RP2D/recommended dose for expansion of LBL-007 in the combination with BGB-A425 and tislelizumab, and LBL-007 in combination with tislelizumab	The MTD or MAD, defined as the highest dose at which < 33% of the patients experience a DLT. The RP2D/ recommended dose for expansion of the combination treatments will be determined based upon the MTD or MAD, and will also take into consideration the long-term tolerability, PK, efficacy, and any other relevant data as available
Secondary: To assess the preliminary antitumor activity of BGB-A425 in combination with LBL-007 and tislelizumab or the combination of LBL-007 with tislelizumab in patients with advanced tumors	ORR, duration of response (DOR), and disease control rate (DCR) will be determined from investigator derived tumor assessments per RECIST v1.1
Secondary: To characterize the PK of BGB-A425, LBL-007, and tislelizumab in the combination treatments	Maximum observed plasma concentration (C_{max}), minimum observed plasma concentration (C_{min}), time to maximum plasma concentration (T_{max}), half-life ($t_{1/2}$), area under the concentration-time curve from zero to 21 days ($AUC_{0\text{-}21d}$), clearance (CL), and apparent volume of distribution (Vz) for BGB-A425 and LBL-007; C_{max} and C_{min} for tislelizumab
Secondary: To assess host immunogenicity to BGB-A425, LBL-007, and tislelizumab in the combination treatments	Immunogenic responses to BGB-A425, LBL-007, and tislelizumab will be assessed by summarizing the number and percentage of patients who develop detectable antidrug antibodies.
Exploratory: To explore drug exposure and response (safety and efficacy) correlations	Assessments of the correlations between drug exposure and response (efficacy and safety endpoints)
Exploratory: To assess predictive, prognostic, and pharmacodynamic biomarkers including	Evaluation of biomarkers from patient derived tumor tissue(s) and blood (or blood derivatives) samples obtained before, during and/or after the combination treatment. Candidate biomarkers may include, but are

any association with response to study treatment and mechanism(s) of resistance	not limited to PD-1, TIM-3, and LAG-3 RO and immune cell subpopulation in peripheral blood cells, concentrations of cytokine and soluble proteins in plasma or serum, circulating tumor DNA (ctDNA) analysis in peripheral blood, programmed cell death ligand-1 (PD-L1), TIM-3, LAG-3, and ligands expression, TILs, gene expression profiling and tumor mutation analysis in tumor tissue
Phase 2 (Dose Expansion)	
Primary: To evaluate antitumor activity based on objective response rate (ORR) of various combinations of BGB-A425 and LBL-007 with tislelizumab in selected tumor types	ORR as determined from investigator derived tumor assessments per RECIST v1.1
Secondary: To evaluate the antitumor activity using other secondary efficacy endpoints of the combination treatments of BGB-A425 and LBL-007 with tislelizumab	Progression-free survival (PFS), DOR, and DCR will be determined from investigator derived tumor assessments as per RECIST v1.1
Secondary: To further characterize the safety and tolerability of various combinations of BGB-A425 and LBL-007 with tislelizumab	The safety of various combinations of BGB-A425 and LBL-007 with tislelizumab will be assessed throughout the study by monitoring AEs and SAEs per NCI-CTCAE v5.0, physical examinations, electrocardiograms (ECGs), and laboratory assessments as needed
Secondary: To further characterize the PK of BGB-A425 and LBL-007 in combination with tislelizumab	PK parameters such as C_{max}, C_{min}, T_{max}, $t_{1/2}$ and $AUC_{0\text{-}21d}$ for BGB-A425and LBL-007; C_{max} and C_{min} for tislelizumab
Secondary: To further assess host immunogenicity to BGB-A425 and LBL-007 in combination with tislelizumab	Immunogenic responses to BGB-A425, LBL-007, and tislelizumab will be assessed by summarizing the number and percentage of patients who develop detectable antidrug antibodies (ADAs)
Exploratory: To assess overall survival (OS)	OS is defined as the date of the first dose of study drug to the date of death due to any cause
Exploratory: To explore drug exposure and responses (safety and efficacy) correlations	Assessments of the correlations between drug exposure and response (efficacy and safety endpoints)
Exploratory: To assess predictive, prognostic, and pharmacodynamic biomarkers including any association with response to study treatment and mechanism(s) of resistance	Evaluation of biomarkers from patient derived tumor tissue(s) and blood (or blood derivatives) samples obtained before, during and/or after treatment. Candidate biomarkers may include, but are not limited to, LAG-3 RO in peripheral blood cells, concentrations of cytokine and soluble proteins in

	plasma or serum, ctDNA analysis in peripheral blood, PDL1, TIM-3, LAG-3, and ligands expression, TILs, gene expression profiling and tumor mutation analysis in tumor tissue
Study Design:	This is an open-label, multicenter, nonrandomized Phase 1 and 2 clinical study evaluating various combinations of BGB-A425 and LBL-007 with tislelizumab. Priority enrollment for Phase 1 (dose escalation) and Phase 2 (safety lead-in) will be granted to patients with non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), hepatocellular carcinoma (HCC), gastric or gastroesophageal junction carcinoma, nasopharyngeal carcinoma, renal cell carcinoma (RCC), cervical cancer, triple-negative breast cancer, and urothelial carcinoma. Prioritization of additional tumor types will also be considered based upon emerging data and after consultation with the medical monitor. Enrollment for Phase 2 dose expansion will be granted to patients with HNSCC, NSCLC and RCC, and details are described as follows. • **Phase 1 (dose escalation):** Sequential cohorts of approximately 8 increasing dose levels of BGB-A425 will be evaluated in combination with tislelizumab 200 mg in patients with advanced solid tumors to determine the RP2D safety, PK, and other key endpoints for BGB-A425 in combination with tislelizumab. • **Phase 2 (safety lead-in):** For the safety lead-in, there are two combination cohorts planned to be evaluated: – Cohort A: LBL-007 + Tislelizumab – Cohort B: BGB-A425 + LBL-007 + Tislelizumab For Cohort A, the dose escalation of LBL-007 starts with LBL-007 300 mg intravenously in combination with tislelizumab 200 mg intravenously every 21 days (Cohort A1, n = 3 to 6); the sequential escalating dose is planned to be LBL-007 600 mg intravenously in combination with tislelizumab 200 mg intravenously every 21 days (Cohort A2, n = 3 to 6). For Cohort B, the dose escalation of LBL-007 starts with LBL-007 300 mg intravenously in combination with BGB-A425 600 mg and tislelizumab 200 mg intravenously every 21 days (Cohort B1, n = 3 to 6), which will be initiated after the evaluation in Cohort A1; the sequential escalating dose is planned to be LBL-007 600 mg intravenously in combination with BGB-A425 600 mg and tislelizumab intravenously every 21 days (Cohort B2, n = 3 to 6). After the evaluation of Cohort A1, which is initiated first, allocation of patients to the respective cohorts (ie, Cohort A2 and Cohort B1) will be carried out through a sequential order of treatment assignment. At least 6 patients will be evaluated in Cohort A2 and Cohort B2 in the dose escalation part of Phase 2 safety lead-in. During safety lead-in dose escalation, if the combination of BGB-A425 600 mg, LBL-007 600 mg, and tislelizumab 200 mg

	once every 21 days is deemed safe in Cohort B2, dose expansion will be evaluated in HNSCC and NSCLC cohorts following discussion and in agreement with the Safety Monitoring Committee (SMC). However, in addition to the above mentioned dose, lower or higher dose levels of LBL-007 may be evaluated in the safety lead-in cohorts based on the analysis of emerging safety, tolerability, PK, biomarker, and other clinical data, if recommended by the SMC. If a dose level higher than 600 mg of LBL-007 for dose expansion cohorts is recommended by the SMC, a protocol amendment will be implemented. Enrollment will be open to all eligible patients with advanced solid tumors as described in Phase 1 (dose escalation). • **Phase 2 (dose expansion):** Three combination treatments will be evaluated in patients with various tumor types including HNSCC, NSCLC and RCC. A total of 7 cohorts are planned to be conducted as below – Cohort 1: HNSCC - BGB-A425 + Tislelizumab – Cohort 2: NSCLC - BGB-A425 + Tislelizumab – Cohort 3: RCC - BGB-A425 + Tislelizumab – Cohort 4: HNSCC - BGB-A425 + LBL-007 + Tislelizumab – Cohort 5: NSCLC - BGB-A425 + LBL-007 + Tislelizumab – Cohort 6: HNSCC - LBL-007 + Tislelizumab – Cohort 7: NSCLC - LBL-007 + Tislelizumab An interim analysis will be conducted based on approximately the first 20 evaluable patients in each dose expansion cohort (Sections Section 9.1.2 and 9.7). Based upon the interim analysis for a given tumor type cohort, up to approximately 40 evaluable patients for each cohort may be enrolled in that cohort as described in Section 9.7. As of the date of finalization of this protocol amendment v7.0, enrollment of Cohorts 1 and 2 is ongoing. In Phase 2 dose expansion, the enrollment of Cohorts 4 and 5 will be initiated first, followed by the enrollment of Cohorts 6 and 7. The enrollment of Cohorts 6 and 7 will be initiated per the emerging clinical data from the ongoing evaluation in Cohorts 4 and 5. All patients enrolled in Phase 2 dose expansion must have disease progression that occurred ≥ 10 weeks from the initiation of anti-PD-1/PD-L1 treatment for locally advanced or metastatic disease. All eligible patients will receive the respective combination(s) every 21 days starting on Cycle 1 Day 1. Positive PD-L1 expression from either local or central testing will be required for enrollment of patients with HNSCC and NSCLC (refer to Section 7.1 for additional details). Patients will receive study drug until 1) they are no longer considered to receive clinical benefit, 2) unacceptable toxicity, or 3) withdrawal of informed consent.

	Except for the Phase 1 DLT period, a 21-day treatment cycle is planned for the remainder of Phase 1 and all of Phase 2 including Phase 2 safety lead-in. For Phase 1 dose escalation, a 28-day DLT observation period will be utilized for initial dose finding recommendations.
Trial Population:	**Phase 1:** Patients with histologically or cytologically confirmed advanced, metastatic, unresectable solid tumors who have previously received standard systemic therapy as per respective local guidelines, unless standard systemic therapy is not available, not tolerated, or determined not appropriate based on investigator's judgement, and who have not received prior therapy targeting TIM-3. **Phase 2 (Safety lead-in):** Patients with histologically or cytologically confirmed advanced, metastatic, unresectable solid tumors who have previously received standard systemic therapy as per respective local guidelines, unless standard systemic therapy is not available, not tolerated, or determined not appropriate based on investigator's judgement, and who have not received prior therapy targeting TIM-3 and LAG-3. **Phase 2 (Dose Expansion):** Patients with one of the following histologically or cytologically confirmed solid tumors: HNSCC patients (Cohorts 1, 4 and 6) whose disease progressed while receiving up to 3 lines of systemic therapy that includes anti-PD-1/PD-L1 antibody and available standard of care as per respective local guidelines and who are PD-L1 positive (Refer to Section 7.1 for additional details). Squamous or non-squamous NSCLC patients (Cohorts 2, 5 and 7) whose disease progressed while receiving up to 3 lines of systemic therapy that includes anti-PD-1/PD-L1 antibody and available standard of care as per respective local guidelines, and who are PD-L1 positive (Refer to Section 7.1 for additional details). RCC patients (Cohort 3) while receiving up to 3 lines of systemic therapy that includes anti-PD-1/PD-L1 antibody and available standard of care as per respective local guidelines.
Interventions:	**Phase 1 (Dose Escalation) :** A BGB-A425 dose recommended for the respective cohort will be administered intravenously as a single agent on Day 1 of each cycle. In the first cycle, tislelizumab will be administered intravenously on Day 8 (+2 days) at a fixed dose of 200 mg. Patients will be monitored for DLTs for 28 days after the first administration of BGB-A425. If tolerated, patients will receive BGB-A425 + tislelizumab sequentially on Day 29 and every 21 days (ie, once every 21 days) thereafter until they meet a discontinuation criterion. The doses of BGB-A425 to be tested are 2 mg, 6 mg, 20 mg, 60 mg, 200 mg, 400 mg, 800 mg, and 1600 mg. However, lower, intermediate and/or higher dose(s) and/or alternative dosing schedule(s) of BGB-A425 may be evaluated based upon emerging clinical data as appropriate.

	Phase 2: Safety Lead-in For safety lead-in, the respective study drugs of Cohort A and Cohort B will be administered sequentially once every 21 days starting on Cycle 1 Day 1. For Cohort A, the dose escalation of LBL-007 starts with LBL-007 300 mg in combination with tislelizumab 200 mg intravenously every 21 days (Cohort A1); the sequential escalating dose is planned to be LBL-007 600 mg in combination with tislelizumab 200 mg intravenously every 21 days (Cohort A2). For Cohort B, the dose escalation of LBL-007 starts with LBL-007 300 mg in combination with BGB-A425 600 mg and tislelizumab 200 mg intravenously every 21 days (Cohort B1), which will be initiated after the evaluation of Cohort A1; the sequential escalating dose is planned to be LBL-007 600 mg in combination with BGB-A425 600 mg and tislelizumab 200 mg intravenously every 21 days (Cohort B2). However, in addition to the above mentioned dose, lower or higher dose levels of LBL-007 may be evaluated based on the analysis of emerging safety, tolerability, PK, biomarker, and other clinical data, if recommended by the SMC. **Phase 2 Dose Expansion:** Three different combinations will be administered. For Cohorts 1, 2, and 3, the recommended dose level of BGB-A425 is 600 mg in combination with tislelizumab 200 mg administered intravenously once every 21 days. It is planned that BGB-A425 and tislelizumab will be administered sequentially once every 21 days starting on Cycle 1 Day 1. For Cohorts 4 to 7, the recommended dose(s) will be determined based on safety, tolerability, PK data, pharmacodynamic biomarker, and preliminary antitumor activity, in Phase 2 safety lead-in.
Ethical Considerations	The BGB-A425 animal toxicology data showed no toxicity at the maximal allowed dose. There is limited human experience with BGB-A425. Preliminary data from the Phase 1 dose escalation of the study BGB-900-102 shows that increasing dose levels of BGB-A425 of up to 1600 mg in combination with tislelizumab 200 mg has been well tolerated in patients with advanced solid tumors and would support continued evaluation in clinical studies. Tislelizumab is being developed for the treatment of several types of human malignancies in multiple regions as monotherapy or in combination with other therapies. Tislelizumab has also been approved and is currently being marketed in China for indications including classical Hodgkin's lymphoma, urothelial carcinoma, squamous NSCLC, non-squamous NSCLC, esophageal squamous cell carcinoma (ESCC), HCC and advanced unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors. Based on data from clinical studies, tislelizumab has been safe and well tolerated when used as a monotherapy or in combination with other therapeutics. LBL-007 is well tolerated as single dose in malignant tumors and advanced lymphoma in Study WLZB-LBL-007-AST-001b, and in combination with anti-PD-1 antibody, toripalimab, in the treatment of

	advanced malignant tumors LBL-007-CN-003 study. These data from ongoing studies support the development of BGB-A425 in combination with LBL-007 and tislelizumab.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BOR	best overall response
CK	creatine kinase
CK-MB	creatine kinase-cardiac muscle isoenzyme
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CPS	combined positive score
CR	complete response
CT	computed tomography
DCR	disease control rate
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	End of Treatment
Fc	fragment crystallizable region
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
GFR	glomerular filtration rate
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HNSCC	head and neck squamous cell carcinoma

Abbreviation	Definition
ICF	informed consent form
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
imAE	immune-mediated adverse event
IRB	Institutional Review Board
LAG-3	Lymphocyte activation gene-3
mAb	monoclonal antibody
MAD	maximum administered dose
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMCs	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed death ligand-1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RCC	renal cell carcinoma
R/M	recurrent and metastatic
RP2D	recommended Phase 2 dose
SAE	serious adverse event
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TIL	tumor infiltrating lymphocytes
TIM-3	T-cell immunoglobulin and mucin-domain containing-3

Abbreviation	Definition
TPS	tumor proportion score
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
V_{ss}	volume in steady state
Vz	apparent volume of distribution during the terminal phase

1. INTRODUCTION AND RATIONALES

1.1. Introduction

Immune surveillance plays a critical role in preventing cancer cell proliferation and tumor metastasis. However, tumors have developed resistance mechanisms to suppress and/or escape the host immune system, thereby enabling tumorigenesis to proceed unchecked (Schreiber et al 2011; Swann and Smyth 2007). One such resistance mechanism involves upregulation of immune checkpoint receptors expressed on immune cells (eg, effector T-cells), such as programmed cell death protein-1 (PD-1), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) (Koyama et al 2016; Sharma et al 2017) and Lymphocyte Activation Gene-3 (LAG-3 or CD233) (Panda et al 2020).

BGB-A425 is a humanized immunoglobulin G1 (IgG1)-variant monoclonal antibody (mAb) against TIM-3. It is being developed for the treatment of human malignancies. BGB-A425 competitively blocks the binding of phosphatidylserine to TIM-3 while concomitantly inducing TIM-3 internalization. The in vivo studies showed that BGB-A425 elicited potent antitumor effects in combination with anti-PD-1 antibody. The preliminary safety profile of BGB-A425 showed that BGB-A425 is well tolerated in patients with advanced solid tumors (refer to Section 1.2).

LBL-007 is a fully human anti-LAG-3 monoclonal IgG4/κ antibody for the treatment of advanced solid tumors. LBL-007 effectively blocks the binding of LAG-3 to its ligand major histocompatibility complex (MHC) II molecules and prevents the inhibitory signaling by LAG-3 on T cells. The in vivo antitumor efficacy studies showed that the combination of LBL-007 and an anti-mouse PD-1 monoclonal antibody demonstrated a stronger antitumor effect than either monotherapy. LBL-007 has a favorable pharmacokinetics (PK) profile and sufficient safety margins based on toxicity studies and the predicted human efficacious dose (refer to Section 1.3).

Tislelizumab (also known as BGB-A317) is a humanized, IgG4-variant mAb against PD-1 under clinical development for the treatment of several human malignancies. Tislelizumab has been approved and is currently being marketed in China that include the following indications: classical Hodgkin's lymphoma, urothelial carcinoma, esophageal squamous cell carcinoma (ESCC), squamous NSCLC, non-squamous NSCLC, hepatocellular carcinoma, recurrent or metastatic nasopharyngeal cancer, and advanced unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors.

Several anti-PD-1 and anti-PD-L1 agents have been approved for the treatment of histologically distinct tumors whereas there are several anti-TIM-3 agents and anti-LAG-3 agents in the stage of clinical development. Evidence has shown that both TIM-3 and LAG-3 are co-expressed with PD-1 on tumor infiltrating T cells and upregulated in anti-PD-1 resistant patients, suggesting these two immune checkpoint receptors are potential resistant mechanisms for anti-PD-1 therapy. Co-blockade of TIM-3, LAG-3, and PD-1 has the potential to further boost antitumor immunity and improve clinical response.

1.2. BGB-A425 as a TIM-3 Inhibitor

TIM-3 (also known as hepatitis A virus cellular receptor 2 or CD366) is a type I transmembrane glycoprotein receptor that plays an important role in promoting T-cell exhaustion and tumor escape from immune surveillance (Anderson and Anderson 2006; Sabatos et al 2003; Sanchez-Fueyo et al 2003).

TIM-3 is primarily expressed on immune cells, such as T-cells, natural killer cells, dendritic cells, and monocyte/macrophages (Anderson et al 2016). To date, four TIM-3 ligands have been identified, which include phosphatidylserine, Galectin-9, carcinoembryonic antigen-related cell adhesion molecule 1, and high mobility group box 1 (Das et al 2017). As demonstrated from the tumor infiltrating lymphocytes (TILs) of patient samples or animal models, when expressed on effector T-cells (cluster of differentiation [CD]4+ and CD8+), activation of TIM-3 via ligand binding has been shown to reduce cytokine (interferon-gamma, tumor necrosis factor-alpha and interleukin-2) production, T-cell proliferation, and cytotoxicity, all of which could be rescued with TIM-3 blocking antibodies (Fourcade et al 2010; Sakuishi et al 2010). Interestingly, TIM-3's expression is minimal on peripheral effector cells while being significantly upregulated on TILs, which strongly suggest that the tumor microenvironment utilizes TIM-3 signaling to further suppress/evade immune mediated tumor cytotoxicity (Anderson 2014; Das et al 2017; Du et al 2017). A similar repression of natural killer cell proliferation and cytotoxicity was also shown for TIM-3+ peripheral natural killer cells from patients with non-small cell lung cancer (NSCLC) (da Silva et al 2014). However, when expressed on FoxP3+ regulatory T-cells, which has been reported for a variety of human tumor types (Gao et al 2012; Yan et al 2013), the TIM-3+ regulatory T-cells demonstrated greater suppressive functions when compared to TIM-3-negative regulatory T-cells (Sakuishi et al 2013).

In support of TIM-3's role in promoting tumorigenesis, a number of studies analyzing clinical biopsy samples have shown that TIM-3 expression is significantly greater in tumor tissue and/or specifically on TILs relative to nontumor tissue/lymphocytes for various malignancies including non-small cell lung cancer (NSCLC) (Gao et al 2012), head and neck squamous cell carcinoma (HNSCC) (Liu et al 2017), hepatocellular cancer (Li et al 2012), renal cell carcinoma (RCC) (Hu et al 2020) and gastric cancer (Cheng et al 2015; Naghavi et al 2017). Such studies have also demonstrated a robust correlation between TIM-3 expression from clinical biopsy samples and clinicopathological status, response to treatment, acquired resistance and/or survival for a number of different tumor types, including NSCLC (Thommen et al 2015; Zhuang et al 2012), HNSCC (Liu et al 2017; Jie et al 2017), hepatocellular carcinoma (Li et al 2016; Li et al 2012), RCC (Granier et al 2017) and gastric cancer (Cheng et al 2015; Wang et al 2015).

Despite accumulating evidence supporting TIM-3's role in promoting tumor immune escape, the published data clearly shows that the immuno-regulatory functions of TIM-3 overlap and cooperate with the PD-1 checkpoint pathway, although this is not always the case for PD-1 pathway function (Anderson 2014; Das et al 2017; Du et al 2017; Alsaab et al 2017; Sharpe and Pauken 2018). Accordingly, TIM-3 is typically expressed on TILs only when PD-1 is co-expressed but the reverse does not hold true for PD-1 expression. Dual blockade of the PD-1 and TIM-3 pathways is also required to fully reverse TIL exhaustion, and the majority of animal models across tumor types as well as one clinical study (Section 1.2.3) confirm that TIM-3 blockade alone results in minimal tumor stasis but does however significantly increase the antitumor effect (animal models only) when combined with PD-1 blockade. Undoubtedly more

complex than described, but based upon the nonclinical and clinical data, it is believed that TIM-3 blockade by itself is unlikely to result in an efficacious antitumor immune response (Section 1.5.2) but has the potential to significantly improve and/or expand the therapeutic potential derived from PD-1 blockade. Accordingly, the clinical development of BGB-A425 will focus on data driven combination strategies. Therefore, the characterization of BGB-A425 monotherapy is not a clinical objective of this study (see Section 2).

Blocking antibodies targeting the PD-1/PD-L1 pathway have achieved remarkable results in the treatment of many different tumor types. However, based upon the rate of primary and secondary resistance to PD-1 blockade, it is apparent that additional immuno-regulatory mechanism(s) underlie tumor immune escape. Indeed, research shows that the TIM-3 pathway cooperates with PD-1 to maximize the suppression of effector TILs as well as promote resistance to anti-PD-1 therapy. Therefore, TIM-3 represents an ideal target with the potential to significantly improve and/or extend the therapeutic benefit of anti-PD-1 therapy to a greater number of patients.

1.2.1. Pharmacology

BGB-A425 binds to the extracellular domain of human TIM-3 with high specificity and affinity (Kd = 0.22 nM) as demonstrated by target-binding assays and surface plasmon resonance characterization. BGB-A425 competitively blocks the binding of phosphatidylserine to TIM-3 while concomitantly inducing TIM-3 internalization. In in vitro cell-based assays, BGB-A425 consistently and dose-dependently enhances the functional activities of activated human peripheral blood mononuclear cells (PBMCs). Further, BGB-A425 displayed antitumor activity in both the A431 allogenic xenograft tumor model and the MC38 mouse colon cancer model in TIM-3 humanized mice. In the GL261 mouse glioma model in TIM-3-humanized mice, BGB-A425 in combination with radiation therapy significantly improved the survival of tumor-bearing mice compared to radiation therapy alone.

BGB-A425 has been engineered in the heavy chain constant region to eliminate the fragment crystallizable region (Fc)-mediated effector functions. BGB-A425 has demonstrated no or minimal binding to complement 1q (C1q) or all gamma Fc receptors (FcγRs), including FcγRI, FcγRIIA, FcγRIIB, and FcγRIIIA, in in vitro binding assays, and does not induce antibody-dependent cellular toxicity or complement-dependent cytotoxicity in the cell-based assays.

Refer to the BGB-A425 Investigator's Brochure for detailed information regarding pharmacology studies of BGB-A425.

1.2.2. Toxicology

BGB-A425 binds to the cynomolgus monkey TIM-3 with 16-fold weaker affinity compared to human TIM-3 and does not bind to mouse TIM-3 because of the significant sequence divergence between human and mouse TIM-3. Therefore, cynomolgus monkey is considered to be the relevant species for nonclinical safety evaluation based upon the target sequence homology and cross-species TIM-3 binding activities of BGB-A425.

The toxicity and safety profile of BGB-A425 was characterized in single dose toxicology studies in mice and in a 13-week repeat dose toxicology study in monkeys. These toxicity studies were conducted following Good Laboratory Practice regulations. Furthermore, BGB-A425 was

evaluated in a 6-week repeat dose study in humanized TIM-3 knock-in mice with subcutaneous MC38 tumors (humanized mice). The dose levels in the 13-week monkey study spanned from the intended human therapeutic dose to 10-fold higher. The cynomolgus monkey was considered the only relevant species for toxicity studies based upon the target sequence homology and cross-species TIM-3 binding activities of BGB-A425. The tissue cross reactivity was evaluated in the normal frozen tissues from both humans and monkeys. Cytokine release responses were also evaluated using fresh human PBMCs.

No apparent toxicity was noted in either mice or monkeys after a single dose of BGB-A425 ranging from 30 to 300 mg/kg nor in monkeys following a repeat dose ranging from 20 to 200 mg/kg biweekly for 13 weeks. The toxicokinetic profile was characterized in monkey studies and the systemic exposure appeared to be dose proportional with no gender difference or accumulation observed over the dosing period. No apparent immunotoxicity was observed as no changes in clinical pathology or histopathology were observed in these studies. Immunogenicity with positive antidrug antibodies (ADAs) against BGB-A425 was noted in 6/12, 6/12, and 0/12 animals at the repeated dose of 20, 60, and 200 mg/kg, respectively. The anti-BGB-A425 antibody had shown a rapid clearance (CL) of BGB-A425 in serum in a few individual animals but did not appear to have an effect on the overall systemic exposure (area under the concentration-time curve [AUC]) or toxicity assessment.

The tissue cross reactivity of BGB-A425 was evaluated in normal human and cynomolgus monkey frozen tissues using an immunohistochemistry method, with appropriate positive and negative controls. For normal human tissues, specific staining was observed on the membrane of T-cells, dendritic cells, and/or macrophages in lymph nodes, lung, and thymus, consistent with published data. In addition, the staining was also observed in the cytoplasm of interstitial fibroblast cells, which was not considered physiologically meaningful as the monoclonal antibody typically cannot access the cytoplasm of interstitial fibroblast cells in vivo. For normal monkey tissues, no specific staining was observed. This could be attributed to a variety of reasons, including weaker binding affinity, the low target expression in the animals, and the sensitivity of the immunohistochemistry method.

No apparent increase in cytokine release was observed from an in vitro cytokine release assay following treatment of non-activated PBMCs with BGB-A425.

Overall, no apparent toxicity was observed in the monkey or transgenic mice toxicity studies. No unexpected tissue cross reactivity was found in human or monkey tissues. The toxicokinetic profile was well characterized with dose proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity and effect on the systemic exposure. The no observed adverse effect level (NOAEL) of BGB-A425 in the 13-week monkey toxicity study was considered to be 200 mg/kg. The safety profile of BGB-A425 is considered adequate to support first in human dosing.

Refer to the BGB-A425 Investigator's Brochure for more detailed information regarding toxicology studies of BGB-A425.

1.2.3. Current Treatment Landscape of TIM-3 Inhibitors

To date, no anti-TIM-3 therapy has been approved. Currently, 9 other anti-TIM-3 therapies are being evaluated in clinical oncology studies in combination with PD-1 checkpoint blockade: Sabatomimab (MGB453) (Novartis), TSR-022 (Tesaro/GSK), BMS-986258 (Bristol-Myers Squibb), LY3321367 (Eli Lilly) (Harding et al 2019), Sym023 (Symphogen), INCAGN2390 (Incyte/Agenus), SHR-1702 (Jiangsu HengRui Medicine Co.), KL-A293 (Kelun-Biotech), and WBP3425 (Zhikang Hongyi). Of these 9 TIM-3 antagonists, clinical data on TSR-022 and sabatolimab has been reported.

TSR-022 monotherapy was reported to be well tolerated with only one dose limiting toxicity (DLT) of asymptomatic Grade 3 lipase elevation observed at the highest dose level of 10 mg/kg (Weiss et al 2017). Adverse events (AEs) of TSR-022 were manageable and consistent with the safety profiles of other checkpoint inhibitors but only one unconfirmed partial response (PR) (n = 25; 4%) was observed. Published data of TSR-022 in combination with anti-PD-1 therapy (TSR-042; 500 mg once every 21 days) showed good tolerability with no DLT observed up to the TSR-022 900 mg dose level. Clinical activity of the combination was demonstrated in patients with NSCLC who had progressed on prior anti-PD-1 treatment with 4 confirmed PRs observed across TSR-022 100 mg and 300 mg cohorts (n = 31; 13%) (Davar et al 2018). Based on the tolerability and clinical activity of the combination, Tesaro/GSK decided to further evaluate the efficacy of their anti-TIM-3 therapy only in combination with anti-PD-1 in dose expansion cohorts (Tesaro Inc. 2018).

Sabatolimab (800 mg every 4 weeks) in combination with spartalizumab (400 mg every 4 weeks) was determined as the RP2D through dose escalation and was reported to be well tolerated. AEs were manageable and consistent with the safety profiles of other anti-PD-1/PD-L1 and anti-TIM-3 agents. Novartis is performing further evaluation of sabatolimab in multiple indications and in combinations including solid tumors as well as hematological malignancies.

Bispecific monovalent dual checkpoint inhibitory PD-1 antibodies co-targeting TIM-3 are currently being developed. Two PD-1/TIM-3 bispecific antibody, RO7121661/RG7769 (Hoffmann- La Roche) and AZD7789 (AstraZeneca), are being evaluated in Phase 1/2 clinical study in patients with advanced and/or metastatic solid tumors. RO7121661/RG7769 demonstrated superior antitumor TIL activity, IFN-γ secretion, and tumor growth control compared to the monospecific PD-1 antibody in mouse models (Deak et al 2020).

1.2.4. Prior Clinical Experience with BGB-A425

The Phase 1 (Dose Escalation) part of this study is completed. Overall, no dose-dependent toxicities were observed and maximum tolerated dose (MTD) was not reached, with 1 DLT (Grade 3 autoimmune myocarditis) observed at 200 mg dose level of BGB-A425. No treatment-related TEAEs leading to death. The combination of BGB-A425 and tislelizumab showed tolerable safety profile.

As of 15 February 2022, thirty three patients received BGB-A425, either as monotherapy or in combination with 200 mg of tislelizumab. Monotherapy doses were 60 mg (n = 1) and 1600 mg (n = 1). BGB-A425 combination dose regimens with tislelizumab include 2 mg (n = 1), 6 mg (n = 1), 20 mg (n = 3), 60 mg (n = 5), 200 mg (n = 7), 400 mg (n = 4), 800 mg (n = 7), and 1600 mg (n = 3). The median age for the overall group was 59.0 years; 63.6% were female and

87.9% were White. The median prior anticancer therapy regimens was 2.0 (range: 0 to 12). One patient (3.0%) did not have any prior systemic therapy; 6 patients (18.2%) had 1 prior systemic therapy; 10 patients (30.3%) had 2 prior systemic therapies; and 16 patients (48.5%) had ≥ 3 prior systemic therapies. The median treatment exposure duration for BGB-A425 was 2.96 months (range: 0.92 to 26.51 months). The overall median study follow-up duration was 5.29 months (range: 0.46 to 32.95) in the overall Phase 1 Safety Analysis Set.

The Phase 2 (Dose Expansion) part of this study is ongoing, preliminary safety data obtained from a limited number of patients received BGB-A425 600 mg with tislelizumab 200 mg.

As of the 15 February 2022 data cutoff date, 12 evaluable patients (6 patients with HNSCC and 6 patients with NSCLC) received the combination of BGB-A425 600 mg with tislelizumab 200 mg every 21 days starting on Cycle 1 Day 1. The median age for the overall group was 60.5 years (60.0 years in HNSCC and 66.0 years in NSCLC). Among the 12 evaluable patients, 9 patients (75.0%) were male (6 patients [100.0%] in HNSCC and 3 patients [50.0%] in NSCLC) and 50.0% (4 patients [66.7%] in HNSCC and 2 patients [33.3%] in NSCLC) were White. The median prior anticancer therapy regimens were 1.5 (range: 1 to 4), with 2.0 (range: 1 to 4) in HNSCC and 1.0 (range: 1 to 2) in NSCLC. All patients had ≥ 1 prior systemic therapy; 6 patients (50.0%) had 1 prior systemic therapy (2 patients [33.3%] in HNSCC and 4 patients [66.7%] in NSCLC); 4 patients (33.3%) had 2 prior systemic therapies (2 patients [33.3%] for each indication group); and 2 patients (16.7%) in HNSCC group had > 3 prior systemic therapies. The overall Phase 2 Safety Analysis Set median treatment exposure duration for BGB-A425 was 2.89 months (range: 0.07 to 4.63), with 3.385 months (range: 0.69 to 4.21) in HNSCC group and 1.53 months (range: 0.07 to 4.63) in NSCLC. The overall median study follow-up duration was 3.105 months (range: 0.07 to 6.21) with 3.385 months (range: 2.17 to 6.21) in HNSCC group and 2.09 months (range: 0.07 to 4.63) in NSCLC.

Refer to the BGB-A425 Investigator's Brochure for more detailed information regarding preliminary safety results.

1.2.4.1. Preliminary Safety

1.2.4.1.1. Dose-Escalation DLTs

As of 15 February 2022, MTD was not [redacted] One DLT was reported in Study BGB-900-102. This occurred in a [redacted]-year-old [redacted] patient of [redacted] ethnicity who initiated BGB-A425 200 mg treatment on [redacted] 2019 and tislelizumab 200 mg treatment on [redacted] 2019. This patient had concurrent [redacted] Prior to the Cycle 2 Day 1 Visit on [redacted] 2019, the patient experienced a Grade 3 autoimmune myocarditis event and was hospitalized. The diagnosis was based on increased creatine kinase-cardiac muscle isoenzyme (CK-MB) and troponin I as well as probable anterior infarct indicated by electrocardiogram (ECG). The patient was asymptomatic, and echocardiogram showed normal cardiac structure and function. Both investigational agents were temporarily held and the patient initiated corticosteroids. The patient was discharged on [redacted] 2019 and both BGB-A425 and tislelizumab treatment was permanently discontinued. The event of autoimmune myocarditis was reported as recovered/resolved with sequelae on [redacted] 2019. The investigator assessed the autoimmune myocarditis event as serious due to hospitalization. The investigator assessed the event as related to BGB-A425 and tislelizumab.

1.2.4.1.2. Safety Results in Phase 1 Dose Escalation

As of 15 February 2022, of the 33 patients in the Safety Analysis Set, 33 (100.0%) experienced at least 1 treatment-emergent adverse event (TEAE). Nineteen patients (57.6%) had TEAEs which were assessed as related to treatment. Nineteen patients (57.6%) had a Grade 3 or above TEAE, three of which was considered related to treatment. Fifteen patients (45.5%) had serious TEAEs, three of which was considered related to treatment. Eight patients (24.2%) experienced TEAEs leading to treatment discontinuation, 3 of which were assessed as related to treatment. Two patients experienced fatal adverse events which are not related to study drugs.

Most TEAEs occurred in the gastrointestinal disorders (23 patients, 69.7%), followed by musculoskeletal and connective tissue disorders (18 patients, 54.5%), general disorders and administration site conditions (17 patients, 51.5%) and investigations (9 patients, 27.3%). The most commonly occurring TEAEs were nausea and arthralgia (10 patients [30.3%] each) followed by fatigue (8 patients, 24.2%), abdominal pain and oedema peripheral (7 patients [21.2%] each).

Treatment-related TEAEs occurred in a total of 19 (57.6%) patients. Most events occurred as musculoskeletal and connective tissue disorders (9 patients, 27.3%), followed by gastrointestinal disorders SOC and general disorders and administration site conditions SOC (5 patients [15.2%] each). The most commonly occurring treatment-related TEAE was arthralgia (6 patients, 18.2%), followed by fatigue (4 patients, 12.1%), nausea (3 patients, 9.1%), and myalgia, oedema peripheral, hyperthyroidism, hypothyroidism and dry eye (2 patients [6.1%] each).

In total, 15 patients (45.5%) experienced a treatment-emergent SAEs. Most commonly occurring treatment-emergent SAEs presented as gastrointestinal disorders (8 patients, 24.2%), followed by respiratory, thoracic and mediastinal disorders (4 patients, 12.1%), general disorders and administration site conditions, and investigations (2 patients [6.1%] each). All other treatment-emergent SAEs occurred in single instance. Three patients experienced treatment-emergent SAEs assessed as related to study treatments (BGB-A425 or tislelizumab or both). Among these 3 patients, one patient who received 200 mg of BGB-A425 in combination with 200 mg of tislelizumab experienced a SAE of Grade 3 autoimmune myocarditis that was assessed as related to both BGB-A425 and tislelizumab and considered a DLT. One patient who received 20 mg of BGB-A425 in combination with 200 mg of tislelizumab experienced 2 SAEs of Grade 3 diarrhea and Grade 3 immune-mediated enterocolitis assessed as related to both BGB-A425 and tislelizumab. One patient who received 800 mg of BGB-A425 in combination with 200 mg of tislelizumab experienced a SAE of Grade 3 pneumonitis assessed as related to tislelizumab.

Grade 3 or above TEAEs occurred in a total of 19 (57.6%) patients. Most commonly occurring Grade 3 or above TEAEs presented as gastrointestinal disorders (7 patients, 21.2%), followed by investigations (5 patients, 15.2%), and respiratory, thoracic and mediastinal disorders (3 patients, 9.1%). The most commonly occurring Grade 3 or above TEAEs were ALT increased (3 patients, 9.1%), AST increased (3 patients, 9.1%), and anemia (2 patients, 6.1%). Three patients (9.1%) had a Grade 3 or above TEAEs assessed to be related to treatment, which presented as autoimmune myocarditis (1 patient, 3.0%), diarrhea (1 patient, 3.0%), hypoxia and pneumonitis (1 patient had both hypoxia and pneumonitis).

A single occurrence of Grade 4 TEAE of depression (1 patient, 3.3%) in a patient receiving 20 mg of BGB-A425 in combination with 200 mg of tislelizumab was assessed as not related to study treatment.

Two patients experienced fatal adverse events. One patient administered with 60 mg of BGB-A425 in combination with 200 mg of tislelizumab experienced a fatal TEAE of multiple organ dysfunction syndrome. The other patient administered with 400 mg of BGB-A425 in combination with 200 mg of tislelizumab experienced a fatal TEAE of aspiration. Both fatal events were assessed as not related to study treatment.

1.2.4.1.3. Safety Results in Phase 2 Dose Expansion

As of 15 February 2022, among 12 treated patients, 9 patients (75.0%) experienced at least 1 TEAE. Five patients (41.7%) had TEAEs which were assessed as related to treatment, with 4 patients (66.7%) with HNSCC and 1 patient (16.7%) with NSCLC. Four patients (33.3%) had a Grade 3 or above TEAEs. Among them, one patient with HNSCC was considered related to treatment. Four patients (33.3%) had serious TEAEs, one of which was considered related to treatment and this patient was in HNSCC indication group. No patient experienced TEAEs leading to treatment discontinuation. No patient experienced fatal adverse events.

Most TEAEs occurred in the gastrointestinal disorders and general disorders and administration site conditions SOCs (5 patients [41.7%] each), followed by musculoskeletal and connective tissue disorders, metabolism and nutrition disorders, and investigations SOC (4 patients [33.3%] each). The most commonly occurring TEAEs were fatigue (3 patients, 25.0%) followed by constipation, diarrhoea, hypercalcaemia, muscular weakness, pain in extremity, and dyspnoea (2 patients [16.7%] each).

The treatment related TEAEs occurred in a total of 5 patients (41.7%). Treatment-related TEAEs occurred as gastrointestinal disorders, general disorders and administration site conditions, and investigations (2 patients [16.7%] each). The most commonly occurring treatment-related TEAE was diarrhoea (2 patients, 16.7%), followed by fatigue, non-cardiac chest pain, ALT increased, blood creatine phosphokinase increased, blood creatinine increased, blood urea increased, neutrophil count decreased, white blood cell count decreased, hypercalcaemia, peripheral sensory neuropathy, immune-mediated lung disease, and uncoded event (reported verbatim: immune related pneumonia) (1 patient [8.3%] each). One patient (1 patient, 8.3%) with HNSCC had a Grade 3 or above TEAE of immune-mediated lung disease assessed as related to study treatment.

The treatment-emergent SAE occurred in a total of 4 patients (33.3%); two patients (16.7%) with NSCLC experienced musculoskeletal and connective tissue disorders. The treatment-emergent SAEs presented as pain in extremity (2 patients, 16.7%) and musculoskeletal chest pain (1 patient, 8.3%) by PT. Other treatment-emergent SAEs occurred in single instance include nervous system disorders (spinal cord compression in Grade 3), respiratory, thoracic and mediastinal disorders (Immune-mediated lung disease in Grade 3), and uncoded event (reported verbatim: immune related pneumonia) in Grade 2.

Grade 3 or above TEAEs occurred in 4 patients (33.3%). Most commonly occurring Grade 3 or above TEAEs presented as musculoskeletal and connective tissue disorders (2 patients, 16.7%), followed by nervous system disorders (1 patient, 8.3%) and respiratory, thoracic and mediastinal

disorders (1 patient, 8.3%). The most commonly occurring Grade 3 or above TEAE was pain in extremity (2 patients, 16.7%). All the other TEAEs occurred in single instances (1 patient, 8.3%).

The TEAE of Grade 3 immune-mediated lung disease in one patient with HNSCC was assessed as related to study treatment. As of 15 February 2022, no patients in Phase 2 developed fatal adverse events.

1.2.4.2. Pharmacokinetics in Humans

As of the data cutoff date of 15 February 2022, serial PK data were collected from 25 patients from across the first 7 dose cohorts in dose escalation. BGB-A425 exhibited rapid CL and short half-life ($t_{1/2}$) at doses of 6 mg and below which is consistent with target-mediated drug disposition for mAbs at lower dose levels. At 200 mg dose and above, the CL of BGB-A425 appears linear with similar terminal $t_{1/2}$ between 9 and 16 days and near proportional increase in $AUC_{0\text{-inf.}}$ However due to the limitation associated with non-compartmental analysis, the reported $t_{1/2}$ is likely an underestimate of true elimination $t_{1/2}$. In a preliminary population PK analysis with PK data from 20 mg and above, the estimated $t_{1/2}$ of BGB-A425 is approximately 26 days.

Refer to the BGB-A425 Investigator's Brochure for more detailed information regarding Preliminary PK parameters.

1.3. LBL-007 as a LAG-3 Inhibitor

Lymphocyte Activation Gene-3 (LAG-3 or CD223) is an immune checkpoint protein predominantly expressed on the surface of activated T cells (Huard et al 1995), and natural killer (NK) cells (Triebel et al 1990). LAG-3 expression in B cells (Kisielow et al 2005) and plasmacytoid dendritic cells (pDCs) (Workman et al 2009) also have been reported. MHC Class II is the main ligand for LAG-3 (Huard et al 1995), engagement of LAG-3 by MHC II ligand leads to a state of T cell exhaustion, characterized by attenuation of T-cell activation, inability to proliferate in response to antigen and reduced cytokine production (Workman and Vignali 2003, Huang et al 2004, Workman et al 2004). LSECtin (Xu et al 2014), galectin-3 (Kouo et al 2015), and FGL1 (Wang et al 2019) are other immune-inhibitory ligands that have been identified to interact with LAG-3 and mediate its inhibitory function in T cells. Consistent with its inhibitory function, LAG-3 expression is high in chronically exhausted or dysfunctional T cells in cancer, particularly in tumor infiltrated T cells (Matsuzaki et al 2010). In addition, LAG-3 is also expressed on regulatory T (Treg) cells and LAG-3 + Treg cells are highly suppressive compared to LAG-3- Treg cells (Huang et al 2004, Camisaschi et al 2010). LAG-3 blockade is shown to promote T cell proliferation and enhance the function of cytotoxic T cells (Lichtenegger et al 2018). LAG-3 inhibition can also reduce the immunosuppressive activity of LAG-3+ Treg cells, resulting in enhanced activation of effector T cells (Huang et al 2004).

LAG-3 is frequently co-expressed with PD-1 on tumor infiltrating T cells, LAG-3, and PD-1 double positive T cells are in a more severe dysfunction state than T cells expressing PD-1 or LAG-3 alone. Moreover, LAG-3 expression is upregulated following anti-PD-1 treatment, and the frequency of LAG-3+ T cells is significantly higher in anti-PD-L1 resistant or non-responsive patients with solid tumors, including NSCLC, HNSCC, melanoma and bladder cancer (Gettinger et al 2017, Datar et al 2017, Hanna et al 2018, Johnson et al 2018, Kates et al 2021). Co-blockade of PD-1 and LAG-3 synergize to restore the function of exhausted T cells and inhibit tumor growth by enhance antitumor immunity in mouse models (Yang et al 2017, Ghosh

et al 2019, Mimura et al 2021). Those results suggest that the combination of anti-LAG-3 and anti-PD-1 could further improve the clinical outcome of anti-PD-1, and the combination therapy may provide clinical benefit for those patients who are resistant or do not response to anti-PD-1 therapy. Indeed, the combination has been proved to be effective in clinic, in patients with previously untreated metastatic or unresectable melanoma, co-blockade of LAG-3 and PD-1 provided a greater benefit with regard to progression-free survival than inhibition of PD-1 alone (Tawbi et al 2022).

1.3.1. Pharmacology

LBL-007 is a fully human anti-LAG-3 monoclonal IgG4/κ isotype antibody co-developed by Nanjing Leads Biolabs Co., Ltd. and BeiGene, Ltd. for the treatment of advanced solid tumors.

LBL-007 binds to the human LAG-3 extracellular domain with high specificity and affinity ($Kd = 0.439 \times 10^{-10}$ M). LBL-007 effectively blocks the binding of LAG-3 to MHC II molecules, and thereby activates the immune system. In vitro binding assay showed that LBL-007 also blocks the binding of LAG-3 with other ligands, including fibrinogen like-1 (FGL-1), liver sinusoidal endothelial cell lectin (LSECtin) and galectin 3. In addition, in vivo studies in human LAG-3 knock-in mice showed LBL-007 significantly inhibiting the tumor growth when used alone or in combination with an anti-PD-1 monoclonal antibody.

In vitro studies showed that LBL-007 did not bind to either FcγRIIIA or C1q, indicating weak or no antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) effect in humans. Additionally, in vitro experiments showed that LBL-007 with an S228P modification in the hinge region was more stable than wild-type LBL-007, and did not exchange Fab arms with a wild-type human IgG4 antibody. Therefore, it was predicted that the LBL-007 antibody would be stable in vivo.

Refer to the LBL-007 Investigator's Brochure for detailed information regarding pharmacology studies of LBL-007.

1.3.2. Toxicology

Cynomolgus monkey is considered to be the relevant species for nonclinical safety evaluation because it is the pharmacologically relevant species based on sequence homology of LAG-3 and binding affinity activity; and it is a commonly used species for biologic products with a substantial historical toxicology database.

The nonclinical toxicity and toxicokinetic profile of LBL-007 was characterized in a single dose study in cynomolgus monkeys and in repeat dose studies in rats and cynomolgus monkeys. These toxicity studies were conducted following Good Laboratory Practice regulations.

At the single dose of 150 or 300 mg/kg (3 animals per group), the MTD was 300 mg/kg; no mortality or moribundity was observed in cynomolgus monkeys.

In the 3-week repeat dose study in rats, no LBL-007-related abnormal changes were observed in body weight, food consumption, ophthalmological examination, urinalysis, lymphocyte subsets, complement counts, immunoglobulin counts (IgA, IgG, IgM, IgE) following intravenous infusion of LBL-007 at 20 mg/kg, 60 mg/kg, and 150 mg/kg once a week for 3 consecutive weeks (4 doses). Other abnormalities in hematology and blood chemistry recovered after

4 weeks of dose interruption. The weight coefficient of the liver was increased in female rats in the 150 mg/kg group, and slight to mild hepatocellular necrosis or inflammatory cell infiltration was observed in the histopathological examination. Considering the lack of binding activity of LBL-007 to the LAG-3 in rats, the effects of LBL-007 on the liver were considered to be mostly off-target toxicities. Given that in vitro data indicated cellular and tissue binding with LBL-007 were highly specific to monkey and human, and the absence of LBL-007 pharmacological activity in the rat, the findings in the 3-week repeat dose study are of uncertain clinical relevance.

The 4-week repeat dose study in cynomolgus monkeys indicated that LBL-007 was well tolerated. Five consecutive weekly doses of LBL-007 at 10, 30, and 100 mg/kg in monkeys between 3 to 5 years old were not associated with any adverse effects. The no-observed-adverse-effect-level (NOAEL) was 100 mg/kg. LAG-3 receptor occupancy (RO) was increased in female and male cynomolgus monkeys at 1 to 2, 24 to 25, and 168 to 169 hours after the first dose as well as at 24 to 25 and 168 to 169 hours after the last dose. No significant dosage-related increase of LAG-3 RO was observed at all dose levels. At the dose level of 10, 30, and 100 mg/kg, after the first dose, the increased exposure of LBL-007 in the serum of monkeys in each LBL-007 group was correlated with increase of the infusion dose. No gender differences in exposure were observed. After 5 consecutive doses, the accumulation factors of LBL-007 ranged from 2.02 to 0.61, indicating a slight accumulation.

The in vitro studies to assess hemolytic potential were conducted in erythrocytes from Japanese white rabbits. There was no evidence of hemolysis or agglutination observed in vitro in rabbit erythrocytes with LBL-007 at a concentration of 5 mg/mL.

The tissue cross-reactivity of LBL-007 was evaluated in healthy cynomolgus monkeys and healthy human frozen tissues using immunohistochemistry. LBL-007 specifically bound to human tissues of colon, ileum, pituitary gland, skeletal muscle, testis, lymph nodes, duodenum, and parathyroid gland, while LBL-007 specifically bound to cynomolgus monkey tissue of the cerebellum.

The in vitro cytokine release study indicated that LBL-007 did not evoke cytokine release in human peripheral blood mononuclear cells.

Refer to the LBL-007 Investigator's Brochure for more details on the toxicology of LBL-007.

1.3.3. Current Landscape of LAG-3 Inhibitors

In 2022, BMS announced that Relatlimab (in combination with nivolumab, Opdualag™) has been approved by the U.S. Food and Drug Administration (FDA) and European Commission (EC) for marketing, thus becoming the first LAG-3 antibody approved in the US and EU, while multiple LAG-3 antibody drugs have entered clinical studies worldwide.

MK4280/Favezelimab (LAG-3 antibody) and pembrolizumab (PD-1 antibody) developed by Merck is currently being evaluated in combination in Phase 3 clinical study. Likewise, bispecific antibody, MGD013/Tebotelimab (MacroGenics Inc and Zai Lab), targeting PD-1 and LAG-3 is being tested in various unresectable or metastatic tumors. Furthermore, Sym-022 (Symphogen A/S) and Encelimab (GlaxoSmithKline/GSK) are studied in combination with anti-TIM-3 monoclonal antibody and anti-PD-1 monoclonal antibody in Phase 1. Besides, more than 10 antibodies against LAG-3 are explored in the various clinical studies as monotherapy or combined with other checkpoint inhibitors.

In a Phase 2/3 trial of Relatlimab in combination with nivolumab versus nivolumab monotherapy in previously untreated metastatic or unresectable melanoma (registration number NCT03470922, Study RELATIVITY-047), a total of 714 patients were included in clinical studies randomized 1: 1, 355 patients received BMS-986016 (160 mg) in combination with nivolumab 480 mg (Q4W) and 359 patients received nivolumab 480 mg monotherapy (Q4W). The primary endpoint was progression-free survival (PFS) according to RECIST v1.1 and the secondary endpoints were overall survival and objective response rate. The results showed that with a median follow-up time of 13.2 months, the median PFS was significantly longer in the combination group (10.1 months) than in the monotherapy group (4.6 months), and the 12-month PFS rates were 47.7% and 36.0% in the combination group and the monotherapy group, respectively. Overall, the combination regimen of relatlimab and nivolumab has a manageable safety profile, with no new safety signals compared to nivolumab monotherapy (Tawbi et al 2022). Numerically higher incidence of immune-mediated adverse events such as hypothyroidism or thyroiditis, diarrhea or colitis, hepatitis, adrenal insufficiency, pneumonitis and myocarditis was observed in the combination group than nivolumab monotherapy.

1.3.4. Clinical Pharmacology

Study WLZB-LBL-007-AST-001:

After single intravenous infusion of LBL-007 in patients at 0.05 mg/kg, 0.25 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg or 10 mg/kg, the mean $t_{1/2}$ values were determined, 49.54 hours, 105 hours, 196 hours, 184 hours, and 182 hours, respectively; the mean C_{max} values were 0.37 μg/mL, 3.10 μg/mL, 13.03 μg/mL, 43.77 μg/mL, 80.23 μg/mL, 99.5 μg/mL, respectively; and the mean AUC_{0-t} values were 6.19 h•μg/mL, 258 h•μg/mL, 1810 h•μg/mL, 6790 h•μg/mL, 14,800 h•μg/mL, 192,00 h•μg/mL, respectively, indicating that both C_{max} and AUC_{0-t} increased with increasing dose, and the in vivo drug exposure increased in a dose-proportional manner. The mean time to peak (T_{max}) was 1 to 9 h in each dose level of LBL-007. Most subjects reached the peak T_{max} at the end of administration. For each dose group of LBL-007, when the dosage was increased from 0.05 mg/kg to 1 mg/kg, the $t_{1/2}$ of LBL-007 tended to increase with increasing dose, and the clearance rate (CL) tended to decrease with increasing dose; however, when the dosage reached 3 mg/kg, CL did not change with the increase of dosage. There was no dose-dependent trend for T_{max}, volume of distribution during terminal phase (V_z), or volume of distribution at steady state (V_{ss}).

The PK characteristics of multiple doses were similar to those of single dose, with T_{max} values of 1 to 9 hours in most patients in each dose group. After multiple intravenous infusion (every 2 weeks) of LBL-007 in patients 0.05 mg/kg, 0.25 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg, C_{max} and AUC_{0-t} were observed to increase with increasing dose. No obvious accumulation was observed after multiple consecutive doses of 0.05 to 3 mg/kg, but the serum level increased slightly at doses between 6 and 10 mg/kg dose groups, suggesting that there may be limited accumulation

Study LBL-007-CN-002:

After a single intravenous infusion of 0.25 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg LBL-007 in combination with toripalimab (3 mg/kg), the mean time to maximum LBL-007 concentration ranged from 1.0 to 2.0 h; $t_{1/2}$ was 43.63 h, 108.40 h, 165.89 h, 192.30 h, respectively, with a dose-dependent trend; the mean C_{max} values were 3.350 μg/mL, 9.927 μg/mL, 36.707 μg/mL,

and 73.050 µg/mL, respectively; the mean AUC_{0-336} values were 266.264 h•µg/mL, 1486.522 h•µg/mL, 5011.602 h•µg/mL, and 11175.155 h•µg/mL, respectively. The exposure parameter C_{max} increased dose proportionally and increased slightly more compared with the increase of dosage. Mean changes in V_{ss} ranged from 4.785 to 6.829 L, and mean changes in CL ranged from 0.024 to 0.074 L/h, indicating that the drug was mainly distributed in plasma.

The PK profile of LBL-007 after multiple doses was similar to that after a single dose.

The accumulation ratios for C_{max} and AUC after multiple doses of LBL-007 ranged from 1.018 to 1.553 and 1.019 to 1.543, respectively, suggesting a slight accumulation of LBL-007 in vivo.

Refer to the LBL-007 Investigator's Brochure for more details on the clinical pharmacology studies of LBL-007.

1.3.5. Prior Clinical Experience With LBL-007

As of January 30, 2022, a total of 3 clinical studies (sponsored by Nanjing Leads Biolabs Co., Ltd.), one completed and two ongoing, have been initiated with LBL-007:

WLZB-LBL-007-AST-001 is a Phase 1a study to evaluate the safety, tolerability, pharmacokinetics and efficacy of anti-LAG-3 monoclonal antibody injection (LBL-007) in patients with malignant tumors and advanced lymphoma. The study has been completed.

LBL-007-CN-007-CN-002 is a multicenter Phase 1 clinical trial to evaluate the safety, tolerability and efficacy of LBL-007 in combination with toripalimab or LBL-007 in combination with toripalimab and axitinib in the treatment of unresectable or metastatic melanoma. The study is ongoing (in the enrollment phase).

LBL-007-CN-003 is a multicenter Phase 1b/2 clinical study of LBL-007 in combination with toripalimab in the treatment of advanced malignant tumors (eg, esophageal squamous cell carcinoma, head and neck squamous cell carcinoma, cervical cancer, nasopharyngeal cancer, small cell lung cancer, diffuse large B lymphoma). The study is ongoing (in the enrollment phase).

Study WLZB-LBL-007-AST-001:

As of 15 January 2022, a total of 22 patients were enrolled and received LBL-007 every two weeks at 0.05 mg/kg (n = 2), 0.25 mg/kg (n = 4), 1 mg/kg (n = 3), 3 mg/kg (n = 3), 6 mg/kg (n = 3), or 10 mg/kg (n = 7), 20 of whom completed the tolerability evaluation. The median age of the 22 patients was 58.5 (range: 19 to 70) years, and included 18 (81.8%) male patients and 4 (18.2%) female patients.

Preliminary safety results showed that the doses were well tolerated with no DLTs in any dose group. MTD was not reached with the maximum-administrated dose of 10 mg/kg in this study. Of the 22 patients, 21 (95.5%) experienced a total of 224 treatment-emergent adverse events (TEAEs), and TEAEs occurred in ≥ 10% of the patients were anemia (59.1%), hyperglycemia (27.3%), neutrophil count increased, hypocalcemia, upper respiratory tract infection, hyponatremia, and pyrexia (22.7% each), gamma-glutamyltransferase increased (18.2%), white blood cell count increased (18.2%), weight decreased, platelet count decreased, hypoalbuminemia, hypercalcemia, decreased appetite, asthenia, and sinus tachycardia (13.6% each).

Two patients (9.1%) had TEAE leading to permanent discontinuation of study treatment, including hypocalcemia (0.25 mg/kg dose group, possibly related to study drug) and gastrointestinal hemorrhage (3 mg/kg dose group, unlikely related to study drug) each in 1 patient, with the outcomes of ongoing and unknown, respectively. No TEAE leading to death was reported each.

During the treatment period, 8 patients (36.4%) experienced 13 serious adverse events (SAEs). Of them, 9 SAEs occurred in 5 patients (22.7%) were considered to be related to the study drug. The 9 SAEs occurred that happened in 1 patient each with an incidence of 4.5% each and included upper gastrointestinal hemorrhage (Grade 2, resolved without sequelae), gastrointestinal hemorrhage (Grade 3, ongoing), hypoalbuminemia (Grade 2, resolving to Grade 1), hypocalcemia (Grade 4, outcome unknown), bronchitis and bronchiectasis (reported by investigator as one AE term, Grade 3, ongoing), deep vein thrombosis (Grade 3, outcome other: resolving to Grade 2), and anemia (2 events of Grade 3, resolving to Grade 2 and Grade 1, respectively; 1 event of Grade 2, upgraded to Grade 3). The remaining 4 SAEs were considered not to be related to the study drug. The events included enteritis (Grade 2, resolved without sequelae), abdominal pain upper (Grade 3, ongoing), hyponatremia (Grade 3, outcome other: downgraded), and blindness unilateral (Grade 3, outcome unknown) and all occurred in 1 patient with an incidence of 4.5%.

Efficacy results showed that of the 18 evaluable patients (2 patients in the 0.05 mg/kg group, 1 patient in the 0.25 mg/kg group, 3 patients in the 1 mg/kg group, 3 patients in the 3 mg/kg group, 3 patients in the 6 mg/kg group, and 6 patients in the 10 mg/kg group), the objective response rate (ORR) was 5.6% (1 patient with esophageal cancer in 10 mg/kg group had PR) and the disease control rate (DCR) was 55.6% (1 patient of PR and 9 patients of stable disease).

Study LBL-007-CN-002:

As of January 15, 2022, a total of 37 patients were enrolled and treated with LBL-007 at different dose (0.25, 1, 3, and 6 mg/kg, every 2 weeks) in combination with toripalimab (3 mg/kg, every 2 weeks). Four patients enrolled in the 0.25 mg/kg dose group, 3 patients in the 1 mg/kg dose group, 16 patients in the 3 mg/kg dose group, and 11 patients in the 6 mg/kg dose group. Seventeen patients completed the DLT assessment, and no DLT events were observed.

Of the 37 patients, 35 (94.6%) experienced a total of 344 TEAEs. Frequently reported TEAEs (incidence ≥ 10%) were blood lactate dehydrogenase increased (35.1%), blood creatine phosphokinase increased (24.3%), anemia (24.3%), aspartate aminotransferase increased (21.6%), hypothyroidism (21.6%), blood glucose increased (18.9%), pyrexia (18.9%), asthenia (18.9%), blood bilirubin increased (16.2%), hypokalemia (16.2%), alanine aminotransferase increased (13.5%), bilirubin conjugated increased (13.5%), and gamma-glutamyltransferase increased, blood cholesterol increased, blood pressure increased, hypoalbuminemia, hyponatremia, hypertriglyceridemia, nausea, vomiting, hyperthyroidism, proteinuria, and back pain (10.8% for each).

The incidence of TEAEs leading to dose delay and permanent discontinuation were 16.2% and 2.7%, respectively.

Nine SAEs were reported in 6 patients: obstructive jaundice (3.0 mg/kg, Grade 3, unlikely related), T2 bone destruction: melanoma metastasis (suspected; 3.0 mg/kg, Grade 3, definitely not related), hypopituitarism (0.25 mg/kg, Grade 3, possibly related), disease progression

(6.0 mg/kg, Grade 5, unlikely related), nausea (3.0 mg/kg, Grade 2, unlikely related), vomiting (3.0 mg/kg, Grade 2, unlikely related), myocarditis (6.0 mg/kg, Grade 2, probably related), severe anemia (6.0 mg/kg, Grade 3, possibly related), unknown death (3.0 mg/kg, Grade 5, to be evaluated).

A total of 32 patients with melanoma were evaluable for response assessment, 21 had not received anti-PD-L1 antibody therapy (abbreviated as immunotherapy naive), 11 had previously received prior anti-PD-L1 antibody therapy (abbreviated as immunotherapy treated), of whom 4 patients achieved PR (3 acral cutaneous melanoma and 1 non-acral cutaneous melanoma, with all were immunotherapy naive patients), 13 patients achieved stable disease, of whom 11 were immunotherapy naive patients and 2 were immunotherapy-treated patients (1 mucosal melanoma and 1 non-acral cutaneous melanoma).

Study LBL-007-CN-003:

As of 30 January 2022, a total of 10 patients received LBL-007 in combination with toripalimab (3 mg/kg, every 3 weeks), including 4 patients in the dose group of LBL-007 200 mg (every 3 weeks) and 6 patients in the dose group of LBL-007 400 mg (every 3 weeks). The tolerability evaluation for 400 mg was completed with no DLT cases, and the MTD for this study was not reached with the maximum-administrated dose of 400 mg. A total of 12 TEAEs were reported in 7 patients, including pain in the left lower extremity and anemia (2 patients each), and constipation, vomiting, oropharyngeal pain, rash, peripheral neuralgia, back pain, hyperuricemia, and lymphocyte count decreased in 1patient each. There were no SAEs of any grade.

Response assessment was performed in 4 patients, all of which were stable disease (2 patients with lung adenocarcinoma, 1 patient each with nonkeratinizing pleomorphic nasopharyngeal carcinoma and small cell lung cancer).

Refer to the LBL-007 Investigator's Brochure for more details on the clinical studies of LBL-007.

1.4. Tislelizumab as a PD-1 Inhibitor

Immune checkpoint-inhibitory receptor PD-1 is mainly expressed in activated T-cells including CD8+ cytotoxic T-lymphocytes and CD4+ T-helper lymphocytes. It is believed that PD-1 plays an important role in immune modulation of tumor progression by regulating the key inhibitory signaling in the T-cells when engaged by its ligands. The PD-1 signaling cascade negatively regulates the T-cell receptor and attenuates T-cell proliferation and functional activities, leading to T-cell exhaustion. PD-1 expression is markedly upregulated in TILs, while the expression of PD-1 ligand, PD-L1, is significantly increased in tumor cells and tumor-associated immune cells in the presence of stimulating cytokines such as interferon-gamma (IFN-γ) and interferon-alpha (IFN-α) in the tumor microenvironment. Furthermore, the increased PD-1 expression in TILs and/or PD-L1 expression in tumor and tumor-associated stromal cells is observed in many types of solid human tumors including, but not limited to, melanoma, squamous cell carcinoma, uveal melanoma, NSCLC, HNSCC, triple-negative breast cancer, renal cell carcinoma, bladder cancer, and ovarian cancer. Several anti-PD-1 agents have been approved for the treatment of several cancers. Thus, PD-1 is an established target for cancer immunotherapy.

1.4.1. Pharmacology

Tislelizumab is a humanized, IgG4-variant mAb against PD-1 under clinical development for the treatment of several human malignancies.

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant = 0.15 nM). It competitively blocks binding efforts by both PD-L1 and PD-L2, thus inhibiting PD-1-mediated negative signaling in T-cells in in vitro cell-based assays. In addition, tislelizumab has demonstrated antitumor activity in human PD-1 transgenic mice in vivo.

The IgG4 variant antibody has very low binding affinity to FcγRI, FcγRIIIA, and complement 1q, a subunit of complement 1, by in vitro assays, suggesting either low or no antibody-dependent cellular phagocytosis, antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity effects in humans.

Please refer to the Tislelizumab Investigator's Brochure for more detailed information on the pharmacology of tislelizumab.

1.4.2. Toxicology

In single dose toxicity studies in both mice and cynomolgus monkeys, no mortality or apparent toxicity was noted at a single dose up to 100 mg/kg.

In the repeat dose study in cynomolgus monkeys, no apparent toxicity, including inflammation, was noted following intravenous infusion of tislelizumab at 3, 10, or 30 mg/kg once every 2 weeks for 13 weeks (7 doses). No test-article-related histopathologic changes were noted in any tissues. No specific concerns were identified for the vital organ system functions, including the cardiovascular system, the central nervous system, and the respiratory system. Antidrug antibodies with neutralization activity were noted but appeared to have no impact on systemic exposure except at the low dose of 3 mg/kg; thus, with sustained systemic drug exposure, the efficacy of the drug would not be impacted. The NOAEL was considered to be 30 mg/kg in this study.

The systemic exposure appeared to increase dose proportionally without apparent sex difference or accumulation. The systemic exposure of tislelizumab at 30 mg/kg (NOAEL) appears to be significantly higher in cynomolgus monkeys (approximately 5- to 8-fold) than in humans at all dose levels tested based on clinical human PK data.

The tissue cross-reactivity of tislelizumab was evaluated in healthy cynomolgus monkey and healthy human frozen tissues using immunohistochemistry. No specific tissue cross-reactivity with tislelizumab was noted in cynomolgus monkey or human tissues. No apparent cytokine release was detected in a human PBMCs assay. The potential of enhanced immune recall responses was observed in an in vitro human PBMC-based cell assay but not in human PD-1 transgenic mice in vivo.

Overall, the available toxicological data are considered adequate in the clinical development of tislelizumab in patients with advanced cancer.

Please refer to the Tislelizumab Investigator's Brochure for more detailed information on the toxicology of tislelizumab.

1.4.3. Clinical Pharmacology

A population PK analysis was performed based on the pooled data (PK, dosing information, demographics, and patient or disease characteristics) from 2596 patients across 12 clinical studies. The PK of tislelizumab was best characterized using a 3-compartmental model with linear clearance mechanism. No time-varying clearance was observed in tislelizumab PK. The typical estimates of clearance (CL), central volume of distribution (Vc), and peripheral volumes 2 and 3 (V2 and V3, respectively), were 0.153 L/day, 3.05 L, 1.27 L, and 2.10 L, respectively, with interindividual variability in CL (26.3%), Vc (16.7%), V2 (74.7%), and V3 (99.9%). The terminal $t_{1/2}$ was estimated to be approximately 23.8 days. The accumulation ratios were estimated to be 2.14 and 2.49 for AUC at steady state (AUC_{ss}) and minimum serum concentration at steady state ($C_{min,ss}$), respectively. Steady state is expected to be reached in approximately 12 weeks.

The population PK analyses demonstrated that race, baseline alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, lactate dehydrogenase, estimated glomerular filtration rate, Eastern Cooperative Oncology Group (ECOG) Performance Status score, and sum of products of perpendicular diameters of classical Hodgkin Lymphoma had no statistically significant influences on tislelizumab PK. Baseline body weight, tumor size of solid tumors, albumin, age, sex, immunogenicity, and tumor type were found to be statistically significant covariates on the PK of tislelizumab; however, the exposure changes by these covariates were small compared to the overall estimated PK exposures range and thus are not considered clinically meaningful.

1.4.4. Prior Clinical Experience with Tislelizumab

Tislelizumab is being developed for the treatment of several types of human malignancies in multiple regions as monotherapy or in combination with other therapies. Tislelizumab has also been approved and is currently being marketed in China for indications including classical Hodgkin's lymphoma, urothelial carcinoma, ESCC, squamous NSCLC, non-squamous NSCLC, hepatocellular carcinoma, and advanced unresectable or MSI-H or dMMR solid tumors.

The overall safety experience with tislelizumab, as a monotherapy or in combination with other therapeutics, is based on experience in 3498 patients (2150 patients treated with monotherapy and 1348 patients treated with combination therapy) as of the cutoff date 20 May 2021.

For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AE to tislelizumab dose level. The safety profile for single-agent tislelizumab is similar to those observed in other PD-1 inhibitors. The initial data collected in these studies suggest that tislelizumab can result in antitumor activity across a variety of tumor types. Antitumor activity has been observed across the dose ranges evaluated in patients.

For combination studies, the safety profile of tislelizumab is generally consistent with use as a single agent and appears to be safe and well tolerated when used in combination with other agents and in multiple different chemotherapy backbones. Preliminary antitumor activities of tislelizumab in combination with chemotherapy and other agents have been observed in multiple tumor types.

As of 20 May 2021, there are currently 33 studies with tislelizumab ongoing and 9 studies have been completed. Of the 33 ongoing studies, 15 have preliminary data available for presentation in the Investigator's Brochure, Edition 9.0 (effective 20 October 2021): 6 monotherapy studies (BGB-A317-207, BGB-A317-208, BGB-A317-209, BGB-A317-210, BGB-A317-302, and BGB-A317-303); 2 chemotherapy combination therapy studies (BGB-A317-304 and BGB-A317-307); and 7 targeted therapy combination studies (BGB-900-102 [tislelizumab in combination with BGB-A425 (anti-TIM-3 mAb)], BGB-900-103 [tislelizumab in combination with sitravatinib (also known as MGCD516, a receptor tyrosine kinase inhibitor)], BGB-900-104 (sitravatinib alone and in combination with tislelizumab), BGB-900-105 [tislelizumab in combination with ociperlimab (also known as BGB-A1217, an anti-TIGIT mAb)], BGB-A317-211 [tislelizumab in combination with lenvatinib], BGB-A317-A445-101 [tislelizumab in combination with BGB-A445 (anti-OX40 agonist mAb)], BGB-A317-ZW25-101 [zanidatamab (also known as ZW25) in combination with chemotherapy with and without tislelizumab].

Additionally, there are 18 ongoing studies that do not have clinical data presented in the Investigator's Brochure, Edition 9.0 (effective 20 October 2021): 10 studies that are blinded or have a data integrity plan in place (BGB-A317-301, BGB-A317-305, BGB-A317-306, BGB-A317-309, BGB-A317-310, BGB-A317-311, BGB-A317-312, BGB-A317-314, and BGB-A317-315, and BGB-A317-A1217-203; 7 studies with ≤ 10 patients enrolled (BGB-A317-15025-101, BGB-A317-212, BGB-A317-213, BGB-A317-214, BGB-A317-3111-10188-101, BGB-A317-A1217-202, and BGB-fruquintinib-201); 1 study focused on drug supply where safety data collection is limited (BGB-A317-290-LTE1).

Please refer to the Tislelizumab Investigator's Brochure for more detailed information on efficacy and safety of tislelizumab.

1.4.4.1. Pooled Safety Assessment of Monotherapy Studies

A pooled analysis of monotherapy studies in total of 2150 patients was conducted to provide a comprehensive safety assessment presented based either as solid tumors (1992 patients) or hematologic malignancies (158 patients).

The patients in the solid tumor group of pooled monotherapy studies had a median treatment exposure duration of 4.07 months (range: 0.10 to 41.46) and median study follow-up duration of 11.53 months (range: 0.07 to 58.91). The median age of the patients was 60 years and 72.1% were male. These patients had a median of 1.0 prior systemic anticancer therapy regimens (range: 0 to 12).

The patients in the hematologic malignancy group of pooled monotherapy studies had a median treatment exposure duration of 6.99 months (range: 0.33 to 38.60) and median study follow-up duration of 18.37 months (range: 0.33 to 38.64). The median age of the patients was 43 years and 61.4% were male. These patients had a median of 3.0 prior systemic anticancer therapy regimens (range: 1 to 11).

Of the 1992 patients in the solid tumor group of monotherapy studies, 1922 (96.5%) of patients experienced ≥ 1 TEAE, while 69.8% of patients (n = 1391) experienced ≥ 1 TEAE considered treatment related TEAEs ≥ Grade 3 in severity were experienced by 847 of 1992 patients (42.5%) and 269 patients (13.5%) experienced a ≥ Grade 3 TEAE considered treatment related. Serious TEAEs were reported in 706 patients (35.4%) and 209 patients (10.5%) experienced

≥ 1 serious TEAE considered treatment related. A total of 141 patients (7.1%) experienced a TEAE leading to death.

The most commonly occurring TEAEs in the solid tumor group of pooled monotherapy studies were anemia (502 of 1992 patients, 25.2%), AST increased (359 patients, 18.0%), ALT increased (333 patients, 16.7%), decreased appetite (329 patients, 16.5%), and cough (301 patients, 15.1%).

Of the 158 patients in the hematologic malignancy group of monotherapy studies, 149 (94.3%) of patients experienced ≥ 1 TEAE and 129 patients (81.6%) experienced ≥ 1 TEAE considered treatment related. TEAEs ≥ Grade 3 in severity were experienced by 82 of 158 patients (51.9%) and 33 patients (20.9%) experienced a ≥ Grade 3 TEAE considered treatment related. Serious TEAEs were reported in 59 patients (37.3%) and 31 patients (19.6%) experienced ≥ 1 serious TEAE considered treatment related. A total of 15 patients (9.5%) died as a result of a TEAE in this group.

The most commonly occurring TEAEs in the hematologic malignancy group of pooled monotherapy studies were pyrexia (66 of 158 patients, 41.8%), upper respiratory tract infection (37 patients, 23.4%), hypothyroidism (37 patients, 23.4%), weight increased (29 patients, 18.4%), and anemia (28 patients, 17.7%).

1.5. Study Rationale

1.5.1. Rationale for Phase 1 Dose Escalation Study Design

As described earlier, despite the wealth of evidence supporting TIM-3's role in promoting tumor immune tolerance, TIM-3 blockade alone (ie, BGB-A425 monotherapy) is unlikely to result in an efficacious antitumor response (see Section 1.2). Therefore, the clinical development of BGB-A425 focuses on rationale combinations, such as with tislelizumab. Taking this into account, the dose escalation study was designed to minimize a patient's exposure to BGB-A425 monotherapy and therefore maximize the patient's potential therapeutic benefit while simultaneously achieving the clinical objective of characterizing the safety and efficacy of BGB-A425 in combination with tislelizumab.

The appropriateness of the study design is also based upon the following data, which suggest the combination of BGB-A425 + tislelizumab will be safe and tolerable with a manageable safety profile:

1. Based upon the BGB-A425 animal toxicology data, which showed no toxicity at the maximal allowed dose (Section 1.2.2), and confirmed clinically by another anti-TIM-3 therapy (Weiss et al 2017), BGB-A425/TIM-3 blockade is expected to be safe and well tolerated;
2. Tislelizumab and/or other anti-PD-1 therapies have shown to be safe and tolerable, both as a monotherapy and in combination with other effector T-cell stimulating immuno-oncology agents (Section 1.3, Wang et al 2017; Esin et al 2017; Boutros et al 2016; Naing et al 2018);

3. The combination of anti-TIM-3 and anti-PD-1 was publicly reported to be well tolerated in patients and showed preliminary efficacy, resulting in further evaluation of the combination in dose expansion (Davar et al 2018);
4. The starting dose of BGB-A425 encompasses a 3950-fold safety margin (Section 1.5.4.2);
5. An extensive clinical, laboratory and ECG monitoring plan has been established to closely monitor patient safety so as to identify and address immune-mediated toxicities as early as possible (Appendix 1);
6. A comprehensive and effective algorithm based upon guidelines from the European Society for Medical Oncology or American Society for Clinical Oncology has been established to monitor, diagnose and manage immune-mediated toxicities (Appendix 8).
7. For reasons described in Section 1.2, there is currently no intention to clinically evaluate, characterize and/or develop BGB-A425 for use as a monotherapy

It is important to emphasize the safety experience gained from prior clinical studies whereby anti-PD-1 has been evaluated in combination with other effector T-cell stimulating immune-oncology agents. In general, the combinations lead to similar AEs compared to anti-PD-1 alone, although in some cases with greater frequency, severity and/or earlier onset but ultimately shown to be safe, tolerable and if necessary, manageable with standard of care (Section 1.3, Wang et al 2017; Esin et al 2017; Boutros et al 2016; Naing et al 2018). However, TIM-3 and PD-1 have overlapping immuno-regulatory functions and in the absence of activation, peripheral effector T-cells typically do not express TIM-3, thereby limiting the potential for peripheral immune autoreactivity (Anderson 2014; Das et al 2017; Du et al 2017). Therefore, there is a distinct possibility that the combination of BGB-A425 and tislelizumab will result in a safety profile (type, frequency, severity, timing etc.) that is similar to tislelizumab alone. Regardless, an effective diagnostic and treatment algorithm is available to address immune mediated toxicities related to PD-1 blockade alone or the combined blockade of multiple immuno-regulatory pathways.

The DLT dosing schema was designed based upon the following rationale: 1) allows for the evaluation of acute toxicities related to BGB-A425 alone (eg, immediate and/or non-immediate hypersensitivity reactions, cytokine release syndrome, delayed infusion reactions etc. [Baldo 2013 Picard and Galvao 2017]) as well as early onset immune mediated toxicities related to the combination of BGB-A425 and tislelizumab; 2) based upon the projected $t_{1/2}$ and trough levels of BGB-A425, the DLT dosing schema also provides sufficient exposure throughout the DLT period that is estimated to achieve 90% TIM-3 RO in PBMCs, which is necessary to fully and consistently evaluate the safety of BGB-A425 alone or in combination with tislelizumab; 3) based upon the time to event profile of immune mediated toxicities related to checkpoint therapies, it is unlikely that the toxicity profile of BGB-A425 monotherapy will differ significantly for a 3-week versus 1-week observation period thereby negating the benefit of evaluating BGB-A425 alone for the first cycle while only serving to delay optimal treatment of cancer patients with advanced disease; 4) all toxicities regardless of when they occur will be taken into consideration regarding dosing decisions; 5) if unexpected toxicity is observed, the protocol does allow for immediate implementation of additional dose escalation criteria (eg, extension of the DLT period) as described in Section 3.5.

Another important consideration is that the safety profile of tislelizumab has been characterized in over 1,705 patients (Tislelizumab Investigator's Brochure), thereby serving as a safety reference when evaluating and/or characterizing the safety of BGB-A425 in combination with tislelizumab. Finally, BeiGene has in place a multi-layered process for ensuring patient safety in part through close collaboration between study investigators and the BeiGene study team. The study will also utilize BeiGene's established processes for the continual collection, review, and aggregate analyses of all safety data.

In summary, the current dose escalation study design allows patients, most of whom have failed multiple prior lines of therapy and/or experiencing rapid disease progression typical for a Phase 1 study, the opportunity to obtain maximal therapeutic benefit without compromising patient safety nor clinical objectives.

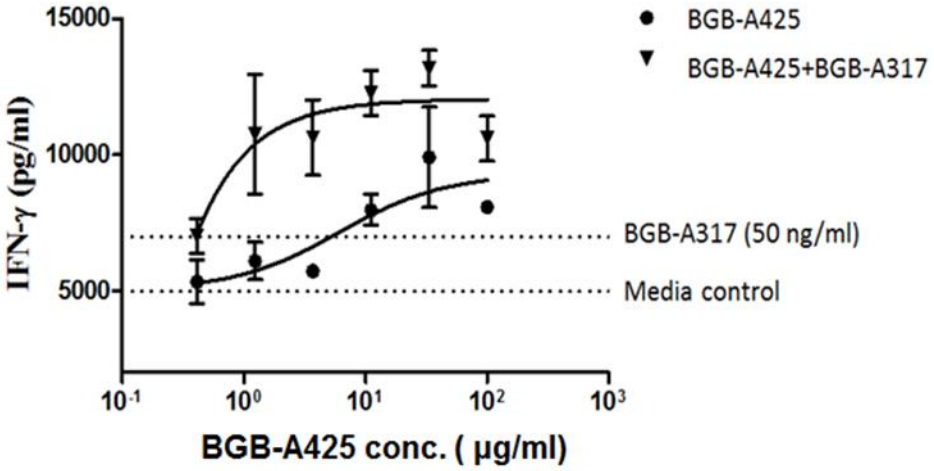
1.5.2. Rationale for Combination of BGB-A425 and Tislelizumab in the Treatment of Advanced Solid Tumors

Blocking antibodies targeting PD-1 have achieved remarkable results in the treatment of many types of tumors. However, it is also worth noting that this therapeutic strategy typically achieves a < 30% ORR as a monotherapy in patients whose tumors exhibit low positive PD-L1 expression and/or are microsatellite stable (Chen and Han 2015).

TIM-3 and PD-1 function as immune checkpoint receptors in the overlapping regulation of immune tolerance. As noted above, TIM-3 and PD-1 have been shown to be overexpressed on the TILs from patient samples of various solid tumors including, but not limited to HNSCC, NSCLC and RCC. Subsequently, the activation of TIM-3 and PD-1 represent TILs from both patients or animals across solid tumor types with the most exhausted immunophenotype (ie, cytokine expression, proliferation etc.), which can be reversed with combined blockade of TIM-3 and PD-1. Interestingly, TIM-3 is typically only expressed on effector T-cells when PD-1 is co-expressed (Du et al 2017; Thommen et al 2015) and the expression both of which is upregulated following effector activation (Gao et al 2012). As such, immune escape via PD-1 will be sustained in patients with PD-L1 positive tumors thereby negating TIM-3 blockade alone.

The overlap in expression and function indicates that TIM-3 and PD-1 cooperate to promote effector cell exhaustion which may impede an effective antitumor immune response. Indeed, the combined blockade of TIM-3 and PD-1 significantly increased IFN-□ production in vitro relative to the increase seen for TIM-3 or PD-1 blockade alone, thus demonstrating that the combined blockade of TIM-3 and PD-1 can mitigate effector cell exhaustion following activation and chronic antigen stimulation (Figure 1).

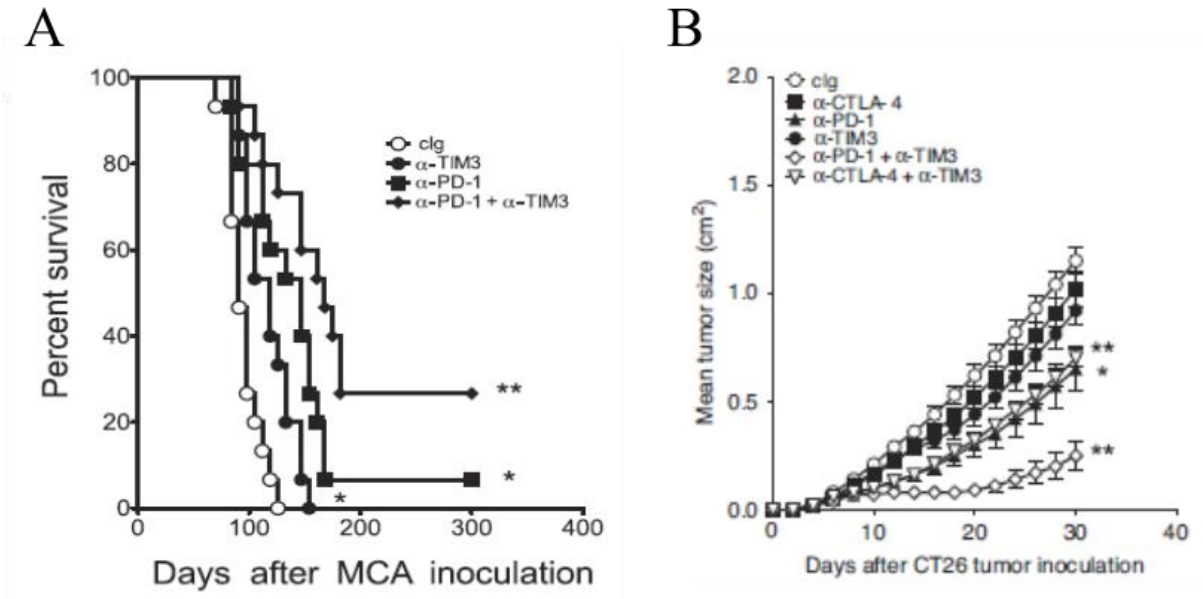
Figure 1: Combined Blockade of TIM-3 and PD-1 with BGB-A425 and tislelizumab (BGB-A317) Enhances IFN-γ secretion in Mixed Lymphocyte Reaction



Abbreviations: IFN-γ, interferon-gamma; PBMC, peripheral blood mononuclear cell; PD-1, programmed cell death protein-1; TIM-3, T-cell immunoglobulin and mucin-domain containing-3
A conventional mixed lymphocyte reaction assay was performed. In brief, "stimulator PBMCs" from a healthy donor were pre-treated with mitomycin-c (100 µg/ml, Sigma) and co-cultured with "responder PBMCs" of a different donor in the complete RPMI1640 media with 10% AB serum (Sigma) plus BGB-A425 and/or tislelizumab/BGB-A317 (50 ng/ml) in a 96-well flat-bottom plates for 4 days. The secretion of IFN-γ into the cell culture was analyzed as a readout of T-cell function. All conditions were performed in triplicates and results are shown as mean ± SD. The EC_{50} for BGB-A425 alone is 6.1 µg/mL, and the EC_{50} for combination of BGB-A425 and tislelizumab/BGB-A317 is 0.89 µg/mL.

Further, combined blockade of TIM-3 and PD-1 resulted in a greater antitumor effect in vivo compared to PD-1 blockade alone as observed for various solid tumor models (Figure 2) (Ngiow et al 2011; Fourcade et al 2010; Kim et al 2017; Sakuishi et al 2010). Importantly, following treatment with anti-PD-1, the expression of TIM-3 was shown to be upregulated on TILs in both patient samples and animal models of NSCLC and HNSCC, which was temporally correlated with the development of resistance to anti-PD-1 treatment (Koyama et al 2016; Shayan et al 2016; Oweida et al 2018). Subsequently, following this “adaptive resistance” to anti-PD-1 monotherapy, sequential treatment with anti-TIM-3 significantly improved the antitumor effects in both NSCLC and HNSCC mouse models (Figure 3).

Figure 2: The Combination of Anti-TIM-3 and Anti-PD-1 Treatment Is More Effective Than Anti-PD-1 Inhibitors Alone

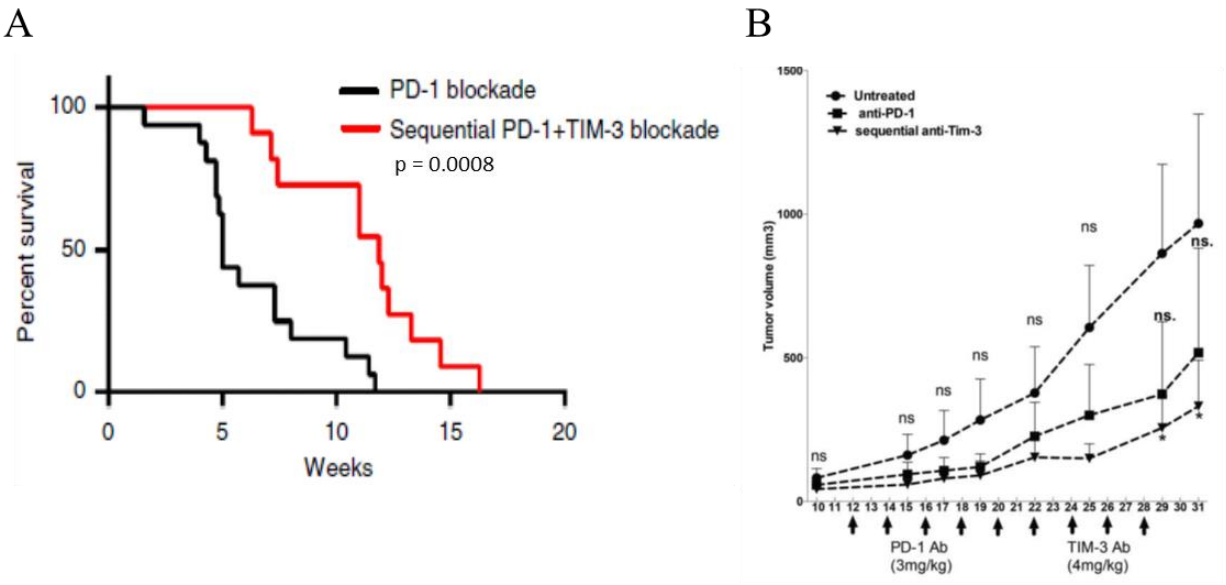


Abbreviations: cIg, control immunoglobulin; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; MCA, methylcholanthrene; PD-1, programmed cell death protein-1; TIM-3, T-cell immunoglobulin and mucin-domain containing-3

Figure 2A: MCA (induced sarcoma model) mice were treated prophylactically with control (cIg), anti- TIM-3, anti-PD-1, or anti-PD-1 + anti-TIM-3 (100 mg administered intraperitoneally) on Days -1, 0, and weekly for 8 weeks. Statistical differences determined by a Log Rank Mantel–Cox test (*, monotherapy compared with cIg; **, anti-PD-1 + anti-TIM-3 compared with either anti-PD-1 or anti-TIM-3 alone) (Ngiow et al 2011).

Figure 2B: Groups of B6 mice (n = 5) were inoculated subcutaneously with CT26. On Days 3, 7, 11, and 15, mice were treated intraperitoneally with either control (cIg), anti-TIM-3, anti-CTLA-4, anti-PD-1, or their combination (100 mg) as indicated. Tumor sizes are represented as the mean standard error of the mean. Statistical differences in tumor sizes between mice treated with cIg and single monoclonal antibody therapy were determined by a Mann-Whitney test (*, $p < 0.05$). Statistical differences between mice treated with single monoclonal antibody therapy or a dual combination were determined by a Mann–Whitney test (**, $p < 0.05$). (Ngiow et al 2011).

Figure 3: Sequential Anti-TIM-3 and Anti-PD-1 Treatment Increases Survival and Suppresses Tumor Growth Compared to Anti-PD-1 Treatment Alone



Abbreviations: Ab, antibody; PD-1, programmed cell death protein-1; TIM-3, T-cell immunoglobulin and mucin-domain containing-3

Figure 3A: Non-small cell lung cancer mouse survival model. Survival following PD-1 blockade alone (anti-PD-1 resistant) or PD-1 and sequential TIM-3 blockade combination treatment (PD-1 alone: n = 16 and sequential combination treatment: n = 11) (p = 0.0008) after documented tumor burden. Treatment with anti-PD-1 started at week 0. Median survival with anti-PD-1 = 5 weeks versus anti-PD-1 + anti-TIM-3 sequential treatment = 11.9 weeks (Koyama et al 2016).

Figure 3B: Metastatic human papilloma virus + oropharyngeal squamous cell carcinoma mouse model. Mice were treated with anti-mouse PD-1monoclonal antibody given at 5 doses every 2 days, and sequential anti-TIM-3 monoclonal antibody treatments were given to one group of mice starting from Day 22 for 4 doses every 2 days. Tumor volume was measured every 2 days (*, $p < 0.05$) (Shayan et al 2016).

Based upon the overlapping expression profiles and immuno-regulatory functions, the improved in vivo antitumor effects, as well as the potential for TIM-3 mediated adaptive resistance, there is strong scientific rationale to evaluate the antitumor effects derived from the combined blockade of TIM-3 and PD-1 in advanced solid tumors.

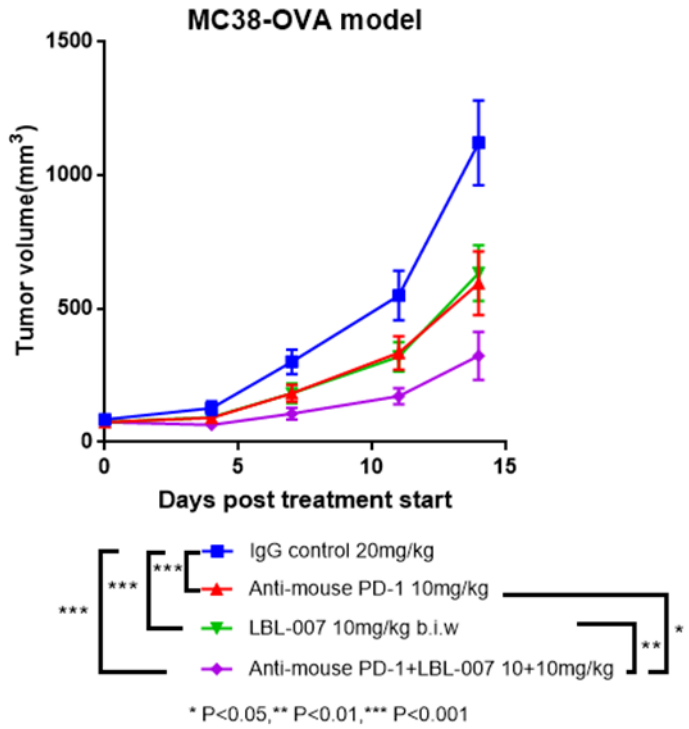
1.5.3. Rationale for Combination of BGB-A425, LBL-007, and Tislelizumab in the Treatment of Advanced Solid Tumors

Co-expression of multiple immune checkpoint proteins occurs frequently on tumor infiltrating T cells and is associated with their dysfunction state. Both LAG-3 and TIM-3 were shown to be co-expressed with PD-1 on tumor infiltrating T cells and were upregulated in anti-PD-1 resistant and non-responder patients, suggesting co-blockade of PD-1 with LAG-3 or TIM-3 could further enhance antitumor immunity (Gettinger et al 2017, Hanna et al 2018, Johnson et al 2018, Kates et al 2021).

In preclinical mouse study, LBL-007 in combination with anti-PD-1 significantly improved antitumor effect with a tumor growth inhibition (TGI) of 77.63%, superior to LBL-007 (TGI=56.10%) or anti-PD-1(TGI=58.99%) monotherapy in MC38-OVA (mouse colorectal

cancer cell line stably expressing OVA protein) xenograft model in a human LAG-3 transgenic mouse (Figure 4). There were no significant differences in body weight between groups.

Figure 4: Tumor growth curve after treatment with LBL-007, anti-mouse PD-1 and the combination in MC38-OVA model

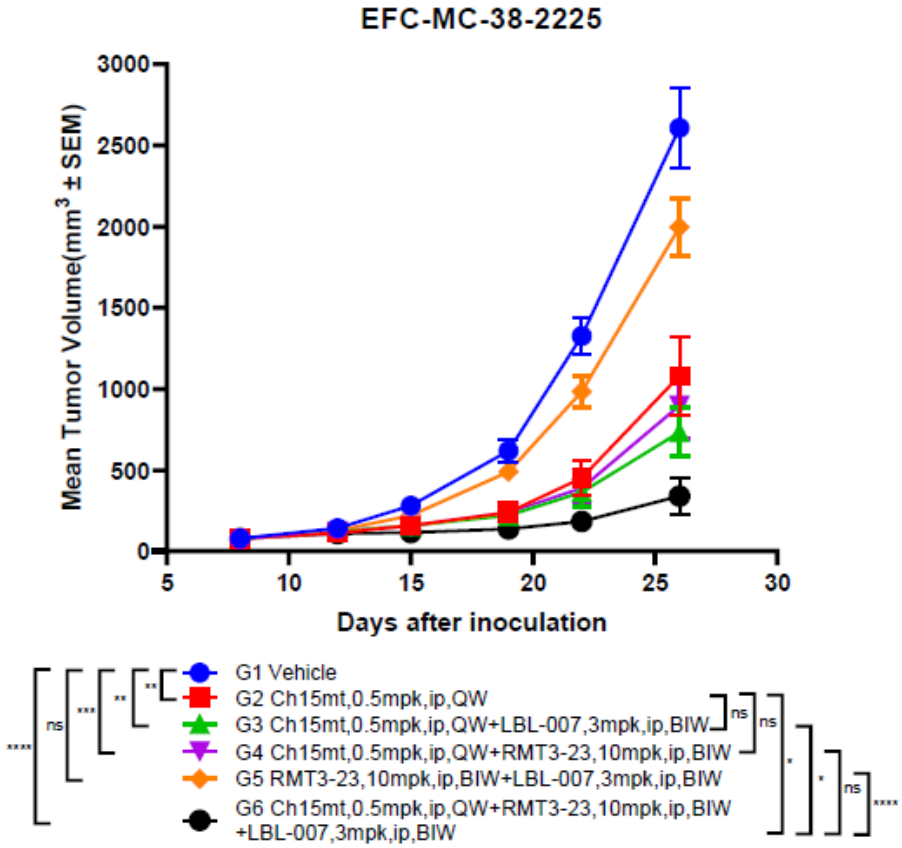


The synergic antitumor efficacy for anti-LAG-3 antibody in combination with anti-PD-1 antibody has been preliminarily validated in clinical study. The first anti-LAG-3 antibody was recently approved by FDA based on the significant clinical benefit of LAG-3/PD-1 combinational therapy compared to anti-PD-1 alone in unresectable metastatic melanoma (Tawbi et al 2022). The combination of LBL-007 with anti-PD-1 (toripalimab) is now under clinical evaluation in melanoma (LBL-007-CN-002). A total of 32 evaluable patients had an ORR of 12.5% (4 patients experiencing partial response) and a DCR of 53.1% (4 patients experiencing partial response and 13 patients experiencing stable disease). Of the 11 evaluable patients with cutaneous acral melanoma who did not receive anti-PD-L1 antibody treatment before, the ORR was 27.3% and the DCR was 81.8%. Moreover, in the study of LBL-007 in combination with toripalimab in the treatment of advanced malignancies (Study LBL-007-CN003), the antitumor efficacy was assessed in 4 patients, all of whom experienced stable disease.

Furthermore, LAG-3 was shown to confer resistance to anti-TIM-3/PD-1 combination therapy. LAG-3 expression on tumor infiltrating T cells was increased following the combinational treatment of anti-PD-1 and anti-TIM-3 in preclinical settings (Yang et al 2020). In an in-vivo efficacy study in MC38 syngeneic tumor model, anti-mouse PD-1 antibody Ch15mt, anti-human LAG-3 antibody LBL-007, and anti-mouse TIM-3 antibody RMT3-23 combination demonstrated a greater antitumor effect than either anti-TIM-3/anti-PD-1 or anti-LAG-3/anti-PD-1 combinations (data on file; see Figure 5).

Taken together, those data suggest a combination targeting TIM-3, LAG-3, and PD-1 could synergistically improve the responses of antitumor immunotherapy, and thus providing a strong scientific rationale for testing the triple combination in clinical studies.

Figure 5: Synergy efficacy in the combination of anti-PD-1, anti-TIM-3, and anti-LAG-3 on tumor growth inhibition in the MC38 syngeneic model in human LAG-3 knock-in mice



Abbreviations: biw, twice a week; ip, intraperitoneal; LAG-3, lymphocyte activation gene-3; qw, once a week.
MC38 xenograft tumor growth curve in B6-hLAG-3 mice under different treatments. On Day 8 after cell inoculation, the mice were randomized into 6 groups according to tumor volume. The mice were treated with Ch15mt, LBL-007, and RMT3-23 and tumor volumes were plotted to Day 26 after tumor inoculation. Data were presented as mean tumor volume ± standard error of the mean of 15 animals. One-way ANOVA was used to analyze logarithmic transformed tumor volume data, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

1.5.4. Rationale for Selection of BGB-A425 Starting Dose

1.5.4.1. Allometric Scaling

Serum concentration-time profiles from 6 monkeys receiving single doses of BGB-A425 at 12, 40, and 120 mg/kg, respectively, and 6 monkeys receiving 5 weekly doses of 40 mg/kg (BGB-A425 Investigator's Brochure) were used in a population PK analysis with NONMEM version 7.3.

A 2-compartment model with first order elimination described the data well. Inter-subject variability was estimated for the CL and central volume of distribution. Human PK parameters were obtained by scaling respective monkey PK parameters multiplied by the ratio of body weight (human/monkey) and taken to the power of 0.75 for CL and inter-compartmental CL and 1.0 for the volume for the central compartment and the peripheral compartment.

Table 1: Population PK Parameters Estimate for Monkey and Projected PK Parameters in Humans

Parameter	Monkey		Human
	Estimate	%RSV	Projection
CL (L/h)	0.000785	7.4	0.00892
V_c (L)	0.159	6.2	4.06
V_p (L)	0.0465	29	1.19
Q (L/h)	0.00226	34	0.0257
IIV CL (%)	28	34	NA
IIV V_c (%)	22	33	NA
Residual error	59	10	NA

Abbreviations: CL, clearance; h, hour; IIV, inter-subject variability; L, liter; NA, not applicable; PK, pharmacokinetics; Q, inter-compartmental clearance; RSV, relative standard error; V_c, volume of central compartment; V_p, volume of peripheral compartment

The simulation of serum BGB-A425 concentration-time profiles in humans was conducted in Berkeley Madonna version 8.3.

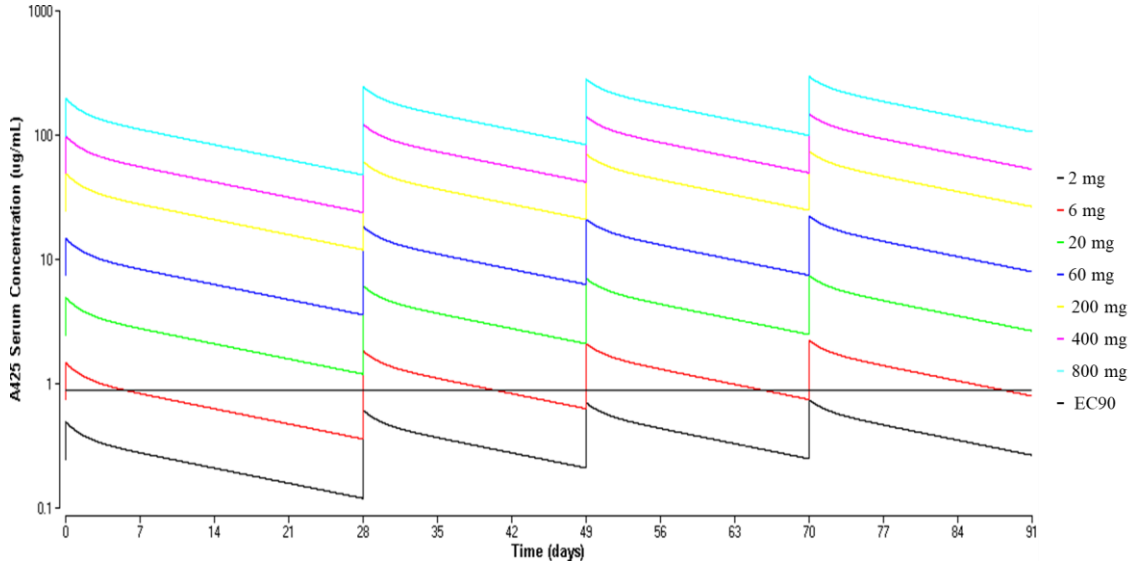
1.5.4.2. Recommendation of the First in Human Dose of BGB-A425

Similar to anti-PD-1, anti-TIM-3 is a checkpoint inhibitor. Therefore, both the minimally anticipated biologic effect level (MABEL) and NOAEL approaches were used to determine the starting dose in humans.

To define MABEL, the mixed lymphocyte reaction (MLR) assay was performed to evaluate the effect of BGB-A425 alone or in combination with BGB-A317 on effector cell exhaustion (Section 1.5.2). In the presence of 50 ng/mL of BGB-A317, the EC_{90} value of BGB-A425 was 0.89 µg/mL. A starting dose of 2 mg was selected because its C_{max} after a single dose is projected to be 0.5 µg/mL, which is below the EC_{90} value for the combination of BGB-A425 and BGB-A317 in the MLR assay. The projected $t_{1/2}$ of approximately 17 days in humans supports a flat dosing regimen given every 21 days.

Figure 6 presents the simulated human doses of 2, 6, 20, 60, 200, 400, and 800 mg of BGB-A425 given once every 4 weeks in Cycle 1 and every 21 days starting from Cycle 2. The step size in dose was approximately tripled for the first 3 doses and doubled thereafter.

Figure 6: Simulated Serum Concentration-Time Profiles in Humans



Abbreviations: EC_{90}, concentration corresponding to 90% receptor occupancy of TIM-3

Based on the steady state AUC at 200 mg/kg in the 3-month toxicity study in monkeys (BGB-A425 Investigator's Brochure), the projected safety margins at the proposed human dose are provided in Table 2. At the proposed starting dose of 2 mg, the projected safety margins based on AUC and C_{max} are 3950 and 6960, respectively, which reflects favorably on the safety profile of BGB-A425.

Table 2: Projected Safety Margins at Steady State at the Proposed Doses in Humans

Doses (mg)	**2**	**6**	**20**	**60**	**200**	**400**	**800**
AUC Safety Margin	3950	1320	395	132	39	20	13
C_{max} Safety Margin	6960	2320	696	232	70	35	17

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum observed concentration.

1.5.5. Rationale for BGB-A425 Recommended Phase 2 Dose

The combination RP2D was determined primarily from the Phase 1 safety, tolerability, preliminary antitumor activity, pharmacodynamic biomarker and PK data. The RP2D is determined as BGB-A425 600 mg in combination with tislelizumab 200 mg administered every 21 days, which will be evaluated in the Phase 2 dose expansion phase.

1.5.6. Rationale for Selection of LBL-007 Dose

In the single-agent dose escalation trial of WLZB-LBL-007-AST-001b (as mentioned in Section 1.3.5), the highest dose of 10 mg/kg (every 2 weeks) was tested in 7 patients with no DLT and generally well tolerated. Little accumulation was observed at steady-state due to its short half-life. The dose of 10 mg/kg (every 2 weeks) provides exposure coverage up to LBL-007 600 mg dosed every 3 weeks, and LBL-007 600 mg (every 3 weeks) could be chosen as the highest dose as in the range of the LBL-007 starting dose in combination with tislelizumab

200 mg administered every 21 days or BGB-A425 600 mg and tislelizumab 200 mg administered every 21 days for Phase 2 safety lead-in.

Additionally, in LBL-007-CN-003 study, doses ranging up through 400 mg of LBL-007 (every 3 weeks) was evaluated with toripalimab (anti-PD-1 antibody) with no DLT (n = 6). Similarly, in LBL-007-CN-002, the combination of LBL-007 (doses ranging up through 6 mg/kg; every 2 weeks) with toripalimab was well tolerated with no DLT observed in 14 patients at this dose.

Since this is the first-in-human study where BGB-A425 will be combined with LBL-007 and tislelizumab, considering the safety and tolerability of this combination, we plan to evaluate LBL-007 at 300 mg as the starting dose of LBL-007, which is one dose level below the highest LBL-007 dose (ie, 600 mg; every 21 days) as mentioned above, for combining with tislelizumab 200 mg or with BGB-A425 600 mg and tislelizumab 200 mg. Then the dose level of LBL-007 will be escalated to 600 mg in the combination treatment cohorts. If LBL-007 600 mg in combination with tislelizumab or BGB-A425 and tislelizumab are well tolerated, a higher dose of LBL-007 (eg, 900 mg every 21 days) may be explored based on emerging safety, tolerability, PK, and other clinical data.

1.5.7. Rationale for Selection of Tislelizumab Dose

The PK, safety, and efficacy data obtained from the first in human study BGB-A317_Study_001, as well as other clinical study data, were analyzed in aggregate to determine the recommended dose for pivotal studies of tislelizumab. The flat dose of tislelizumab 200 mg intravenously once every 21 days was selected for further evaluation.

Rates of treatment-related AEs and serious AEs (SAEs) observed in patients receiving 2 mg/kg and 5 mg/kg once every 2 weeks and once every 21 days were comparable, suggesting no clear dose-dependence across these regimens. Similarly, confirmed ORRs in patients treated with tislelizumab 2 mg/kg and 5 mg/kg once every 2 weeks ranged between 10% and 15%, compared to a range of 15% to 38% for patients treated at 2 mg/kg and 5 mg/kg once every 21 days.

According to PK data from BGB-A317_Study_001, Phase 1a, the CL of tislelizumab was found to be independent of body weight, ethnicity, and gender, and the observed serum exposure of a 200 mg dose fell between serum exposure observed after 2 mg/kg and 5 mg/kg doses (dose range with comparable safety and efficacy rates).

Additionally, no unexpected treatment-related AEs occurred in the 200 mg fixed dose cohort (BGB-A317_Study_001, Phase 1a, Part 3) when compared to body-weight-based cohorts. Of the evaluable patients treated (n = 13), 3 patients (23%) had a best overall response (BOR) of PR, 4 patients (31%) had a BOR of stable disease, and 6 patients (46%) had a BOR of progressive disease (PD). Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg every 21 days.

In conclusion, tislelizumab 200 mg once every 21 days is the recommended dose for pivotal studies.

1.5.8. Rationale for Phase 2 Tumor Type Selection

1.5.8.1. Head and Neck Squamous Cell Carcinoma

HNSCC, the ninth most common cancer globally, represents nearly 700,000 new cases and 380,000 deaths worldwide (Cohen et al 2019). Traditional treatment for HNSCC is associated with substantial morbidity and toxicity. Recurrent and metastatic (R/M) disease is usually incurable.

However, analysis of tissue samples from patients with HNSCC shows a highly immunogenic tumor microenvironment (Mandal et al 2016). Indeed, it has been shown that over 40 to 80% of patients with R/M disease have a combined positive score (CPS) for PD-L1 expression ≥ 1 to 20. An analysis of 280 different tumors also showed that HNSCC are among the most highly immune-infiltrated cancer types among other phenotypes indicative of an inflamed tumor. In 2016, the United States Food and Drug Administration (FDA) approved two immunotherapeutic agents, the anti-PD-1 monoclonal antibodies, nivolumab (Opdivo®, Bristol-Myers Squibb Company) and pembrolizumab (Keytruda®, Merck Sharp & Dohme Corp.), for the treatment of patients with R/M HNSCC refractory to platinum-based therapy. Subsequently in 2019, the FDA approved pembrolizumab for the first-line treatment of patients with unresectable R/M HNSCC. For frontline therapy, pembrolizumab was approved for use in combination with platinum and fluorouracil for all patients with R/M HNSCC and as a single agent for patients whose tumors express PD-L1 with CPS ≥ 1 as determined by an FDA-approved test (Cohen et al 2019). As anti-PD-1 therapy becomes the standard of care for first and second-line patients with unresectable R/M disease, patients who develop resistance to anti PD-1 therapy have limited therapeutic options thereby creating a significant unmet need to address anti-PD-1 resistance.

Accumulating data strongly supports TIM-3's role in the immunosuppression of TILs in HNSCC. Analysis of patient biopsy samples showed TIM-3's expression was significantly increased relative to paired non-tumor, non-diseased tissue as well as nonpaired dysplastic tissue (Liu et al 2017; Liu Z et al 2018; Liu JF et al 2018; Partlova et al 2015). Expression of TIM-3 was correlated with recurrence and lymph node metastases (Liu et al 2017; Liu Z et al 2018; Partlova et al 2015). TILs isolated from patient biopsy samples also showed the co-expression of TIM-3 and PD-1 CD8 TILs resulted in the greatest reduction in proinflammatory cytokines, compared with TIM-3+/PD-1- or TIM-3-/PD-1+ CD8 TILs, as well as in the proliferation of TILs (Shayan et al 2016). Nonclinical studies showed from two different groups showed anti-PD-1 treatment significantly increased TIM-3 expression on CD4+ and CD8+ T effector cells from both patient samples and murine models (in vitro, ex vivo, and in vivo) of HNSCC. Induction of TIM-3 expression was further associated with resistance to anti-PD-1 therapy such that combined blockade of TIM-3 and PD-1 pathways significantly increased in vivo tumor growth inhibition in mouse models of HNSCC.

LAG-3 also plays an important role in the immunosuppression of TILs in HNSCC. Analysis from TCGA database showed LAG-3 expression ranked high in HNSCC, compared with all the indications. Expression frequency of LAG-3 was also high in HNSCC (Chen et al 2020). Meanwhile, expression of LAG-3 was correlated with clinical state, including pathological grades and larger tumor size (Deng et al 2016). Importantly, a 3-year observational study followed with HNSCC patients who treated with anti-PD-L1 therapy, showed that both TIM-3+/PD-1+ and LAG-3+/PD-1+ co-expressed CD8+T cells was increased among

nonresponders, compared with anti-PD-L1 responders (12.4% vs. 4.4%, P= 0.03; 23.1% vs. 1.2%, P = 0.02, respectively); whereas the expression of CTLA4 was not significantly changed, which could be a driven mechanism of anti-PD-L1 resistance (Hanna et al 2018).

Taken as a whole, there is significant scientific rationale that blockade of the TIM-3 and/or LAG-3 pathway in patients with HNSCC may overcome resistance to anti-PD-1 therapy. The Cohorts 1, 4, 6 of Phase 2 dose expansion will evaluate the preliminary antitumor activity of BGB-A425 + tislelizumab, BGB-A425 + LBL-007 + tislelizumab, and LBL-007 + tislelizumab in patients with R/M HNSCC who developed resistance to prior anti-PD-1/PD-L1 therapy, respectively.

1.5.8.2. Non-Small Cell Lung Cancer

Lung cancer is the most common type of cancer occurring in both men and women in the past decade and is the leading cause of cancer deaths worldwide. With 2.1 million new lung cancer cases and 1.8 million deaths predicted in 2018, lung cancer represents close to 1 in 5 (18.4%) cancer deaths. NSCLC accounts for 80% to 85% of all lung cancers (American Cancer Society 2020).

The success of immune checkpoint therapy in recent years has revolutionized traditional cancer treatment. The biggest breakthrough of NSCLC treatment with immunotherapy has been demonstrating clinical practice change of durable efficacy from a late-line to a first-line setting. The FDA has approved 4 different monoclonal antibodies targeting the PD-1/PD-L1 pathway in NSCLC, covering stage III chemoradiation treatment to late-line in metastatic setting: pembrolizumab (PD-1 inhibitor) (KEYTRUDA® prescribing information), nivolumab (PD-1 inhibitor) (OPDIVO® prescribing information), atezolizumab (PD-L1 inhibitor) (TECENTRIQ® prescribing information), durvalumab (PD-L1 inhibitor) (IMFINZI™ prescribing information). Mounting evidence suggests that PD-L1 expression is useful biomarkers in NSCLC and widely used in clinical practice. The expression of PD-L1 in the tumor tissue is the most widely used biomarker and considered a companion diagnostic for the immunotherapy monotherapy for the first-line treatment of NSCLC after the results of KEYNOTE-024 (Garon et al 2015; Garon et al 2019). The KEYNOTE-024 study demonstrated a significant progression-free survival (PFS) (10.3 versus 6 months) and overall survival (OS) benefit with pembrolizumab alone compared with chemotherapy as the first-line treatment in patients with PD-L1 expression ≥ 50% (Reck et al 2016). In addition, KEYNOTE-042 study demonstrated a survival benefit with pembrolizumab in the first-line setting in patients with PD-L1 expression > 1% tumors (Mok et al 2019). Similar efficacy trend in correlation with PD-L1 status has also been observed in other PD-L1 clinical studies (Borghaei et al 2015; Gandhi et al 2018; Ancevski et al 2018).

Despite this stream of new life-extending treatments involving anti-PD-1/PD-L1 therapy, advanced or metastatic NSCLC remains an incurable disease for most patients. The interactions between the human immune system and tumor cells are continuous, dynamic, and evolving. Acquired resistance is described as the lack of response to immunotherapy after the patient initially responds to anti-PD-L1 treatment then relapses or progresses (Sharma et al 2017). The frequencies of primary resistance in advanced NSCLC patients whose best responses were progressive disease in first-line immune checkpoint inhibitors with or without chemotherapy varied from 7% to 27%; whilst in a pretreated setting with immune checkpoint monotherapy, the

reported rates ranged from 20% to 44% (Walsh and Soo 2020). For patients who experienced complete response, partial response, or stable disease from immunotherapy but tumor eventually relapsed or progressed, more effective treatment options with combating resistance and expanding the duration of response are needed.

Accumulating data also support TIM-3's role in the immunosuppression environment in NSCLC. Flow cytometry data of patient-derived TILs obtained at baseline showed that both squamous and adenocarcinoma patients had higher TIM-3 positive CD4+ and CD8+ T-cell percentage than the normal healthy people (Koyama et al 2016). By comparing the immune cells isolated from PD-1 native control effusions, PD-1 resistant effusions and primary tumor, it showed that the PD-1 resistant patients had higher TIM-3 positive CD4+ and CD8+ T-cell percentage than PD-1-naive patients. The RNA-seq data from 2 NSCLC mouse models also suggested upregulation of TIM-3 (HAVCR2) in PD-1 resistant mice than the untreated group (Lizotte et al 2016).

In addition, preliminary clinical efficacy signals were observed in anti-TIM-3 treatment, though the sample size was very limited. TSR-022 in combination with TSR-042, both developed by Tesaro, demonstrated 4 confirmed PRs observed across TSR-022 100 mg and 300 mg cohorts (n = 31; 13%) (Davar et al 2018) in patients with non-small cell lung cancer whose disease had progressed on prior anti-PD-1 treatment.

Similar as in HNSCC, LAG-3 also plays an important role in the immunosuppression of TILs in NSCLC. Analysis from TCGA database showed LAG-3 expression also ranked high in NSCLC, compared with all the indications. Multiplex quantitative immunofluorescence data from 730 clinically annotated NSCLC tissue analysis showed LAG-3 and TIM-3 were detected in TILs from 41.5% and 25.3% of NSCLC cases, respectively (Datar et al 2019, indicated high LAG-3 and TIM-3 expression frequency in NSCLC. Besides, elevated LAG-3 ligands (FGL1 or Galectin3) are found associated with worse response to anti-PD-L1 therapy (Wang et al 2019).

Taken together, the increasingly huge unmet medical needs, the pre-clinical research evidence, and the preliminary efficacy signals in TIM-3 clinical studies support the rationale to explore the hypothesis that anti-TIM-3 and/or anti-LAG-3 in combination with anti-PD-1 treatment has the potential to overcome the resistance from prior checkpoint inhibitor treatment. The Cohort 2, 5, 7 of Phase 2 dose expansion will evaluate the preliminary antitumor activity of BGB-A425 + tislelizumab, BGB-A425 + LBL-007 + tislelizumab, and LBL-007 + tislelizumab in patients with NSCLC who have been previously treated with checkpoint inhibitors, respectively.

1.5.8.3. Renal Cell Carcinoma

RCC represents 2% to 3% of all cancers, corresponding to 338,000 new cases diagnosed each year worldwide. Around 30% of patients will present metastatic disease at the time of diagnosis and metastases are found in 30% to 40% of those initially treated in curative intent. Clear cell RCC account for about 75% of RCC (Ferlay et al 2015). The management and treatment of metastatic RCC have undergone major improvements over the last 20 years. The development of targeted therapies, including vascular endothelial growth factor pathway inhibitors, mammalian target of rapamycin inhibitors; and, more recently, the emergence of checkpoint inhibitors, including PD-1 inhibitors, PD-L1 inhibitors, and anti-CTLA-4 antibodies have led to a wide treatment landscape remodeling (Kammerer-Jacquet et al 2019). FDA-approved immunotherapy include nivolumab, either alone or in combination with ipilimumab, as well as pembrolizumab and avelumab, both in combination with axitinib. These therapies produce response rates of 40%

to 60%, and median OS now approaches 4 years in patients with intermediate or poor risk treated with ipilimumab and nivolumab (Tannir et al 2020; Rini et al 2019; Motzer et al 2019).

Nonetheless, most patients with RCC receiving checkpoint inhibitors ultimately experience disease progression and require subsequent therapies. Current guideline recommendations regarding sequential therapy were based on data from the VEGFR-TKI era (Level of Evidence IV) (Albiges et al 2019; Auvray et al 2019; Escudier et al 2019). As checkpoint inhibition therapy becomes the standard of care in frontline setting, patients with RCC who develop resistance have no widely established treatment options thereby creating a significant unmet need to address checkpoint inhibition resistance.

Nonclinical research has discovered some evidence of TIM-3 role in the RCC disease pathological features. Immunofluorescence in tissue chips showed RCC tumors had significant higher TIM-3 fluorescence score in tumor infiltrating CD8-positive T-cells than the normal tissues. Looking at the clinical data, PFS is also different between the patients expressing PD-1 and TIM-3 above and below the median. Those above the median level of PD-1 and TIM-3 co-expression were more likely to relapse after locoregional treatment. In comparison, there was no such differentiation in the TIM-3 negative population. In addition, an in vitro cytokine release assay was conducted using CD8+ T-cells isolated from 2 RCC patients' tumors and then stimulated with CD3 and CD28. The results showed IFN-γ production significantly decreased in CD8+ T-cells co-expressing PD-1 and TIM-3 compared with the other 2 populations, which suggested impaired functions by PD-1 and TIM-3 co-expression (Hu et al 2020; Granier et al 2017).

In short, these research findings and the unmet medical needs in checkpoint inhibition resistant RCC supports the rationale to explore the hypothesis that anti-TIM-3 in combination with anti-PD-1 treatment has the potential to overcome the resistance mechanism. Cohort 3 of Phase 2 will evaluate the preliminary antitumor activity of BGB-A425 in combination with tislelizumab as the second-line or third-line treatment in RCC patients who have been pre-exposed to prior checkpoint inhibition and have demonstrated disease progression.

1.6. Benefit-Risk Assessment

There is limited human experience with BGB-A425 and LBL-007; therefore, their clinical benefit in patients with advanced solid tumors has not been determined. However, as discussed above, there is extensive evidence supporting the role of immune checkpoint protein TIM-3 and LAG-3 in promoting tumor immune escape, the combination of anti-TIM-3 or anti-LAG-3 with anti-PD-1 could further improve the antitumor response (Section 1.2, Section 1.3, Section 1.5.2, Section 1.5.3).

Combined with the clinical efficacy that has been demonstrated for PD-1 blockade via tislelizumab (Section 1.4), the data strongly suggest that BGB-A425 has the potential to significantly improve and/or extend the therapeutic benefits of tislelizumab. Similarly, clinical studies of LBL-007 or similar drugs in combination with anti-PD-1 monoclonal antibody show that anti-LAG-3 antibody has synergistic effects with anti-PD-1 antibody, and can greatly improve antitumor activity. The clinical study results of LBL-007 or same class drug in combination with anti-PD-1 monoclonal antibody showed favorable benefit risk profile. Therefore, the development of LBL-007 in combination with tislelizumab is expected to have a

potential favorable benefit risk ratio in patients with advanced solid tumors. As discussed in Section 1.4.4, PD-1 blockade by tislelizumab has been evaluated in more than 3498 patients with a safety and efficacy profile similar to what has been reported for other anti-PD-1 therapies. As discussed earlier in Section 1.2 to 1.5, based upon the mechanism(s) of action, nonclinical as well as clinical data, the combined blockade of TIM-3 and PD-1 by BGB-A425 and tislelizumab, respectively, or combined blockade of LAG-3 and PD-1 by LBL-007 and tislelizumab, respectively, or combined blockade of TIM-3, LAG-3 and PD-1 by BGB-A425, LBL-007 and tislelizumab, respectively, are expected to result in the observation of a increase in immune-mediated toxicities compared with what has been observed with tislelizumab alone.

Although a increased safety risk has been shown for other anti-PD-1 based immuno-oncology combinations, a comprehensive algorithm derived from the European Society for Medical Oncology and American Society for Clinical Oncology, has been established to monitor, diagnose as well as manage such immune-mediated toxicities (Appendix 8). It is important to note that peripheral effector T-cells typically do not express TIM-3, which is in contrast to TILs stimulated by the antigenic tumor microenvironment. Therefore, this mechanism provides the combination an opportunity to specifically augment the activity of effector T-cells at the level of the tumor rather than periphery and/or nontumor tissue (Anderson 2014; Das et al 2017; Du et al 2017).

As shown in Appendix 1, a comprehensive monitoring plan will be utilized to monitor patient safety. The subsequent safety data will be continuously analyzed by the sponsor's study team and in consultation with investigator(s) as needed. Refer to Section 1.5.1 and Section 8 for information regarding additional safeguards and considerations related to potential risk.

In summary, there is strong scientific rationale that the combined blockade of the TIM-3 and PD-1 pathway, or combined blockade of LAG-3 and PD-1 pathway or combined blockade of TIM-3 and LAG-3 and PD-1 pathway may significantly enhance the antitumor properties of anti-PD-1 monotherapy. Therefore, the potential risks associated with proposed combinations are justified by the potential treatment benefits to patients with advanced solid tumors.

1.7. Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and in accordance with Good Clinical Practice standards and the applicable regional regulatory requirements (eg, Regulation [EU] No. 536/2014).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives for Phase 1 (Dose Escalation)

2.1.1. Primary Objectives

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

2.1.2. Secondary Objectives

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

2.1.3. Exploratory Objectives

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

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

2.2.1. Primary Objective

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

2.2.2. Secondary Objectives

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

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

2.2.3. Exploratory Objectives

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

2.3. Study Objectives for Phase 2 (Dose Expansion)

2.3.1. Primary Objective

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

2.3.2. Secondary Objectives

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

2.3.3. Exploratory Objectives

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

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

2.4.1. Primary Endpoints

- Adverse events (AEs) and serious AE (SAEs) as characterized by type, frequency, severity (as graded by National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 5.0), timing, seriousness, and relationship to study therapy; laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v5.0), and timing; AEs meeting protocol defined dose limiting toxicity (DLT) criteria

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

2.4.2. Secondary Endpoints

- Efficacy evaluations: ORR, duration of response (DOR), and disease control rate (DCR) will be determined from investigator derived tumor assessments per RECIST v1.1 (as described in Section 9.2.1)
- PK: Maximum observed plasma concentration (C_{max}), minimum observed plasma concentration (C_{min}), time to maximum plasma concentration (T_{max}), half-life ($t_{1/2}$), area under the concentration-time curve from zero to 21 days ($AUC_{0\text{-}21d}$), CL, and apparent volume of distribution (Vz) for BGB-A425 and LBL-007; C_{max} and C_{min} for tislelizumab
- Immunogenicity: Immunogenic responses to BGB-A425, LBL-007, and tislelizumab will be assessed by summarizing the number and percentage of patients who develop detectable antidrug antibodies

2.4.3. Exploratory Endpoints

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

2.5. Study Endpoints for Phase 2 (Dose Expansion)

2.5.1. Primary Endpoint

- ORR as determined from investigator derived tumor assessments per RECIST v1.1 (as described in Section 9.2.2)

2.5.2. Secondary Endpoints

- Progression-free survival (PFS), DOR, and DCR will be determined from investigator derived tumor assessments as per RECIST v1.1 (as described in Section 9.2.3)
- Safety and tolerability: The safety of various combinations of BGB-A425 and LBL-007 with tislelizumab will be assessed throughout the study by monitoring AEs and SAEs per

NCI-CTCAE v5.0, physical examinations, electrocardiograms (ECGs), and laboratory assessments as needed

- PK: PK parameters such as C_{max}, C_{min}, T_{max}, $t_{1/2}$, and $AUC_{0\text{-}21d}$ for BGB-A425 and LBL-007; C_{max} and C_{min} for tislelizumab
- Immunogenicity: Immunogenic responses to BGB-A425, LBL-007, and tislelizumab will be assessed by summarizing the number and percentage of patients who develop detectable antidrug antibodies (ADAs).

2.5.3. Exploratory Endpoints

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

3. STUDY DESIGN

3.1. Summary of Study Design

This is an open-label, multicenter, nonrandomized Phase 1 and 2 clinical study evaluating various combinations of BGB-A425 and LBL-007 with tislelizumab. The study design schematic is presented in Figure 7. For all Phase 1 and Phase 2 study assessments and procedures, see Section 7 and Appendix 1.

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

This study consists of the following phases:

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

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

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

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

  During safety lead-in dose escalation, if the combination of BGB-A425 600 mg, LBL-007 600 mg, and tislelizumab 200 mg once every 21 days is deemed safe in Cohort B2, dose expansion will be evaluated in HNSCC and NSCLC cohorts following discussion and in agreement with the Safety Monitoring Committee (SMC). However, in

addition to the above mentioned dose, lower or higher dose levels of LBL-007 may be evaluated in the safety lead-in cohorts based on the analysis of emerging safety, tolerability, PK, biomarker, and other clinical data, if recommended by the SMC. If a dose level higher than 600 mg of LBL-007 for dose expansion cohorts is recommended by the SMC, a protocol amendment will be implemented.

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

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

  An interim analysis will be conducted based on approximately the first 20 evaluable patients in each dose expansion cohort (Sections 9.1.2 and 9.7). Based upon the interim analysis for a given tumor type cohort, up to approximately 40 evaluable patients for each cohort may be enrolled in that cohort as described in Section 9.7. As of the date of finalization of this protocol amendment v7.0, enrollment of Cohorts 1 and 2 is ongoing.

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

  All patients enrolled in Phase 2 dose expansion must have disease progression that occurred ≥ 10 weeks from the initiation of anti-PD-1/PD-L1 treatment for locally advanced or metastatic disease. All eligible patients will receive the respective combination(s) every 21 days starting on Cycle 1 Day 1. Positive PD-L1 expression from either local or central testing will be required in HNSCC and NSCLC patients in all dose expansion cohorts prior to enrollment. For baseline tumor tissue, fresh biopsy will be mandatory in the absence of sufficient archival tissue prior to the patient commencing first drug administration on Cycle 1 Day 1 (refer to Section 7.1 for additional details).

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

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

For Phase 1 dose escalation, a 28-day DLT observation period will be utilized for the initial dose-finding recommendations. To incorporate this DLT period into one cycle, only Cycle 1 will

have a duration of 28 days from Day 1. During this DLT period, patients must receive BGB-A425 alone on Cycle 1 Day 1 followed by tislelizumab alone on Cycle 1 Day 8 (+2 days) to be DLT evaluable. If no DLT(s) are observed thereafter and through the completion of the initial 28-day cycle, patients will receive both BGB-A425 and tislelizumab sequentially on Day 29 and every 21 days (ie, once every 21 days) until they meet a treatment discontinuation criterion. The occurrence of a DLT during the DLT observation period will result in expansion of that dose level cohort as discussed below. Refer to Section 5.6.1 and Section 5.6.2 regarding continued treatment of patients who are unable to receive tislelizumab on Cycle 1 Day 8 (+2 days).

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

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

a) BGB-A425 (Phase 1) dose escalation will advance if the first cycle DLT rate < 33%;

b) BGB-A425 (Phase 1) dose escalation will stop if the first cycle DLT rate is ≥ 33%. A minimum of 6 patients will be enrolled to the current dose level of BGB-A425 (Phase 1), if DLT rate is 33% (eg, 1/3) or the next lower dose level if DLT rate is > 33% (eg, 2/3 or 3/3);

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

More than 3 patients may be enrolled simultaneously during the DLT period(s) for a given dose level. In such cases, the dose escalation decision will be made based upon the above 3+3 rules. Further, for dose escalation decisions, only DLTs occurring within 28 days of Cycle 1 Day 1 for the corresponding dose level will be evaluated. However, as noted below and in Section 3.5, additional considerations may be taken into account if clinically significant toxicity(ies) is observed regardless of when it occurred.

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

As of the date of finalization of this protocol amendment v7.0, the Phase 1 dose escalation phase has been completed. The BGB-A425 + tislelizumab combination RP2D was determined primarily from the Phase 1 safety, tolerability, preliminary antitumor activity, pharmacodynamic biomarker, and PK data. The combination RP2D will be evaluated in the Phase 2 dose expansion.

For the Phase 2 safety lead-in, a dose escalation of LBL-007 will be carried out in Cohort A and Cohort B. In Cohort A, the dose escalation will start with Cohort A1; for Cohort B, the dose

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

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

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

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

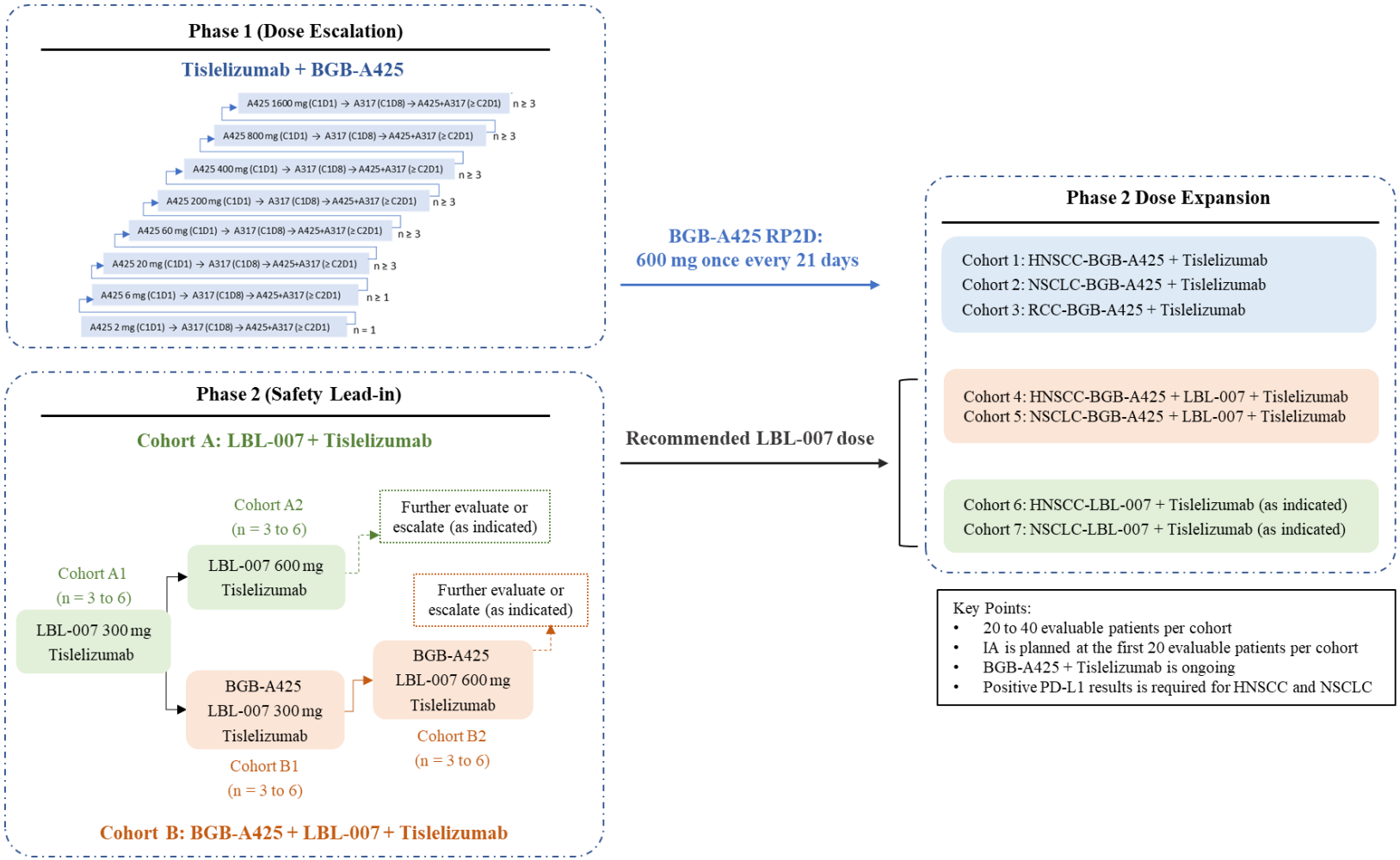
b) LBL-007 (Phase 2 Safety lead-in) dose escalation will stop if the first cycle DLT rate is ≥ 33%. A minimum of 6 patients will be enrolled to the current dose level of LBL-007, if DLT rate is 33% (eg, 1/3) or the next lower dose level if DLT rate is > 33% (eg, 2/3 or 3/3);

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

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

The recommended dose(s) for the 2 combinations (BGB-A425 + LBL-007 + tislelizumab and LBL-007 + tislelizumab) in Phase 2 dose expansion (Cohorts 4 to 7) will be determined based on safety, tolerability, PK data , pharmacodynamic biomarker, and preliminary antitumor activity from the Phase 2 safety lead-in.

Figure 7: Study Schema



Abbreviations: A317, tislelizumab (BGB-A317); A425, BGB-A425; C, Cycle; D, Day; HNSCC, head and neck squamous cell cancer; IA, interim analysis; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma; RP2D, recommended Phase 2 dose; TBD, to be determined
Notes: For Phase 2 safety lead-in, the dose for BGB-A425 and tislelizumab are 600 mg and 200 mg, respectively; Cohort A1 will be initiated first (as in Section 3.1). For Phase 2 dose expansion, Cohort 3 will be initiated per the results in Cohort 1 and Cohort 2; the enrollment of Cohorts 6 and 7 will be initiated per the emerging clinical data from the ongoing evaluation in Cohorts 4 and 5.

3.2. Study Periods

This study consists of the following periods. See Section 7 and Appendix 1 for study procedures to be conducted in each period.

3.2.1. Prescreening Period (Phase 2 Dose Expansion Only)

The purpose of the prescreening period in Phase 2 dose expansion is to allow time for confirmation of the PD-L1 test for HNSCC and NSCLC patients only. HNSCC and NSCLC patients with positive PD-L1 expression are eligible for enrollment.

The prescreening period has a maximum duration of 56 days prior to the first administration of study drug(s) and starts with the signing of the Prescreening ICF. Extension of the 56-day period may be granted on a case-by-case basis after discussion and written approval from the sponsor's medical monitor approval in discussion with the investigator.

Refer to Section 7.1 for additional details.

3.2.2. Screening Period

Unless otherwise specified, patients who agree to participate in this study will sign the ICF prior to undergoing any screening procedure.

The screening period has a maximum duration of 28 days prior to the first administration of study drug(s) and starts with the signing of the Screening ICF.

If a patient does not meet eligibility criteria for the study, they can be rescreened once with the sponsor's medical monitor approval, in discussion with the investigator. Patients who are planned to be rescreened (following sponsor approval) are required to be reconsented if assessments cannot be completed within the original 28-day screening period.

Refer to Section 7.2 for additional details.

3.2.3. Treatment Period

After completing all screening activities, patients confirmed to be eligible by the investigator will be treated with combination treatments as described in Section 3.1, Section 5.3, or Appendix 1.

All patients will receive study drug until 1) they are no longer considered to receive clinical benefit, 2) unacceptable toxicity, or 3) withdrawal of informed consent. Refer to Section 3.3.1 for more details.

The End of Treatment (EOT) Visit is conducted within 7 days from the date the investigator determines that study drug(s) will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT Visit, these tests need not be repeated. Tumor assessment is not required at the EOT Visit provided that fewer than 6 weeks have passed since the last assessment.

3.2.4. Safety Follow-up Period

Patients who discontinue treatment for any reason will be asked to return to the clinic for the Safety Follow-up Visit (see Appendix 1 for assessments), which is to occur within 30 days

(± 7 days) after last dose of the study drug(s) or before initiation of a new anticancer treatment, whichever occurs first. The EOT Visit may also be used as the Safety Follow-up Visit, provided that it occurred 30 days (± 7 days) after the last study treatment. If the EOT Visit and Safety Follow-up Visit are combined, all individual study assessments (for both visits per Appendix 1) will need to be completed.

In addition, telephone contact and/or clinic visits with patients will be conducted to assess imAEs (serious and nonserious), anticancer therapy, and concomitant medications/procedures where appropriate (ie, associated with an imAE etc) at 60 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 imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated. In Phase 2, an additional pregnancy test must be performed for women of childbearing potential at approximately 120 days after the last dose of study treatment.

All AEs, including SAEs, will be collected as described in Section 8.7.

3.2.5. Efficacy Follow-up Period

Patients who discontinue study treatment for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan (Section 7.6 or Appendix 1) until the patient meets one of the discontinuation criteria (Section 3.3.2).

3.2.6. Survival Follow Up Period (Phase 2 Dose Expansion Only)

In Phase 2 dose expansion, patients will be followed for survival and further anticancer therapy information after discontinuation of study treatment. This will occur via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the 90 days Safety Follow-up phone call (at the expected date) or as directed by the sponsor until death, withdrawal of consent, loss to follow-up, or end of study.

3.3. Discontinuation from the Study Treatment or from the Study

3.3.1. Patient Discontinuation from Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue one of the study drugs will be required to discontinue other study drugs. Rare exceptions may be made after approval from the medical monitor. Patients who discontinue study treatment must undergo follow-up as described in Section 7.5 and Section 7.6), where 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 which include, but are not limited to, the following:

- Progressive disease (PD)

  Note: Patients who experience PD should be assessed to exclude pseudo-progression by additional tumor imaging at 4 weeks or later, but no less than 12 weeks, after the initial date of disease progression (as per Section 7.6). If the patient has confirmed PD on the

follow-up scan and the investigator believes that the patient could continue to benefit from the assigned study drug treatment after PD, the patient may continue their assigned treatment after patient re-consent using the Treatment Through Progression ICF, only after discussion and agreement by both investigator and sponsor's medical monitor.

- Adverse events
- Patient withdrawal of consent for study treatment
- 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 antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including herbal medicine and Chinese patent medicines] for the treatment of cancer)
- Patient noncompliance

If patients have confirmed compete response (CR), partial response (PR), or stable disease after 24 months, the study treatment can be paused for a period of time (at patient request) after the investigator's agreement and sponsor's written approval. The decision to pause treatment should be based on the investigator's evaluation, with the patient's clinical benefit and risk taken into consideration. The investigator should notify and seek written agreement from the sponsor's medical monitor that treatment will be paused prior to the event. In such a case, the study assessments and procedures will be performed every 12 weeks (in conjunction with repeated radiographic imaging) as per section 7.6.

Following a period of paused treatment, the recommencement of combination therapies will be determined by the investigator and sponsor following the clinical risk/benefit assessment, and will be contingent on the continued availability of study drug(s).

3.3.2. Patient Discontinuation from Study (End of Study for an Individual Patient)

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

- Patient withdrawal of consent for the study
- Death
- Lost to follow-up (at minimum, 3 contact attempts must be made and documented in the source documents)
- Patients have completed all study assessments

Once the patients decide to discontinue from the study, they will be provided with Patient's Discontinuation From Study Participation ICF to sign. If a patient is unable to sign the Patient's Discontinuation From Study Participation ICF for any reason, the investigator should document the patient's decision to discontinue from the study and, if possible, the reason for discontinuation in the patient history. The reason for discontinuation should also be entered into the relevant section of the eCRF.

3.4. End of Study

The end of study is defined as whichever timepoint comes first: the last study patient dies, is lost to follow-up, or withdraws from study; or the sponsor decides to terminate or complete 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 Visit and 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 Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) of the early termination of the study.

The sponsor also has the right to close a site at any time. The decision will be notified to the site 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
- Noncompliance with Good Clinical Practice
- Study activity is completed (ie, all patients have completed, and all obligations have been fulfilled)

Currently, the sponsor does not have any plans to provide any study drug or other treatments or interventions to the patients after the completion of the study or after patients withdraw informed consent for this study. The patients are suggested to return to their primary physician to determine the following standard of care. If the study is successfully completed, any patients who have completed the study and, in the opinion of the investigator, continue to benefit from study drugs at study termination may be offered the option to continue the study treatment in a company-sponsored clinical trial, subject to local regulatory requirements and availability of study drug.

3.5. DLT Definition

All toxicities or AEs will be graded according to the NCI-CTCAE v5.0. The occurrence of any of the following toxicities will be considered a DLT: 1) during the Phase 1 dose escalation if it occurs within 28 days of receiving BGB-A425 on Cycle 1 Day 1 and is deemed to be related to study drug; 2) during the Phase 2 safety lead-in if it occurs within 21 days of receiving LBL-007 combination treatments on Cycle 1 Day 1 and is deemed to be related to study drug.

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 infection
4. Grade 3 thrombocytopenia with bleeding
5. Grade 4 thrombocytopenia
6. Grade 4 anemia (life threatening)

Nonhematologic:

1. ≥ Grade 4 toxicity
2. Grade 3 toxicity that is clinically significant and does not resolve to baseline or ≤ Grade 1 within 3 days of initiating optimal supportive care

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

1. Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
2. Grade 3 tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumors)
3. Grade 3 rash
4. Grade 3 infusion-related AE that is transient (resolving within 6 hours of onset).

All available safety data, including AEs, laboratory assessments, and PK analyses (as available), will be reviewed by the sponsor's medical monitor and study team members from Pharmacovigilance/Drug Safety, Clinical Pharmacology and Biostatistics with input from other members as appropriate. On the basis of a review of these data and in consultation with the investigators, a determination will be made regarding dose finding decisions and/or safety management. As such, clinically important or persistent toxicities that are not included above may also be considered a DLT following review by the sponsor in consultation with investigators or following review by the SMC (see Section 10.1). Additionally, any clinically significant toxicities that occur after the DLT observation period (eg, late immune-mediated AE) for a given dose level, may be taken into account regarding subsequent dose escalation and/or RP2D decisions. In such cases where patients have been safely dosed at the next dose level, additional dose escalation criteria (eg, increase minimum number of patients, expand the DLT observation period, etc.) for subsequent dose levels will be considered by the sponsor in consultation with participating investigators.

Patients must meet <u>one</u> of the following during the DLT observation period to be considered DLT evaluable:

1) For Phase 1 dose escalation: received ≥ 80% of the assigned doses of BGB-A425 on Cycle 1 Day 1 and tislelizumab on Cycle 1 Day 8 (+2 days) and remained on study for 28 days following Cycle 1 Day 1 administration of BGB-A425; or

2) For Phase 2 safety lead-in: received ≥ 80% of the assigned doses of LBL-007 with the respective combination treatments (Cohort A and Cohort B) on Cycle 1 Day 1 and remained on study for 21 days following Cycle 1 Day 1 administration of combinations; or

3) Experienced a DLT.

Patients who fail to meet one of the above criteria may be replaced.

4. STUDY POPULATION

The specific eligibility criteria for 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 must meet all of the following inclusion criteria to be considered eligible for participation in this study:

1. Able to provide written informed consent by the patient and can understand and 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. **Phase 1 and Phase 2 safety lead-in:** Patients with histologically or cytologically confirmed advanced, metastatic, unresectable solid tumors who have previously received standard systemic therapy as per respective local guidelines, unless standard systemic therapy is not available, not tolerated, or determined not appropriate based on investigator's judgement
4. Patient has not received prior therapy targeting TIM-3 and/or LAG-3
5. **Phase 2 dose expansion:** Patients with one of the following histologically or cytologically confirmed solid tumors:

For HNSCC patients in Cohort 1, 4 and 6:

- Recurrent/metastatic head and neck squamous cell cancer of the oral cavity, oropharynx, hypopharynx, and/or larynx whose tumor is not amenable to local therapy with curative intent (ie, surgery or radiation therapy with or without chemotherapy)
- Have received up to 3 lines* of prior systemic therapy that includes anti-PD-1/PD-L1 antibody and available standard of care (such as anti-PD-1 and cetuximab) as per respective local guidelines, unless standard systemic therapy is not available, not tolerated, or determined not appropriate based on investigator's judgement
- Anti-PD-1/PD-L1 antibody treatment for local disease will count as a line of therapy if disease progression occurred ≤ 6 months between the completion of treatment and date of recurrence
- Disease progression occurred ≥ 10 weeks from the initiation of anti-PD-1/PD-L1 treatment for locally advanced or metastatic disease
- PD-L1 expression positivity defined as PD-L1 CPS ≥ 1 by PD-L1 IHC 22C3 pharmDx assay (preferred) or PD-L1 (CPS ≥ 1, vCPS or TAP ≥ 1%) by VENTANA PD-L1 (SP263) in local testing, or 22C3 pharmDx assay in central testing on recently obtained archival tissue or fresh tumor biopsy. Refer to Section 7.1 for additional details

  Note: PD-L1 positivity determined by PD-L1 IHC 22C3 pharmDx assay will be used for HNSCC patients in the EU.

- No prior treatment with an anti-TIM-3, anti-LAG-3 or any therapies targeting T-cell costimulation or checkpoint pathway other than the above noted prior anti-PD-1/PD-L1 treatment. Prior anti-CTLA-4 treatment is allowed
- Patients' tumor status for human papillomavirus must be known. Documentation of p16 is sufficient to determine human papillomavirus status for tumor originating from the oropharynx

For NSCLC patients in Cohort 2, 5 and 7:

- Stage IIIB, IIIC, or Stage IV squamous or non-squamous non-small cell lung cancer
- Have received up to 3 lines* of prior systemic therapy that includes anti-PD-1/PD-L1 antibody and available standard of care (such as combination of anti-PD-1 and chemotherapy, received either as combination therapy or 2 separate lines) as per respective local guidelines, unless standard systemic therapy is not available, not tolerated, or determined not appropriate based on investigator's judgement
- Anti-PD-1/PD-L1 antibody treatment for local disease will count as a line of therapy if disease progression occurred ≤ 6 months between the completion of treatment and date of recurrence
- Disease progression occurred ≥ 10 weeks from the initiation of anti-PD-1/PD-L1 treatment for locally advanced or metastatic disease
- PD-L1 expression positivity defined as PD-L1 TPS or TC ≥ 1% by PD-L1 IHC 22C3 or 28-8 pharmDx or VENTANA PD-L1 (SP263) assay in local testing, or 22C3 pharmDx assay in central testing on recently obtained archival tissue or fresh tumor biopsy. Refer to Section 7.1 for additional details

  Note: If PD-L1 IHC 28-8 assay is to be used for determining PD-L1 positivity, it will be used for nonsquamous NSCLC patients only in the EU.
- No prior treatment with an anti-TIM-3, anti-LAG-3, or any therapies targeting T-cell costimulation or checkpoint pathway other than the above noted prior anti-PD-1/PD-L1 treatment). Prior anti-CTLA-4 treatment is allowed

For RCC patients in Cohort 3:

- Locally advanced unresectable or metastatic and histologically confirmed renal cell carcinoma with a clear cell histology
- Have received up to 3 lines* of prior systemic therapy that includes anti-PD-1/PD-L1 antibody and available standard of care (such as a second line of treatment based on tyrosine kinase inhibitor) as per respective local guidelines, unless standard systemic therapy is not available, not tolerated, or determined not appropriate based on investigator's judgement
- Anti-PD-1/PD-L1 antibody treatment for local disease will count as a line of therapy if disease progression occurred ≤ 6 months between the completion of treatment and date of recurrence

- Disease progression occurred ≥ 10 weeks from the initiation of anti-PD-1/PD-L1 treatment for locally advanced or metastatic disease
- No prior treatment with an anti-TIM-3 or any therapies targeting T-cell costimulation or checkpoint pathway other than the above noted prior anti-PD-1/PD-L1 treatment. Prior anti-CTLA-4 treatment is allowed
- Able to provide recently obtained archival tumor tissue or fresh tumor biopsy

*Note: A line of treatment includes the following

a. At least 1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens
b. Adjuvant and neo-adjuvant systemic therapy will count as a prior line of systemic therapy if the disease progressed on or within 6 months between the last dose and the date of recurrence
c. In locally advanced and unresectable HNSCC and NSCLC, disease progression on or within 6 months of the end of prior curative intended multimodal therapy will count as a prior line of systemic therapy. If chemoradiation is followed by planned systemic therapy without documented progression between chemoradiation and systemic therapy, the entire treatment course counts as 1 line of therapy

6. Complete the required tumor imaging screening evaluations ≤ 28 days before the first dose of study drug(s):

a. **Phase 2 safety lead-in:** mandatory imaging of the head (preferably MRI), neck, chest, abdomen and pelvis; and other known or suspected sites of disease must be included in the imaging assessments.

b. **Phase 2 dose expansion:** All other known or suspected sites of disease and the following imaging (CT or MRI as appropriate) is required:

   – for HNSCC patients: mandatory imaging of head (preferably MRI), neck, chest, and abdomen

   – for NSCLC and RCC patients: mandatory imaging of head (preferably MRI), chest, abdomen, and pelvis

7. **Phase 1 and Phase 2 safety lead-in:** hepatocellular carcinoma patients must meet the Child-Pugh A classification for liver function as assessed within 7 days before first dose of study drug (Appendix 10)
8. **Phase 1 and Phase 2 safety lead-in:** has at least 1 evaluable lesion per RECIST v1.1
9. **Phase 2 dose expansion:** has at least 1 measurable lesion outside of the central nervous system per RECIST v1.1 that has not undergone prior locoregional therapy regardless of subsequent progression
10. **Phase 1 and Phase 2 safety lead-in:** If available, patients must be able to provide an archived formalin fixed paraffin embedded (FFPE) tumor tissue sample (block or approximately 15 freshly cut unstained FFPE slides)

    Phase 2 dose expansion: Patients must be able to provide a recently obtained FFPE tumor tissue sample (FFPE block or approximately 15 freshly cut unstained FFPE slides).

If archival tissue is insufficient, a fresh tumor biopsy is mandatory prior to commencing treatment on Cycle 1 Day 1.

11. Has ECOG performance status ≤ 1
12. Has adequate organ function as indicated by the following laboratory values within 7 days prior to the first dose of study drug(s):

    - Absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelets ≥ 75×10^9/L, hemoglobin ≥ 90 g/L. Note: Patients must not have required a blood transfusion or growth factor support ≤ 14 days before sample collection
    - Serum creatinine ≤ 1.5 × upper limit of normal (ULN), or estimated glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 7)
    - Serum total bilirubin ≤ 1.5 X ULN (total bilirubin must be < 3 × ULN for patients with Gilbert's syndrome)
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN, or ≤ 5 × ULN for patients with liver metastases

13. Female patients of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and ≥ 6 months after the last dose of study drugs, and have a negative urine or serum pregnancy test ≤ 7 days of enrollment
14. Non-sterile male patients must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 6 months after the last dose of study drugs

4.2. Exclusion Criteria

Patients who meet any of the following criteria must be excluded from this study:

1. **In Phase 2 dose expansion:** NSCLC patients with known sensitizing epidermal growth factor receptor (EGFR) mutation, v-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutation, anaplastic lymphoma kinase (ALK) fusion, or c-ros oncogene 1 (ROS1) fusion are excluded.

a. For non-squamous and squamous NSCLC, patients with known EGFR mutation status, BRAF mutation, ALK fusion, or ROS1 fusion, who are sensitive to available targeted inhibitor therapy are excluded (Note: If no targeted therapy approved by local health authority is available for BRAF or ROS1 mutations, these patients are eligible).
b. Patients with non-squamous histology must have been tested locally for EGFR status preferably using an FDA-approved or local Health Authority approved test at screening. Patients with sensitive EGFR mutation status will be excluded.
c. Patients with non-squamous histology are encouraged to be tested for the mutational status of BRAF, ALK, and ROS1 locally using appropriate health authority recommended molecular test at screening. Patients with sensitive BRAF, ALK, and ROS1 mutation status will be excluded. If not previously tested, patients with unknown ALK, ROS1, or BRAF status may be enrolled.

d. Patients with squamous NSCLC and unknown EGFR mutation, BRAF mutation, ALK fusion, and ROS1 fusion status will not be required to be tested at screening

2. Active leptomeningeal disease or uncontrolled, untreated brain metastasis.

   Patients with equivocal findings or with confirmed brain metastases are only eligible for enrollment if they are asymptomatic and radiologically stable without the need for central nervous system (CNS) disease related corticosteroid treatment for at least 4 weeks prior to the first dose of study drug(s)

3. Active autoimmune diseases or history of autoimmune diseases that may relapse or history of life-threatening toxicity related to prior immune therapy, with the following exception:

   - Controlled type I diabetes
   - Hypothyroidism (provided it is managed with hormone replacement therapy only)
   - Controlled celiac disease
   - Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia)
   - Any other disease that is not expected to recur in the absence of external triggering factors (requires consultation with the medical monitor prior to enrollment)

4. Any active malignancy ≤ 2 years before the first dose of study drug(s), except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast)

5. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before administration of study drug

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

- Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
- Topical, ocular, intra-articular, intranasal, or inhalational corticosteroid with minimal systemic absorption
- Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a non-autoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)

6. With history of interstitial lung disease, noninfectious pneumonitis or uncontrolled lung diseases, including pulmonary fibrosis, acute lung diseases, etc

Note: Patients with significantly impaired pulmonary function, or any patient with non-small cell lung cancer enrolled in Phase 2, must undergo an assessment of pulmonary function at screening (see Section 7.2.4)

7. With uncontrolled diabetes, > 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
8. With infections (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal, or antiviral therapy ≤ 14 days prior to the first dose of study drug(s), or a requirement for chronic prophylactic treatment with antibiotics.

Note: antiviral therapy is permitted for eligible patients with HBV infection.

9. A known history of HIV infection
10. **Phase 1 dose escalation and Phase 2 safety lead-in:** A known history of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, except for patients with hepatocellular carcinoma.

Note: for patients with hepatocellular carcinoma only: Patients with untreated chronic hepatitis B or chronic hepatitis B virus carriers with HBV DNA ≥ 500 IU/mL (or 2500 copies/mL) or patients with detectable HCV RNA at screening

Phase 2 dose expansion: Patients with untreated chronic hepatitis B or chronic hepatitis B virus carriers with HBV DNA ≥ 500 IU/mL (or 2500 copies/mL) or patients with detectable HCV RNA at screening

11. Has undergone any major surgical procedure within 28 days before the first administration of study drug(s)
12. Diagnosis of prior immunodeficiency or has undergone prior allogeneic stem cell transplantation or organ transplantation
13. Has any of the following cardiovascular criteria:
    - Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, within 28 days before the first administration of study drug(s)
    - Pulmonary embolism or other clinically significant episode of thromboembolic disease within 28 days before the first administration of study drug(s)
    - Any history of acute myocardial infarction within 6 months before the first administration of study drug(s)
    - Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 6) within 6 months before the first administration of study drug(s)
    - Any event of ventricular arrhythmia ≥ Grade 2 in severity within 6 months before the first administration of study drug(s)
    - Any history of cerebrovascular accident within 6 months before the first administration of study drug(s)
    - Uncontrolled hypertension: systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg on repeated measurements that cannot be managed by standard antihypertension medications ≤ 28 days before the first dose of study drug(s)
14. Has a history of severe hypersensitivity reactions to other monoclonal antibodies

15. **Phase 1 dose escalation and Phase 2 safety lead-in:** Has received any chemotherapy, radiotherapy, immunotherapy (eg, interleukin, interferon, thymosin, etc) or any investigational therapies within 28 days or 5 half-lives (whichever is shorter) of the first administration of study drug

Phase 2 dose expansion: Has received any chemotherapy, radiotherapy, immunotherapy (eg, interleukin, interferon, thymosin, etc) or any investigational therapies within 14 days or 5 half-lives (whichever is shorter) of the first administration of study drug(s)

Note: Exceptions may be considered for palliative radiotherapy to a limited field following consultation with the medical monitor

16. Has received any herbal medicine or Chinese patent medicines used to control cancer within 14 days of the first study drug(s) administration (see Appendix 11 for examples)
17. Patients with toxicities (as a result of prior anticancer therapy) which have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
18. Was administered a live vaccine ≤ 28 days prior to the first dose of study drug(s) administration

Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed. For COVID-19 vaccines, non-live vaccines are allowed, including inactivated vaccines; live or live-attenuated vaccines ≤ 28 days before the first dose of study treatment are not allowed.

19. Underlying medical conditions (including psychiatric conditions and cognitive dysfunction) or alcohol or drug abuse or dependence that, in the investigator's opinion, will be unfavorable for the administration of study drug or affect the explanation of drug toxicity or AEs; or insufficient compliance during the study according to investigator's judgement
20. Concurrent participation in another therapeutic clinical trial, unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study
21. Women who are pregnant or nursing

5. STUDY TREATMENT

5.1. Medicinal Product Approval Status

A list of all investigational medicinal products (IMPs) that will be used in this study and their regulatory approval status are provided in Table 3. No auxiliary medicinal products, defined by Article 2(8) of Regulation (EU) 536/2014, will be used in this study.

Table 3: Investigational Medicinal Products Used in Study BGB-900-102 and Their Regulatory Approval Status

Country/Region	Approved for Treatment of Advanced Solid Tumors (Yes/No)		
	BGB-A425	Tislelizumab	LBL-007
USA	No	No	No
Korea	No	No	No
Australia	No	No	No
European Union	No	No	No

5.2. Formulation, Packaging, and Handling

5.2.1. BGB-A425

BGB-A425 (20 mg/mL) is a monoclonal antibody formulated for intravenous infusion and is provided as a preservative-free, single-use vial, containing a minimum of 15 mL of a 20 mg/mL concentrated solution (300 mg) antibody in a buffered isotonic solution. BGB-A425 has been aseptically filled in single-use vials (20 mL; USP Type I glass) with a coated butyl rubber stopper and sealed with an aluminum flip-off cap. Each vial is packaged into a single carton box.

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

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

Refer to the Pharmacy Manual for details regarding intravenous administration, accountability, and disposal. Please also refer to the BGB-A425 Investigator's Brochure for other details regarding BGB-A425.

5.2.2. Tislelizumab

Tislelizumab (10 mg/mL) is a monoclonal antibody formulated for intravenous infusion and is provided as a preservative-free, single-use vial, containing a minimum of 10 mL of a 10 mg/mL concentrated solution (100 mg) of antibody in a buffered isotonic solution. Tislelizumab has been aseptically filled in single-use vials (20 mL; USP Type I glass) with a coated butyl rubber stopper and sealed with an aluminum flip-off cap. Each vial is packaged into a single carton box.

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

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

Refer to the Pharmacy Manual for details regarding intravenous administration, accountability, and disposal. Please also refer to the Tislelizumab Investigator's Brochure for other details regarding tislelizumab.

5.2.3. LBL-007

LBL-007 (17 mg/mL) is a monoclonal antibody formulated for intravenous infusion and is provided as a preservative-free, single-use vial, containing a minimum of 5 mL of a 17 mg/mL concentrated solution (85 mg) of antibody in a buffered isotonic solution. LBL-007 is aseptically filled in single-use vials (6 mL; USP Type I glass) with a coated butyl rubber stopper and sealed with an aluminum flip-off cap.

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

The study drug must be kept at the storage condition specified on the label. Do not freeze. Shaking should be avoided.

Refer to the Pharmacy Manual for details regarding intravenous administration, accountability, and disposal. Please also refer to the LBL-007 Investigator's Brochure for additional information.

5.3. Dosage, Administration, and Compliance

All patients will be monitored continuously for AEs. Treatment modifications (eg, dose delay) as described in Section 5.6 will be based on specific laboratory and AE criteria. Guidelines for dose modification, treatment interruption, or discontinuation and for the management of infusion-related reactions and imAEs are provided in detail in Section 5.6, Section 8.7, and Appendix 8.

BGB-A425, tislelizumab and LBL-007 will be administered separately by intravenous infusion, through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2 micron in line or add-on filter. As described below, BGB-A425, tislelizumab and LBL-007 must be prepared and administered as separate infusions and may not be administered with any other drug (refer to Section 6).

Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

5.3.1. Phase 1 (Dose Escalation): BGB-A425 and Tislelizumab Combination

Planned and evaluated Phase 1 dose level(s) and dosing frequency for BGB-A425 and/or tislelizumab are provided in Table 4.

Table 4: Phase 1 Dose Levels for BGB-A425 and/or Tislelizumab

Study Drug	Dose	Frequency of Administration	Route of Administration	Duration of Treatment [a]
BGB-A425	2 mg 6 mg 20 mg 60 mg 200 mg 400 mg 800 mg 1600 mg (lower intermediate and/or higher dose levels may be explored)	Cycle 1 Day 1, Cycle 2 Day 1, then once every 21 days	Intravenous	Until disease progression, unacceptable toxicity, or voluntary withdrawal of consent per patient decision
Tislelizumab	200 mg	Cycle 1 Day 8, Cycle 2 Day 1, then once every 21 days	Intravenous	Until disease progression, unacceptable toxicity, or voluntary withdrawal of consent per patient decision

Abbreviations: CR, complete response; PR, partial response.
[a] For patients who have confirmed CR, PR, or stable disease after 24 months, the treatment can be paused for a period of time (at patient request) following the investigator's agreement and sponsor's written approval. (as in Section 3.3.1).

Only Cycle 1 will be 28 days in length. Thereafter starting with Cycle 2, each cycle will be 21 days in length (ie, once every 21 days). In the first cycle, BGB-A425 will be administered on Day 1, and tislelizumab will be administered on Day 8 (+2 days). Following completion of Cycle 1, patients will then receive tislelizumab followed by the administration of BGB-A425 on Day 1 of each subsequent 21-day cycle (ie, once every 21 days). Other dosing regimens of BGB-A425 may be explored based on safety, tolerability, PK, and antitumor activities observed in dose levels completed. However, the dosing regimen of tislelizumab will remain fixed as shown in Table 4.

For the first 2 cycles (or first 2 administrations of study drug in case of dose delays), tislelizumab will be administered over 60 (± 10) minutes and BGB-A425 over 60 (± 10) minutes. For Cycle 2, tislelizumab will be administered first followed by the administration of BGB-A425. Following final infusion of study drug, patients must be monitored for at least 120 minutes in an area with resuscitation equipment and emergency agents (Table 5).

If infusions of tislelizumab and BGB-A425 are well tolerated in the first 2 cycles, on Cycle 3 Day 1 (or the third administration of study drug in case of dose delays), tislelizumab may be administered for no less than 30 minutes followed by the administration of BGB-A425 over 60 (± 10) minutes. Following final infusion of study drug, patients must be monitored for at least 120 minutes in an area with resuscitation equipment and emergency agents (Table 5).

If infusions of tislelizumab and BGB-A425 are well tolerated in the first 3 cycles, on Cycle 4 Day 1 (or the fourth administration of study drug in case of dose delays) and subsequent cycles, tislelizumab may be administered no less than 30 minutes followed by the administration of BGB-A425 for no less than 30 minutes. Thereafter, patients must be monitored for at least 30 minutes in an area with resuscitation equipment and emergency agents (Table 5).

The infusion rate may be decreased or infusion may be stopped in the event of infusion-related reactions. See Section 8.7 for details.

Table 5: Phase 1 Administration of BGB-A425 and Tislelizumab and Monitoring Time

Cycle	BGB-A425 and Tislelizumab combination
Cycle 1 Day 1	BGB-A425 infusion over 60 (± 10) minutes Patient monitoring for at least 120 minutes post completion of last infusion
Cycle 1 Day 8	Tislelizumab infusion over 60 (± 10) minutes Patient monitoring for at least 120 minutes post completion of last infusion
Cycle 2 Day 1	Tislelizumab infusion over 60 (± 10) minutes followed by BGB-A425 infusion over 60 (± 10) minutes Patient monitoring for at least 120 minutes post completion of last infusion
Cycle 3 Day 1	Tislelizumab infusion for no less than 30 minutes followed by BGB-A425 infusion over 60 (± 10) minutes Patient monitoring for at least 120 minutes post completion of last infusion
Cycle 4 Day 1 onwards	Tislelizumab infusion no less than 30 minutes followed by BGB-A425 infusion for no less than 30 minutes Patient monitoring for at least 30 minutes post completion of last infusion

5.3.2. Phase 2 (Safety Lead-in)

5.3.2.1. Cohort A (LBL-007 + Tislelizumab)

Planned and evaluated Phase 2 safety lead-in dose level(s) and dosing frequency for LBL-007 and tislelizumab are provided in Table 6.

Table 6: Phase 2 Safety Lead-in Dose Levels for Cohort A: LBL-007 and Tislelizumab

Study Drug	Dose	Frequency of Administration	Route of Administration	Duration of Treatment [a]
LBL-007	300 mg 600 mg (higher dose levels such as 900 mg may be explored)	Cycle 1 Day 1, then once every 21 days	Intravenous infusion	Until disease progression, unacceptable toxicity, or voluntary withdrawal of consent per patient decision
Tislelizumab	200 mg			

Abbreviations: CR, complete response; PR, partial response.

[a] For patients who have confirmed CR, PR, or stable disease after 24 months, the treatment can be paused for a period of time (at patient request) following the investigator's agreement and sponsor's written approval. (as in Section 3.3.1).

For the first cycle (or first 2 administrations of study drug in case of dose delays), LBL-007 will be infused over 60 (± 10) minutes, followed by patient monitoring for 60 (± 30) minutes; then tislelizumab will be infused over 60 (± 10) minutes. Following final infusion of study drug, patients must be monitored for at least 120 minutes in an area with resuscitation equipment and emergency agents.

If infusions of LBL-007 and tislelizumab are well tolerated in the first cycle, on Cycle 2 Day 1 and Cycle 3 Day 1, LBL-007 may be infused for no less than 30 minutes followed by patient monitoring for 60 (± 30) minutes; then tislelizumab will be infused for no less than 30 minutes. Following final infusion of study drug, patients must be monitored for at least 120 minutes in an area with resuscitation equipment and emergency agents.

If infusions of LBL-007 and tislelizumab are well tolerated in the first 3 cycles, on Cycle 4 Day 1 and subsequent cycles, LBL-007 may be infused for no less than 30 minutes followed by patient monitoring for 60 (± 30) minutes; then tislelizumab will be infused for no less than 30 minutes. Following final infusion of study drug, patients must be monitored for at least 60 minutes in an area with resuscitation equipment and emergency agents (Table 7).

Table 7: Phase 2 Safety Lead-in Administration of Cohort A: LBL-007 and Tislelizumab and Monitoring Time

Cycle	LBL-007 and Tislelizumab combination
Cycle 1 Day 1	LBL-007 infusion over 60 (± 10) minutes, followed by patient monitoring for 60 (± 30) minutes, followed by tislelizumab infusion over 60 (± 10) minutes Patient monitoring for at least 120 minutes post completion of last infusion
Cycle 2 Day 1 Cycle 3 Day 1	LBL-007 infusion for no less than 30 minutes, followed by patient monitoring for 60 (± 30) minutes, followed by tislelizumab infusion for no less than 30 minutes Patient monitoring for at least 120 minutes post completion of last infusion
Cycle 4 Day 1 onwards	LBL-007 infusion for no less than 30 minutes, followed by patient monitoring for 60 (± 30) minutes, followed by tislelizumab infusion for no less than 30 minutes Patient monitoring for at least 60 minutes post completion of last infusion

5.3.2.2. Cohort B (BGB-A425 + LBL-007 + Tislelizumab)

Planned and evaluated Phase 2 safety lead-in dose level(s) and dosing frequency for BGB-A425, LBL-007, and tislelizumab are provided in Table 8.

Table 8: Phase 2 Safety Lead-in Dose Levels for Cohort B: BGB-A425, LBL-007, and Tislelizumab

Study Drug	Dose	Frequency of Administration	Route of Administration	Duration of Treatment [a]
BGB-A425	600 mg	Cycle 1 Day 1, then once every 21 days	Intravenous infusion	Until disease progression, unacceptable toxicity, or voluntary withdrawal of consent per patient decision
LBL-007	300 mg 600 mg (higher dose levels such as 900 mg may be explored)			
Tislelizumab	200 mg			

Abbreviations: CR, complete response; PR, partial response.
[a] For patients who have confirmed CR, PR, or stable disease after 24 months, the treatment can be paused for a period of time (at patient request) following the investigator's agreement and sponsor's written approval (as in Section 3.3.1).

For the first cycle (or first 3 administrations of study drug in case of dose delays), LBL-007 will be infused over 60 (± 10) minutes, followed by patient monitoring for 60 (± 30) minutes; then tislelizumab will be infused over 60 (± 10) minutes, and BGB-A425 over 60 (± 10) minutes. Following final infusion of study drug, patients must be monitored for at least 120 minutes in an area with resuscitation equipment and emergency agents.

If infusions of LBL-007, tislelizumab, and BGB-A425 are well tolerated in the first cycle, on Cycle 2 Day 1 and Cycle 3 Day 1, LBL-007 may be infused for no less than 30 minutes followed by patient monitoring for 60 (± 30) minutes; then tislelizumab will be infused for no less than 30 minutes followed by the infusion of BGB-A425 for no less than 30 minutes. Following final infusion of study drug, patients must be monitored for at least 120 minutes in an area with resuscitation equipment and emergency agents.

If infusions of LBL-007, tislelizumab, and BGB-A425 are well tolerated in the first 3 cycles, on Cycle 4 Day 1 and subsequent cycles, LBL-007 may be infused for no less than 30 minutes followed by patient monitoring for 60 (± 30) minutes; then tislelizumab will be infused for no less than 30 minutes followed by the infusion of BGB-A425 for no less than 30 minutes. Following final infusion of study drug, patients must be monitored for at least 60 minutes in an area with resuscitation equipment and emergency agents (Table 9).

Table 9: Phase 2 Safety Lead-in Administration of Cohort B: BGB-A425, LBL-007, and Tislelizumab and Monitoring Time

Cycle	BGB-A425, LBL-007, and Tislelizumab combination
Cycle 1 Day 1	LBL-007 infusion over 60 (± 10) minutes, followed by patient monitoring for 60 (± 30) minutes, followed by tislelizumab infusion over 60 (± 10) minutes, followed by BGB-A425 infusion over 60 (± 10) minutes Patient monitoring for at least 120 minutes post completion of last infusion
Cycle 2 Day 1 Cycle 3 Day 1	LBL-007 infusion for no less than 30 minutes, followed by patient monitoring for 60 (± 30) minutes, followed by tislelizumab infusion for no less than 30 minutes, followed by BGB-A425 infusion for no less than 30 minutes Patient monitoring for at least 120 minutes post completion of last infusion
Cycle 4 Day 1 onwards	LBL-007 infusion for no less than 30 minutes, followed by patient monitoring for 60 (± 30) minutes, followed by tislelizumab infusion for no less than 30 minutes, followed by BGB-A425 infusion no less than 30 minutes Patient monitoring for at least 60 minutes post completion of last infusion

5.3.3. Phase 2 (Dose Expansion)

5.3.3.1. BGB-A425 + Tislelizumab (Cohorts 1, 2 and 3)

The RP2D of BGB-A425 (600 mg intravenously) will be administered in combination with tislelizumab (200 mg intravenously). BGB-A425 and tislelizumab will be administered once every 21 days starting on Cycle 1 Day 1.

Table 10: Phase 2 Dose Expansion Administration of BGB-A425 and Tislelizumab and Monitoring Time

Cycle	BGB-A425 and Tislelizumab combination
Cycle 1 Day 1 Cycle 2 Day 1	Tislelizumab infusion over 60 (± 10) minutes, followed by BGB-A425 infusion over 60 (± 10) minutes Patient monitoring for at least 120 minutes post completion of last infusion
Cycle 3 Day 1	Tislelizumab infusion for no less than 30 minutes, followed by BGB-A425 infusion over 60 (± 10) minutes Patient monitoring for at least 120 minutes post completion of last infusion
Cycle 4 Day 1 onwards	Tislelizumab infusion for no less than 30 minutes, followed by BGB-A425 infusion for no less than 30 minutes Patient monitoring for at least 30 minutes post completion of last infusion

5.3.3.2. BGB-A425 + LBL-007 +Tislelizumab (Cohorts 4 and 5)

The recommended doses for LBL-007 in the combination with BGB-A425 and tislelizumab will be determined by the clinical data from the Phase 2 safety lead-in Cohort A.

Refer to Table 11 regarding infusion and monitoring times for Phase 2 dose expansion (Cohorts 4 and 5).

Table 11: Phase 2 Dose Expansion Administration of BGB-A425, LBL-007, and Tislelizumab and Monitoring Time

Cycle	BGB-A425, LBL-007 and Tislelizumab combination
Cycle 1 Day 1	LBL-007 infusion over 60 (± 10) minutes, followed by patient monitoring for 60 (± 30) minutes, followed by Tislelizumab infusion over 60 (± 10) minutes, followed by BGB-A425 infusion over 60 (± 10) minutes Patient monitoring for at least 120 minutes post completion of last infusion
Cycle 2 Day 1 onwards	LBL-007 infusion for no less than 30 minutes, followed by patient monitoring for 60 (± 30) minutes, followed by Tislelizumab infusion for no less than 30 minutes, followed by BGB-A425 infusion no less than 30 minutes Patient monitoring for at least 60 minutes post completion of last infusion

5.3.3.3. LBL-007 + Tislelizumab (Cohorts 6 and 7)

The recommended doses for LBL-007 in combination with tislelizumab will be determined by the clinical data from the Phase 2 safety lead-in Cohort B.

Refer to Table 12 regarding infusion and monitoring times for Phase 2 dose expansion.

Table 12: Phase 2 Dose Expansion Administration of LBL-007 and Tislelizumab and Monitoring Time

Cycle	LBL-007 and Tislelizumab combination
Cycle 1 Day 1	LBL-007 infusion over 60 (± 10) minutes, followed by patient monitoring for 60 (± 30) minutes, followed by Tislelizumab infusion over 60 (± 10) minutes Patient monitoring for at least 120 minutes post completion of last infusion
Cycle 2 Day 1 onwards	LBL-007 infusion for no less than 30 minutes, followed by patient monitoring for 60 (± 30) minutes, followed by Tislelizumab infusion for no less than 30 minutes Patient monitoring for at least 60 minutes post completion of last infusion

5.4. Overdose of Tislelizumab and Incorrect Administration of BGB-A425 and LBL-007

Any overdose of tislelizumab (defined as ≥ 600 mg in a 24-hour period) or incorrect administration of BGB-A425 and LBL-007 should be noted in the patient's chart and on the appropriate eCRF.

Adverse events associated with an overdose or incorrect administration of study drug will be recorded on the Adverse Event eCRF. If an overdose or incorrect administration of study treatment takes place and adversely affects the patient's safety, the sponsor or designee is required to be notified within 24 hours of awareness via the SAE reporting process described in Section 8.6.2. Supportive care measures should be administered as appropriate.

5.5. Investigational Medicinal Product Accountability

The IMPs (BGB-A425, LBL-007, and tislelizumab) required for the completion of this study will be provided by the sponsor. The investigational site will acknowledge receipt of the investigational medicinal products. Any damaged shipments will be replaced.

Accurate records of all investigational medicinal product received, dispensed, returned, and disposed of need to be recorded on the site's Drug Inventory Log. Refer to the Pharmacy Manual for details of investigational medicinal product management.

5.6. Dose Delay and Modification

Every effort should be made to administer the study drug(s) according to the planned dose and schedule. In the event of significant toxicities, dosing may be delayed and/or reduced based on the guidelines provided below. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

Guidelines for treatment modification or discontinuation as well as the management of reactions and -imAEs are provided in detail in Section 8.7 and Appendix 8.

For AEs that are non-imAEs but assessed as related to tislelizumab and/or BGB-A425 and/or LBL-007, the following general guidance should be followed unless otherwise specified:

- ≤ Grade 2: Maintain dose level
- Grade 3: Delay dose until resolved to ≤ Grade 1 or baseline except for alopecia or AEs that, in the opinion of the investigator, are not considered a safety risk for patient
- Grade 4: Permanent discontinuation from study. Exceptions may be considered following consultation with the medical monitor.

5.6.1. Dose Delay for BGB-A425, LBL-007, and Tislelizumab

Except for Cycle 1 of Phase 1, if a dose delay for any study drug is required, all the applicable combination treatments (ie, BGB-A425/LBL-007/Tislelizumab) are to be delayed. Exceptions may be considered following consultation between the investigator and the medical monitor. In Cycle 1 of Phase 1, if tislelizumab is delayed beyond Cycle 1 Day 8 (+2 days), tislelizumab will not be administered in Cycle 1 but treatment may resume in subsequent cycles as outlined in Section 5.6.2.

If treatment is delayed due to treatment-emergent AE(s), treatment may resume only after the AE(s) 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 due to worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

If a dose/visit delay (due to the causes mentioned above) is ≤ 10 days for a planned dosing cycle (eg, Cycle 3 Day 1), the delayed combination treatment(s) in this cycle (eg. Cycle 3) should be administered, and the treatment in the next cycle (eg, Cycle 4 Day 1) will not be delayed and administered as scheduled.

If the dose/visit delay (due to the causes mentioned above) is > 10 days, then the patient should skip the combination treatment(s) in the delayed cycle (eg, Cycle 3 Day 1), and combination treatment(s) should be administered on Day 1 of the next planned cycle (eg, Cycle 4 Day 1).

In general, dose delays for reasons other than management of AEs is prohibited as noted in Section 7.6. A dose delay of ≤ 12 weeks is allowed under the following guidance and at the discretion of the investigator after consultation with the medical monitor or designee.

If treatment-related AEs are persistent without any improvement for more than 12 weeks, permanent discontinuation of the study drug should be considered. If the patient recovers from the treatment-related AE after 12 weeks, re-initiation of study drug is permitted only in patients who are deemed to be deriving clinical benefit per the opinion of the investigator following agreement between the investigator and the medical monitor.

Patients who receive radiotherapy per Section 6.1.1, may resume treatment with study drug only after radiotherapy related AE(s) have returned to baseline or ≤ Grade 1 severity, except for AE(s) that in the opinion of the investigator, are not considered a safety risk to the patient.

The tumor assessment schedule will not be altered even if the administration of study drug is delayed.

Two occurrences of dose delays because of treatment-related AEs will be permitted. In the event of a third occurrence of a dose delay due to toxicity, permanent discontinuation of study drug should be considered after consultation with the medical monitor.

For patients who have confirmed CR, PR, or stable disease after 24 months, the treatment can be paused for a period of time (at patient request) following investigator's agreement and sponsor's written approval. The decision to pause treatment should be based on the investigator's evaluation, with the patient's clinical benefit and risk taken into consideration. The investigator should notify and seek written agreement from the sponsor's medical monitor that treatment will be paused prior to the event (as in Section 3.3.1). Additionally, patients need to undergo disease assessments (as per Section 7.6) and safety follow up if applicable, per the protocol recommendation (Appendix 1A, Appendix 1B, and Appendix 1C) while on study treatment break.

5.6.2. Dose Modification for BGB-A425, LBL-007, and Tislelizumab

No dose reductions will be allowed for tislelizumab. For Phase 2 safety lead-in, no dose reduction of tislelizumab and BGB-A425 will be allowed. For Phase 2 dose expansion, no dose reduction in any study drug will be allowed.

For Phase 1 only, if patients are receiving a dose level of BGB-A425 that is determined to be beyond the MTD, the dose level of BGB-A425 may be reduced following discussion and agreement with the medical monitor. Further, if a patient cannot be dosed with tislelizumab on Cycle 1 Day 8 (+2 days), the patient will not be eligible to receive tislelizumab with the originally assigned dose level of BGB-A425. However, starting on Cycle 2 Day 1 and every 21 days thereafter, the patient will be eligible, assuming any AE related delay has resolved per Section 5.6, to receive the combination of tislelizumab and a lower dose level of BGB-A425 that had previously been shown to be tolerable according to the criteria outlined in Section 3.1 and following discussion with the medical monitor.

For Phase 2 safety lead-in only, if patients are receiving a dose level of LBL-007 (eg, 300 mg or higher) that is determined not well tolerated, the dose level of LBL-007 may be reduced a lower level for further evaluation following discussion and agreement with the medical monitor.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Concomitant Therapy

6.1.1. Permitted Concomitant Medications and Therapy

Most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care at the discretion of the investigator for supportive care (eg, antiemetics, antidiarrheals, granulocyte colony-stimulating factor, and other care) and in a patient's interest are allowed.

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 within 72 hours before or after study drug administration during the first 2 treatment cycles and within 24 hours before or after study drug administration thereafter (ie, from Cycle 3 onwards). Vaccinations are considered a concomitant medication and hence should be entered on the eCRF. The specific COVID-19 vaccine should be recorded instead of generic language, eg, mRNA-1273 vaccine (Moderna), BioNTech vaccine (Pfizer), etc.

All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter, herbal supplements, and intravenous medications and fluids.

All concomitant medication received within 30 days before the first dose of study treatment and 30 days after the last infusion or dose of study treatment should be recorded. 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 on the eCRF.

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

Bisphosphonates, but not RANKL inhibitors, are allowed.

Patients who have detectable HBsAg or HBV DNA at baseline must initiate and/or continue effective antiviral treatment in keeping with local standards of medical care where applicable. For such patients enrolled in the United States, treatment must be initiated at least 2 weeks prior to first dose of study drug(s) and continue until 6 months after the last dose of study drug(s).

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.

The medical monitor should be informed of any on-study radiation therapy. Whenever possible, these patients should have a tumor assessment of the lesion(s) before receiving radiotherapy in order to rule out progression of disease. Study treatment should be withheld until any radiotherapy related AE(s) have returned to baseline or ≤ Grade 1 severity, except for AE(s) that in the opinion of the investigator, are not considered a safety risk to the patient.

6.2. Prohibited or Restricted Concomitant Medications and Therapy

The following medications are prohibited or 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 or for short-term use as prophylactic treatment
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including herbal medicine and Chinese patent medicines] for the treatment of cancer) is not allowed (Appendix 11)
- Radiation therapy is not allowed, unless otherwise noted in Section 6.1.1
- Live vaccines within 28 days prior to the first dose of study drug(s) and 60 days following the last dose of study drug(s)
- Immune-stimulating agents including herbal remedies with immune-stimulating properties (ie, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (ie, hypericin). Patients must notify the investigator of all herbal remedies used during the study.
- 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

6.3. Potential Interactions Between the Study Drugs and Concomitant Medications

Information regarding clinical drug interactions with BGB-A425 is not available. No dedicated drug-drug interaction studies are planned. However, the potential for PK-based drug-drug interaction between BGB-A425 and small-molecule drug products is expected to be very low, given that BGB-A425 is a therapeutic monoclonal antibody. A PK drug-drug interaction of tislelizumab or LBL-007 with other therapeutics is not anticipated given that the primary elimination pathways are protein catabolism via the reticuloendothelial system or target-mediated disposition. Tislelizumab and LBL-007 are not expected to induce or inhibit the major drug metabolizing cytochrome P450 pathways. Because BGB-A425, tislelizumab and LBL-007 are expected to be degraded into amino acids and recycled into other proteins, it is unlikely to have an effect on drug metabolizing enzymes or transporters.

7. STUDY ASSESSMENTS AND PROCEDURES

A table of scheduled study assessments for Phase 1 and 2 is provided in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented in the medical record and eCRF for each patient.

Administration of study drug(s) must occur only after the clinical assessment and local laboratory test values have been reviewed and found to be acceptable per protocol guidelines.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled on the nearest feasible date (within the specified visit windows) with subsequent visits conducted according to the Schedule of Assessments (Appendix 1).

7.1. Prescreening (Phase 2 Dose Expansion)

Unless otherwise specified, all HNSCC and NSCLC patients who agree to participate in Phase 2 dose expansion will sign the Prescreening informed consent form (ICF) prior to undergoing any prescreening procedure, this includes patients who have confirmation of local PD-L1 results (see Appendix 1 for details).

HNSCC and NSCLC patients with positive PD-L1 expression are eligible for enrollment. The Prescreening ICF and the PD-L1 test are not required for RCC patients; therefore, all RCC patients are allowed to proceed directly into screening.

The overall duration for prescreening for Phase 2 dose expansion is 56 days prior to the first dose of study drugs. A longer prescreening period may be granted on a case-by-case basis following discussion and written approval from the sponsor's medical monitor approval in discussion with the principal investigator.

Prescreening starts with the date of Prescreening ICF signature and ends with the receipt of PD-L1 results. Site staff should plan prescreening activities in advance to ensure that all subsequent screening activities (in Section 7.2) can be completed within the allowed Period with a maximum duration of 28 days before the first dose of study drug(s).

Prescreening evaluations may be repeated as needed within the prescreening period; the investigator is to assess patient eligibility according to the latest prescreening assessment results.

Prescreening ICFs for enrolled patients and for patients who are prescreened and/or screened but not enrolled will be maintained at the study site. The investigator will maintain a prescreening log to record details of all patients prescreened and to confirm PD-L1 test results.

7.1.1. PD-L1 Test

During the prescreening period, HNSCC and NSCLC patients in dose expansion cohorts will undergo PD-L1 positivity confirmation by specified PD-L1 IHC assays.

Below are detailed requirements for confirming a patients' PD-L1 status during prescreening.

(1) Local documented PD-L1 result to confirm PD-L1 positivity on archival tumor tissue

HNSCC and NSCLC patients with a local positive PD-L1 result by specified PD-L1 IHC assay on archival tissue can proceed directly to the screening phase. If the patient has more

than 1 PD-L1 test, the most recent PD-L1 result should be used for PD-L1 positivity confirmation.

Local documented PD-L1 positivity result requirement:

- PD-L1 expression must be determined using a CE-marked assay in the EU.
- For HNSCC patients, PD-L1 (CPS ≥ 1) by IHC 22C3 pharmDx assay (preferred) or PD-L1 (CPS ≥ 1, vCPS or TAP ≥ 1%) by VENTANA PD-L1 (SP263) are acceptable for PD-L1 expression confirmation. Note: PD-L1 positivity determined by PD-L1 IHC 22C3 pharmDx assay will be used for HNSCC patients in the EU.
- For NSCLC patients, PD-L1 (TPS or TC ≥ 1%) by IHC 22C3 or 28-8 pharmDx or VENTANA PD-L1 (SP263) assay are acceptable for PD-L1 expression confirmation. Note: If PD-L1 IHC 28-8 assay is to be used for determining PD-L1 positivity, it will be used for nonsquamous NSCLC patients only in the EU.

For all patients who provide a local documented PD-L1 result, recently obtained tissue within 2 years or fresh tissue biopsy is required prior to the patient commencing first drug administration on Cycle 1 Day 1. It is highly recommended to provide the same tissue that was tested for the local PD-L1 assay. Recently obtained tumor tissue or fresh biopsy will be sent to the central laboratory and retrospectively evaluated by VENTANA PD-L1 (SP263) assay and other exploratory biomarkers.

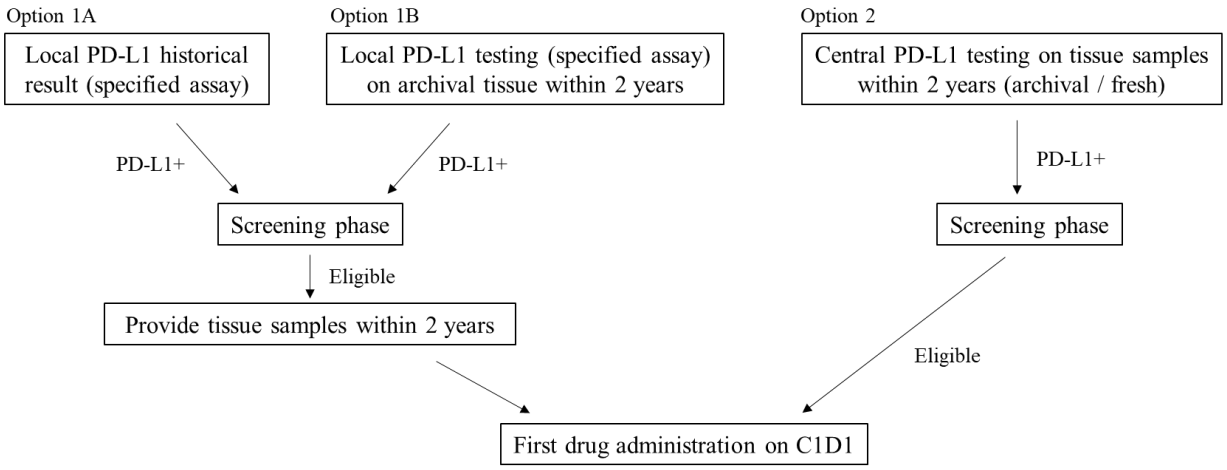
(2) Central PD-L1 testing

During prescreening, if HNSCC and NSCLC patients are unable to provide a local documented PD-L1 result, patients will be required to submit a recently obtained archival tumor tissue within 2 years or fresh biopsy during prescreening. IHC 22C3 pharmDx assay will be used for PD-L1 expression confirmation in HNSCC (PD-L1 CPS ≥ 1), or NSCLC (PD-L1 TPS ≥ 1%), respectively.

The patient can only proceed to the screening period following confirmation of a positive PD-L1 result by either local PD-L1 positive result or following confirmation of PD-L1 positivity from the central laboratory.

The PD-L1 positivity confirmation flow is summarized in Figure 8 below:

Figure 8: PD-L1 Positivity Confirmation Flowchart



Footnote: Option 1 refers to the scenarios in bullet (1) as mentioned above; Option 2 refers to the scenarios in bullet (2) as mentioned above

PD-L1 expression positivity confirmation (in all of above situations) must be obtained before HNSCC and NSCLC patients are allowed to continue to screening. The PD-L1 status of patients will also be retrospectively evaluated by VENTANA PD-L1 (SP263) assay.

The PD-L1 test is not required for RCC patients as part of prescreening or screening. The PD-L1 status of patients will also be retrospectively evaluated by VENTANA PD-L1 (SP263) assay.

7.2. Screening

Unless otherwise specified, patients who agree to participate will sign the ICF prior to undergoing any screening procedures (see Appendix 1 for details).

Any applicable supplementary ICFs should also be presented to the patient at the time of the main ICF being presented to the patient, as part of the informed consent process.

In Phase 1 (dose escalation) and Phase 2 (safety lead-in), the signed Screening ICF and all screening procedures will be required within 28 days prior to the first administration of study drug(s). The ICF signature defines the start of the Screening Period.

In Phase 2 (dose expansion), the signed Screening ICF and all screening procedures will be required within 28 days prior to the first administration of study drug(s).

- For RCC patients, the 28-day Screening Period will start from the signatory date on the Screening ICF.
- For HNSCC and NSCLC patients, the 28-day Screening Period following a local or central laboratory positive PD-L1 result will start from the signatory date on the Screening ICF. Screening evaluations may be repeated as needed within the Screening Period; the investigator is to assess patient eligibility according to the latest screening assessment results.

The results of standard-of-care tests or examinations performed prior to obtaining informed consent and prior to enrollment may be used for the purposes of screening rather than repeating

such tests unless otherwise indicated. Screening evaluations may be repeated as needed within the Screening Period but the investigator is to assess patient eligibility according to the latest screening assessment results.

Rescreening under limited conditions may be allowed after consultation with the sponsor's medical monitor (eg, when a patient narrowly misses a laboratory criterion and it is correctable and not because of rapidly deteriorating condition or disease progression), in discussion with the principal investigator. Rescreening is allowed only once. For NHSCC and NSCLC patients in Phase 2 dose expansion experiencing rescreening during the Screening Period, the prescreening procedures do not need to be repeated.

Patients who are suspected or known to have serious/severe respiratory concurrent illness or exhibit significant respiratory symptoms unrelated to underlying cancer should take a pulmonary function test (refer to Section 7.2.4 for details).

Procedures conducted during the Screening Visit only are described in Section 7.2.1 to Section 7.2.4. For the description of other assessments that are conducted at screening as well as throughout the study, refer to Safety Assessments (Section 7.5), Biomarker Assessments (Section 7.8) and Tumor and Response Evaluation (Section 7.6).

7.2.1. Demographic Data and Medical History

Demographic factors such as age, gender, race, and ethnicity could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. Race and ethnicity data are collected in accordance with ICH guidance (ICH E5 1998, ICH E17 2017) adopted by the EMA and US FDA, to understand whether race/ethnicity could influence the PK, safety, and/or efficacy of the study drug. For example, population PK analysis is a well-established, quantitative method that can quantify and explain the variability in drug concentrations among patients. Such variability can be attributed to intrinsic factors (eg, body weight, age, gender, race/ethnicity), or to extrinsic factors (eg, concomitant medications), and can lead to clinically relevant changes in drug concentrations that require a change in the dose or dosing regimen. Results from race/ethnicity and other demographic analyses will be incorporated into drug product labeling to provide guidance on safety and efficacy variations (if any) linked to certain populations (eg, race or ethnic group) as well as any potential dose adjustment needed for those populations. Therefore, collecting race/ethnicity data in the study is essential to understand whether race/ethnicity could influence the PK, safety, and/or efficacy.

Medical history includes any history of clinically significant disease, surgery, or cancer history; reproductive status (ie, of childbearing potential or no childbearing potential); and history of alcohol consumption and tobacco (ie, presence or absence). If appropriate, clinically significant disease should be graded according to NCI-CTCAE v5.0 and reported in the Medical History eCRF.

Cancer history will include an assessment of prior surgery, prior radiotherapy, prior drug therapy, including start and stop dates, best response and reason for discontinuation.

Radiographic studies performed prior to study entry may be collected for review by the investigator.

7.2.2. Female Patients of Childbearing Potential and Contraception

Childbearing potential is defined as being physiologically capable of becoming pregnant. Refer to Appendix 5 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential".

7.2.3. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures, unless otherwise specified. Informed consent forms 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 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.

7.2.4. Pulmonary Function Tests

During the Screening Period, patients will undergo pulmonary function testing if they are: suspected or known to have serious/severe respiratory conditions, exhibit significant respiratory symptoms unrelated to the underlying cancer; patients with non-small cell lung cancer enrolled in all Phase 2 cohorts will be required to undergo pulmonary function test regardless of their respiratory conditions or symptoms. This may include, but is not limited to, spirometry and assessment of diffusion capacity.

Pulmonary function testing includes assessment of oxygenation, spirometry and/or lung volume tests. The assessment of oxygenation should include at least pulse oximetry (percutaneous arterial oxygen saturation, SpO2) at rest and with exercise; an assessment of diffusion capacity is optional.

The medical monitor needs to be consulted to confirm eligibility if test results indicate significantly impaired pulmonary function. Some examples are: resting pulse oximetry < 90% on room air and further desaturation upon exercise; forced expiratory volume in one second < 60%; or carbon monoxide diffusing capacity (if performed) < 60% of age and sex adjusted predicted performance levels (Pellegrino et al 2005).

7.3. Enrollment

7.3.1. 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.

7.4. BGB-A425, LBL-007, and Tislelizumab Dispensation

BGB-A425, LBL-007, and tislelizumab will be dispensed and administered as described in Section 5.3.

7.5. Safety Assessments

7.5.1. Vital Signs

Vital signs will include measurements of temperature (˚C), pulse rate, respiratory rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes.

Vital signs will be collected at the timepoint in Phase 1 and Phase 2 as described in Appendix 1A, Appendix 1B and Appendix 1C.

7.5.2. Physical Examinations

During the Screening Visit, a complete physical examination will be conducted including an evaluation of 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems. Any abnormality identified during screening will be graded according to NCI-CTCAE v5.0 and recorded on the Medical History eCRF with appropriate disease/condition terms.

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

7.5.3. Ophthalmologic Examination

The ophthalmologic examination including eye examination, visual acuity test, and optical coherence tomography (or equivalent diagnostic test for retinal examination) will be assessed by an ophthalmologist at screening. All tests mentioned above are required as per local ophthalmologist OCT requirements. The ophthalmologic examination captured as standard of care prior to obtaining written informed consent and within 28 days of enrollment may be used for the screening evaluation. Patients will undergo repeat assessments by an appropriate specialist approximately every 15 weeks (± 7 days) during study treatment and a final assessment < 30 days after the last dose of study treatment (see Appendix 1 for timepoints).

In addition, investigators should solicit patients for information 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 (see Appendix 1).

7.5.4. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status (Appendix 3) will be assessed during the study.

7.5.5. Laboratory Safety Test

Laboratory assessments will be conducted for serum chemistry, hematology and coagulation while urinalysis will be performed locally as outlined in Appendix 2 per the Schedule of Assessments (Appendix 1).

For Phase 1, blood-based laboratory assessments will be performed by a central laboratory. Investigators may use results from local laboratories for assessing eligibility, safety monitoring and dosing decision(s); however, central laboratory assessments must still be collected for the timepoints outlined in Appendix 1. For central laboratory assessments, details regarding sample collection and shipment will be provided in a separate laboratory manual. For Phase 2 (safety lead-in and dose expansion), safety laboratory assessments will be conducted via local laboratory only.

If serum chemistry, hematology, and coagulation at screening are not performed within 7 days prior to the administration of study drug(s) on Cycle 1 Day 1, these tests should be repeated and reviewed before study drug(s) administration. After Cycle 1 Day 1, results are to be reviewed within 72 hours before study drug administration.

In addition, the following tests will be conducted at the central laboratory for Phase 1, and the local laboratory for Phase 2 (safety lead-in and dose expansion) at timepoints shown in Appendix 1.

- Urine pregnancy test (local laboratory for Phase 2) (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to enrollment. Further, a negative pregnancy test (by urine or blood) must be completed and recorded on the same day before administration of study drug(s) at each cycle. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal. An additional pregnancy test must be performed for women of childbearing potential at approximately 120 days after the last dose of study treatment.
- Thyroid function testing: thyroid stimulating hormone, free T3, free T4
- Hepatitis serology and viral load, refer to Section 7.5.8
- Creatine kinase (CK) and creatine kinase-cardiac muscle isoenzyme (CK-MB), refer to Section 7.5.9

7.5.6. Electrocardiograms

For Phase 1, a centralized ECG laboratory may be used in this study in selected study sites. Calibrated ECG machines will be provided to these sites and ECG collected from these sites will be reviewed centrally. However, during the course of study, sites may switch to a local ECG laboratory for safety monitoring purposes. Additionally, other sites will use local ECG as per the protocol. All ECG recordings will be performed using a standard high-quality and high-fidelity digital electrocardiograph.

For Phase 2 (dose expansion and safety lead-in), ECG assessment will be performed and evaluated locally using a site's internal resources.

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

When coinciding with blood draws, ECG assessment should be performed prior to blood draws. Patients should rest in semi-recumbent supine position for at least 10 minutes prior to ECG collection.

At each timepoint (see Appendix 1), 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine the mean QT interval corrected by Fridericia's formula (QTcF) interval ($QTcF = QT / [RR]^{1/3}$) (Fridericia 1920) in addition to other ECG parameters as needed.

7.5.7. Adverse Events

Adverse events (AEs) will be graded and recorded throughout the study according to NCI-CTCAE v5.0 (NCI-CTCAE 2017). Characterization of toxicities will include severity, duration, and time to onset.

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

7.5.8. Hepatitis B and C Testing

Testing will include HBV/HCV serology (HBsAg, hepatitis B surface antibody, hepatitis B core antibody, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA) to be performed by a central laboratory for Phase 1 or local laboratory for Phase 2 (safety lead-in and dose expansion).

For Phase 1, patients with hepatocellular carcinoma are required to have hepatitis serology and viral load tested at screening. In patients who have detectable HBV DNA at screening, the respective viral load test will be performed every 4 cycles. Patients with detectable HCV RNA will not be allowed to enroll into the study. In patients without hepatocellular carcinoma, samples for hepatitis serology and viral load will be collected at screening and may be tested if patients have hepatic AE (≥ Grade 3) during the study.

For Phase 2 (safety lead-in and dose expansion), testing will be performed by the local laboratory at screening and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody, hepatitis B core antibody, and HCV antibody). In case of positive HBsAg or positive HCV antibody results, these tests will be followed by viral load assessment (HBV DNA and HCV RNA). Viral load assessment (HBV DNA and HCV RNA) may be performed at the same time as HBV/HCV serology at investigator's discretion in line with the clinical history of the patient. Patients who have detectable HBV DNA at screening but remain eligible for enrollment will have their respective viral load tested every 4 cycles. Testing should also be performed as needed for any patient during treatment where clinically indicated.

7.5.9. Creatine Kinase and Creatine Kinase-Cardiac Muscle Isoenzyme

Testing of CK and CK-MB will be performed by a central laboratory for Phase 1 or local laboratory for Phase 2 (safety lead-in and dose expansion) at the timepoints specified in Appendix 1. If your laboratory does not perform CK-MB testing, serum troponins (troponin I

and/or T) measurements should be performed instead; if only either troponin is assessed per local standards that same should be evaluated throughout.

If significant abnormalities are detected, please evaluate the affected patients for possible myocarditis/myositis per institutional guidelines, including additional serum CK/CK-MB, serum troponin levels, ECG, etc. Please report all clinically significant abnormalities as an AE or SAE as described in Appendix 8.

7.6. Tumor and Response Evaluations

Tumor imaging will be performed approximately every 6 weeks (± 7 days) in the first 52 weeks and thereafter approximately every 12 weeks (± 7 days) as shown in Appendix 1A, Appendix 1B and Appendix 1C. The first tumor assessment will be performed 6 weeks (± 7 days) after the first administration of the study drugs.

Screening assessments and each subsequent assessment of the tumor must include computed tomography (CT) scans (with oral/intravenous contrast, unless contraindicated) or magnetic resonance imaging (MRI).

For Phase 1, the chest, abdomen, pelvis, and other known or suspected sites (eg, head and neck) of disease must be included in the imaging assessments at baseline and during the study.

Phase 2 safety lead-in, the head (including brain, preferably MRI), neck, chest, abdomen, pelvis, and other known or suspected sites of disease must be included in the imaging assessments at baseline and during the study.

For Phase 2 dose expansion, in addition to all other known or suspected sites of disease (eg, bone and extremities), the following imaging is required at baseline and during the study:

- For HNSCC patients:
  - Imaging assessment during screening/baseline: head (including brain), neck, chest, and abdomen
  - Imaging assessment during the treatment: head (including brain), neck, chest, and abdomen
  - Pelvic imaging is not required during screening/baseline or the treatment unless clinically indicated.
- For NSCLC patients:
  - Imaging assessment during screening/baseline: head (including brain), chest, abdomen, and pelvis.
  - Imaging assessment during the treatment: chest, abdomen, and pelvis.
- For RCC patients:
  - Imaging assessment during screening/baseline: head (including brain), chest, abdomen, and pelvis.
  - Imaging assessment during the treatment: 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 is required to be used throughout the study (eg, the same contrast protocol for CT scans).
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the trial, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis (where required) should be performed.
- If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.
- Bone scans (Technetium-99m [TC-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, TC-99m or PET bone scans should be repeated when a complete response (CR) is suspected in target lesion or when progression in bone is suspected.
- CT scans of extremities should also be performed at screening, only if clinically indicated, and should be followed throughout the study if there is evidence of metastatic disease in these regions at screening.
- For NSCLC and RCC patients, imaging of the brain (preferably MRI) during the treatment is not required unless clinically indicated.
- At the investigator's discretion, other methods of assessment of target lesion and nontarget lesions per RECIST v1.1 may be used.

Response will be assessed by the investigators using RECIST v1.1 (see Appendix 9). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

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

After the first documentation of PD, confirmation of PD should occur at 4 weeks or later (≥ 4 weeks) after the first PD or at the next scheduled assessment timepoint.

A patient who discontinues study drugs early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments as described in Section 3.2.5 until the patient begins a new anticancer therapy, experiences PD per RECIST v1.1, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first.

If at the investigator's discretion a patient could continue to benefit from BGB-A425 and/or tislelizumab and/or LAG-3 after PD per RECIST v1.1, the patient may continue their assigned treatment, following sponsor's agreement and written approval. The following criteria must be met:

- Absence of clinical symptoms and signs of PD (including clinically significant worsening of laboratory values)
- Stable ECOG Performance Status ≤ 1

- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer
- The decision to continue study drugs beyond initial investigator-assessed progression must be agreed with the medical monitor following confirmation of investigator-assessed radiological progression, and documented in the study records. In such cases, patients are also required to be re-consented on the Treatment Through Progression ICF (as described in Section 3.3.1). Patients who receive study treatment beyond disease progression will have tumor assessments performed according to the original schedule until study treatment discontinuation.

Patients with the radiographic progression in tumor burden or the appearance of new lesions in the absence of significant clinical deterioration (decline in performance status and/or laboratory values) are permitted to continue with treatment (after re-consented) until confirmation of PD with follow-up imaging at least 4 weeks later or at the next scheduled imaging time point. The next imaging to confirm disease progression must not exceed 12 weeks from initial documentation of PD. Per investigator's judgement, if a patient could draw benefit from the combination treatments after radiographic disease progression, the patient may continue the treatment as per the protocol following sponsor's agreement and written approval. The subsequent disease assessment could be conducted as assigned in the protocol.

A patient who discontinues study drug(s) early for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments as described in Section 3.2.5 until the patient begins a new anticancer therapy, experiences PD, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first.

Tumor assessments must be performed on schedule regardless of whether study treatment has been administered or withheld, ie, they should not be adjusted for delays in cycles.

7.7. Pharmacokinetic Assessment and Antidrug Antibody Testing

BGB-A425, LBL-007, and tislelizumab may elicit an immune response. Patients with signs of any potential immune response will be closely monitored. Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints throughout the study (see Appendix 1D, Appendix 1E, Appendix 1F and Appendix 1G). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Koren et al 2008; Worobec and Rosenberg 2004a; Worobec and Rosenberg 2004b) to characterize ADA responses to BGB-A425, LBL-007 and tislelizumab in support of the clinical development program. This tiered strategy will include an assessment of whether ADA responses correlate with relevant clinical endpoints. Implementation of ADA characterization assays will depend on the safety profile and clinical immunogenicity data.

The following assessments will be performed at a central laboratory:

- ADA assays: serum samples will be tested for the presence of ADAs to BGB-A425, LBL-007 and tislelizumab using a validated immunoassay.

- PK assay: serum samples will be assayed for BGB-A425, LBL-007 and tislelizumab concentration with use of a validated pharmacokinetic assay.

In Phase 1 dose escalation, serial PK and immunogenetic samples for BGB-A425 will be collected; sparse PK and immunogenetic samples for tislelizumab will be collected.

In Phase 2 safety lead-in, serial PK and immunogenetic samples for LBL-007 will be collected; sparse PK and immunogenetic samples for BGB-A425 and tislelizumab will be collected.

In Cohorts 1, 2, and 3 of Phase 2 dose expansion, serial PK samples and sparse immunogenetic samples for BGB-A425 will be collected in approximately 15 patients enrolled, 10 patients from South Korea, and 5 patients from Australia. In these 15 patients, sparse immunogenetic samples for tislelizumab will be collected. Besides, sparse PK samples and immunogenetic samples for BGB-A425 and tislelizumab will be collected for the rest of the patients.

In Cohorts 4 to 7 of Phase 2 dose expansion, sparse PK and immunogenetic samples for LBL-007, BGB-A425, and tislelizumab will be collected.

The table below has summarized types of PK and immunogenetic samplings of 3 study drugs in Phase 1 and Phase 2. The appendixes for sampling schedules are also added as reference in Table 13.

Table 13: Types of PK and Immunogenetic Samplings for BGB-A425, LBL-007, and Tislelizumab in Phase 1 and Phase 2

Compound	Phase 1 Dose Escalation	Phase 2 Safety Lead-in	Phase 2 Dose Expansion (Cohorts 1, 2, and 3)	Phase 2 Dose Expansion (Cohorts 4 to 7)
BGB-A425	Serial sampling (Appendix 1D)	Sparse sampling (Appendix 1E)	Serial PK sampling and sparse immunogenetic samples for the first 15 patients (Appendix 1G) Sparse sampling for the rest patients (Appendix 1F)	Sparse sampling (Appendix 1F)
LBL-007	NA	Serial sampling (Appendix 1D)	NA	Sparse sampling (Appendix 1F)
Tislelizumab	Sparse sampling (Appendix 1E)	Sparse sampling (Appendix 1E)	Sparse sampling (Appendix 1F)	Sparse sampling (Appendix 1F)

Abbreviations: NA, not applicable.

Shipping, storage, and handling of samples for the assessment of BGB-A425, LBL-007, and tislelizumab PK and ADA assays will be managed through a central laboratory. Instruction manuals and supply kits will be provided for all central laboratory assessments.

7.8. Biomarkers

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

laboratory manual for details of sample handling and the Schedule of Assessment (Appendix 1H, Appendix 1I, and Appendix 1J) for timepoints.

Blood samples will be collected at specified times as described in Appendix 1H (Phase 1) or Appendix 1I (Phase 2-safety lead-in), or Appendix 1J (Phase 2-expansion) will be used for the evaluation of biomarkers including but not limited to, TIM-3, LAG-3, and PD-1 RO, immunophenotyping in peripheral blood cells, concentrations of cytokine and soluble proteins in plasma and serum, and ctDNA analysis in peripheral blood.

In Phase 1 and Phase 2 safety lead-in, patients will provide archival tumor tissues (FFPE blocks or approximately 15 freshly cut unstained slides) for biomarker analysis, if available. If archival tissue is not available, a fresh tumor biopsy is strongly encouraged but not mandatory.

In Phase 2 dose expansion, during the prescreening period, designated PD-L1 results are required for HNSCC and NSCLC patients. Either local documented results or a central analysis on recently obtained tissue will be acceptable. For both HNSCC and NSCLC patients, PD-L1 IHC 22C3 pharmDx assay will be used for PD-L1 expression detection in a central lab. If local testing is used, PD-L1 (CPS ≥ 1) by IHC 22C3 pharmDx assay (preferred) or PD-L1 (CPS ≥ 1, vCPS or TAP ≥ 1%) by VENTANA PD-L1 (SP263) are acceptable for HNSCC patients (Note: PD-L1 positivity determined by PD-L1 IHC 22C3 pharmDx assay will be used for HNSCC patients in the EU); PD-L1 (TPS or TC ≥ 1%) by IHC 22C3 or 28-8 pharmDx or VENTANA PD-L1 (SP263) assay are acceptable for NSCLC patients (Note: If PD-L1 IHC 28-8 assay is to be used for determining PD-L1 positivity, it will be used for nonsquamous NSCLC patients only in the EU). This requires tissue samples obtained recently within 2 years. For patients who have known PD-L1 positivity, a historically documented result is acceptable for PD-L1 positivity confirmation by specified PD-L1 assay at the prescreening phase. Tissue obtained within 2 years or fresh biopsy is required prior to the patient commencing first drug administration on Cycle 1 Day 1. It is highly recommended to provide the same tissue that was tested for the local PD-L1 assay. If a patient has more than 1 archival tumor tissue, the most recent one is preferred. Positivity confirmation of PD-L1 must be obtained before HNSCC and NSCLC patients are allowed to continue to screening. The PD-L1 test is not required for RCC patients as part of prescreening or screening. For all the cohorts, PD-L1 status will also be evaluated with recently obtained tumor tissues or fresh biopsy, by VENTANA PD-L1 (SP263) assay.

In Phase 2 dose expansion, patients in all cohorts must provide recent tumor tissues obtained within 2 years (FFPE blocks or approximately 15 freshly cut unstained slides). If recently obtained tumor tissue is insufficient, a fresh tumor biopsy is mandatory. If qualified tumor tissue samples were received in the prescreening period then a repeat tumor biopsy need not be done.

For Phases 1 and 2, an optional biopsy after 2 cycles of treatment (approximately Cycle 3 Day 1) is strongly recommended to obtain tumor samples for the evaluation of pharmacodynamic effects. An optional biopsy will also be taken from accessible tumor sites for patients who have confirmed disease progression during the study in order to evaluate potential resistance mechanism(s). Ideally and if feasible, post-treatment biopsies should be taken from the same tumor lesion as the baseline biopsy/fresh tumor tissues.

Tissue samples obtained as described above will be shipped to a BeiGene designated central laboratory for biomarker testing after local regulatory approval. This may occur after the start of study treatment if necessary. Tumor tissues will be used for immunohistochemistry analysis of

PD-L1, TIM-3, LAG-3, and ligands expression. In addition, other exploratory biomarkers, such as TIL assessment, tumor mutation burden, and gene expression profiling, that are related to response or clinical benefit of BGB-A425, LBL-007 and tislelizumab may also be evaluated.

Written patient consent is required for any optional fresh tumor biopsies. 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. Bone derived tissue samples should be avoided.

7.9. Visit Windows

All visits must occur within ± 3 days from the scheduled date, unless otherwise specified (see Appendix 1). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment administration of each cycle should be performed before any study treatment is given unless otherwise noted. Laboratory results must be reviewed before dosing. For the case of dose/visit delay, the details for scheduling the subsequent treatment visits are described in Section 5.6.1.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled on the nearest feasible date (within the visit window provided in Appendix 1). A cycle is defined as every 21 days based on the schedule of administration of BGB-A425. Subsequent visits should be conducted according to the planned schedule of assessments 21 days from Day 1 of Cycle 1.

7.10. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or investigator's request and may include vital signs/focused physical examination; ECOG Performance Status; AE review; concomitant medications and procedures review; radiographic assessments; physical examination of liver, spleen, and lymph nodes; disease-related constitutional symptoms; and hematology and chemistry laboratory assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected disease progression, then diagnostic tests may be performed based on investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

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 BGB-A425, LBL-007, and Tislelizumab

BGB-A425, LBL-007, and tislelizumab are investigational agents that are currently in clinical development. Limited clinical information is available for BGB-A425 and LBL-007 (Section 1.2.4 and Section 1.3.5). Safety data is available from 33 patients treated with BGB-A425, 22 patients treated with LBL-007, and 2596 patients treated with tislelizumab (Section 1.2 and BGB-A425 Investigator's Brochure; Section 1.3 and LBL-007 Investigator's Brochure, Section 1.4 and Tislelizumab Investigator's Brochure). The following recommendation is based primarily upon results from nonclinical studies of BGB-A425, clinical data of BGB-A425 from the dose escalation phase of this study, clinical data of LBL-007, nonclinical and clinical studies with tislelizumab, as well as published data on other anti-TIM-3, anti-LAG-3, and anti-PD-1 agents given alone or in combination with one another.

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of imAEs, specifically the induction or enhancement of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Appendix 8. BGB-A425 mediated TIM-3 inhibition may increase the risk of immune-mediated AEs, though no apparent immunotoxicity, or toxicity in general, have been observed in animal models treated with BGB-A425 (Section 1.2.2 and BGB-A425 Investigator's Brochure). Further, in the absence of activation, peripheral effector T-cells do not typically express TIM-3, thereby minimizing any potential negative additive affect as it relates to peripheral immune tolerance. Clinical data from the dose escalation phase of this study is still under review (Section 1.2.4 and BGB-A425 Investigator's Brochure).

According to clinical studies for which safety results are currently available, the possible toxicities of LBL-007 include general reactions (fatigue), allergic reactions, infusion-related reactions, digestive tract toxicity (loss of appetite, diarrhea, nausea, and vomiting), hepatotoxicity, pulmonary toxicity (pneumonia), and cutaneous reactions (pruritis and rash).

Although most imAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. To assist with this, a comprehensive algorithm to aid in the diagnostic evaluation and management of immune-mediated toxicities is provided in Appendix 8.

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

Eligibility criteria were selected to maintain the safety of patients in this trial. Results from the nonclinical toxicology studies of BGB-A425, LBL-007 and tislelizumab and clinical data with tislelizumab, as well as the nonclinical/clinical data from other anti-TIM-3, anti-LAG-3 and PD-L1/PD-1 inhibitors, were taken into account. Specifically, patients at risk for study-emergent active autoimmune diseases or history of autoimmune diseases that may relapse and patients who

have received a live viral vaccine within 28 days before administration of study drug(s) are excluded from the study (see Section 4.2).

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. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Clinical laboratory results must be reviewed prior to the start of each cycle.

In this study, all enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs, physical examinations, laboratory measurements (hematology, chemistry, etc.), and other assessments. In addition, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

Serum samples will be drawn for determination of ADAs to BGB-A425 and to tislelizumab in patients for both Phase 1 and Phase 2 portions of the study. 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 (for additional information, see Section 5.3).

All AEs will be recorded during the study (AE from the time of the first dose and SAEs from the time of signing the prescreening informed consent) and for up to 30 days after the last dose of study drug(s) or until the initiation of another anticancer therapy, whichever occurs first. At the end of treatment, ongoing AEs considered related to study treatment will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE.

Immune-mediated AEs will be recorded until up to 90 days after the last dose of study drug(s), regardless of whether or not the patient starts a new anticancer therapy. All drug related SAEs will be recorded by investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow-up, whichever occurs first.

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

The potential safety issues anticipated in this trial, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

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 pre-existing condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study drug administration even though it 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 will be blinded on the copies of the medical records prior to submission to the sponsor.

8.3.2. Assessment of Severity

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

Toxicities that are not specified in the 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
- Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare, activities of daily living
- 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 (for example, 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 8.4.

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 judgement. 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 study drug should be considered and investigated. The investigator should consult the Tislelizumab Investigator's Brochure, BGB-A425 Investigator's Brochure and LBL-007 Investigator's Brochure in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every SAE prior to transmission of the SAE report to the sponsor, since the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality considering follow-up information, amending the SAE report accordingly.

2-point Causality Assessment

The causality of each AE should be assessed and classified by the investigator as "related" or "not related." 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:

- Temporal relationship of the AE to the administration of study treatment/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 are met, otherwise the event should be assessed as not related:
    a. There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
    b. There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
    c. 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).

An AE should be considered "unrelated" to study drug if any of the following are met:

- An unreasonable temporal relationship between administration of the product and the onset on the AE (eg, the AE occurred either before, or too long after administration of the product for it to be considered product-related)
- A causal relationship between the product and the AE is biologically implausible (eg, death as a passenger in an automobile accident)

- A clearly more likely alternative explanation for the AE is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related AE).

8.3.4. Following Adverse Events

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

All AEs and SAEs 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 consultation 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 post-mortem 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, chemistry, hematology, coagulation) or other abnormal assessments (ECGs, X-rays, 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 judgement of the investigator; in general, these are the abnormalities that are associated with clinical signs or symptoms, require active medical intervention, or lead to dose interruption or discontinuation, or require close observation, or more frequent follow-up assessments, or further diagnostic investigation.

8.4. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- 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, which 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 ward 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 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 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 SAEs:

- Hospitalization for elective treatment of a pre-existing 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 is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the Investigator's Brochure.

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

8.6.1. Adverse Event Reporting Period

After the Prescreening ICF has been signed but prior to the administration of the study drug, only SAEs should be reported.

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study drug or initiation of new anticancer therapy, whichever occurs first. In addition, telephone contacts and/or clinic visits with patients should be conducted to assess imAEs (serious and nonserious), anticancer therapy, and concomitant medications/procedures where appropriate (ie, associated with an imAE, etc.) at 60 and 90 days (±14 days) after the last dose of study drugs regardless of whether or not the patient starts a new anticancer therapy. If a patient reports a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated. The

investigator should report any SAEs that are assessed as related to study drug(s), at any time after treatment discontinuation.

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 (after the Prescreening ICF is signed), the event must be reported immediately, without undue delay, but no later than within 24 hours of obtaining knowledge of the event to the sponsor or designee as described in Table 14.

Table 14: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-Up Report	Documentation Method	Reporting Method
All SAEs	Within 24 hours of first knowledge of the AE	SAE report	As expeditiously as possible	SAE report	Email or fax SAE form

Abbreviations: AE, adverse event; SAE, serious adverse event.

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 (after the Prescreening ICF is signed), he/she 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, he/she is not to 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 at the time of the initial report 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 promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.2.1 and Section 8.6.2.2. 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 responsible person 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 suspected unexpected serious adverse reactions (as defined in Section 8.5), will be submitted to all applicable regulatory authorities and investigators for BGB-A425, LBL-007 and tislelizumab 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/her IRB or 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 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. Recording Disease Progression

Disease progression and death because of disease progression, which is expected in this study population and measured as an efficacy endpoint, should not be reported as an AE term. Instead, the symptoms, signs or clinical sequelae that result from disease progression should be reported as the AE(s).

For instance, a patient presents with pleural effusion resulting from disease progression of metastasis to lungs. The event term should be reported as "pleural effusion" instead of disease progression. If a patient experienced a fatal multi-organ failure because of disease progression, the term "multi-organ failure" should be reported as the SAE with death as outcome instead of reporting "fatal disease progression" or "death because of disease progression." All SAEs and deaths, regardless of relatedness to disease progression, should be recorded and reported.

8.6.5. Recording Deaths

Death is an outcome and not usually considered an AE. If the only information available is death and the cause of death is unknown, then the death is reported as an event, eg, "death", "death of unknown cause", or "death unexplained".

8.6.6. Recording Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving investigational therapy or within 6 months after the last dose of tislelizumab or BGB-A425 or LBL-007, a pregnancy report form is required to be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be 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 be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug should be recorded and reported as an SAE.

8.6.7. Recording Post Study Adverse Events

A post study AE or SAE is defined as any AE that occurs outside of the AE/SAE reporting period that is defined in Section 8.6.1.

Investigators are not obligated to actively seek AEs or SAEs in former patients. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the SAE related to the study drug, the investigator will notify the sponsor.

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 following Reference Safety Information documents:

- Tislelizumab Investigator's Brochure
- BGB-A425 Investigator's Brochure
- LBL-007 Investigator's Brochure

8.6.9. Assessing and Recording Immune-Mediated Adverse Events

Since treatment with anti-PD-1 (and potentially anti-TIM-3 or anti-LAG-3) therapy can cause autoimmune disorders, AEs considered by the investigator to be immune-mediated (see Section 8.7.3) should be classified as imAEs and identified as such in the eCRF AE page until Day 90, after treatment discontinuation.

Investigators should consult the guidance on diagnostic evaluation and management of imAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 8.

An extensive list of potential imAEs appears in Appendix 8. All conditions similar to those listed should be evaluated to determine whether they are imAEs, based upon a similar diagnostic process as presented in Appendix 8.

8.7. Management of Adverse Events of Special Interest

As a routine precaution, following completion of study drug(s) administration, patients must be monitored for a period afterwards in an area with resuscitation equipment and emergency agents. See Section 5.3 for additional details.

Adverse events of special interest (AESI) do not require expedited reporting to BeiGene within 24 hours of awareness, using the SAE report form. AESIs are only required to be entered into the clinical database.

The management for infusion-related reactions, severe hypersensitivity reactions, and imAEs according to the NCI-CTCAE criteria are outlined below.

8.7.1. Infusion-Related Reactions

The symptoms of infusion-related reactions include fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be closely monitored for such reactions. Immediate access to an Intensive Care Unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modification for symptoms of infusion-related reactions because of study drug(s) is provided in Table 15.

Table 15: Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

NCI-CTCAE Grade	Treatment Modification for Study Drugs
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions has resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 – severe Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment.
Grade 4 – life threatening Life threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment. Hospitalization is recommended.

Abbreviations: IV, intravenous; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs, nonsteroidal anti-inflammatory drugs

Once the infusion rate of the study drug(s) has been decreased by 50% or suspended because of an infusion-related reaction, it must remain decreased for all subsequent infusions with premedication. 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 treatment.

CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted, as indicated per type of the reaction. This includes but is not limited to an antihistamine (eg, diphenhydramine or equivalent), antipyretic (eg, paracetamol or equivalent), and if considered indicated oral or intravenous glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, patients should receive oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and an antipyretic (eg, paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion reaction.

CTCAE Grade 3 or 4 infusion reaction: Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes but is not limited to oral or intravenous antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

8.7.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice as described in the complete 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.

In the event of a systemic anaphylactic/anaphylactoid reaction (typically manifested within minutes following administration of the drug/antigen, and characterized by: respiratory distress; laryngeal edema; and/or intense bronchospasm; and often followed by vascular collapse or shock without antecedent respiratory difficulty; cutaneous manifestations such as pruritus and urticaria with/without edema; and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea), the infusion must be immediately stopped and the patient discontinued from study treatment.

The patients will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed and then the patient should be placed on monitor immediately and the Intensive Care Unit should be alerted for possible transfer if needed.

For prophylaxis of flu-like symptoms, a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (ie, 600 mg ibuprofen, 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 (ie, paracetamol) may be given to patients at the discretion of the investigator.

8.7.3. Immune-Mediated Adverse Events

Immune-mediated AEs are of special interest in this study. If the events listed in Appendix 8 or similar events occur, the investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic, toxin, disease progression, or other neoplastic causes) with appropriate diagnostic tests which may include but is not limited to serologic, immunologic, and

histologic (biopsy) data. The imAEs listed in Appendix 8 or similar conditions should be evaluated in patients receiving study drugs to determine whether they are immune-mediated. If alternative causes have been ruled out; the AE that required the use of systemic steroids, other immunosuppressants, or endocrine therapy and is consistent with an immune-mediated mechanism of action, the imAE indicator in the eCRF AE page should be checked. However, these imAEs do not require expedited reporting to the sponsor within 24 hours via the SAE reporting method.

Refer to Appendix 8 for a list of the most common imAEs as well as detailed recommendations for the diagnostic evaluation and management of imAEs according to European Society for Medical Oncology and American Society of Clinical Oncology guidelines (Haanen et al 2017; Brahmer et al 2018) as well as common immune-mediated toxicities. 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.

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

8.7.4. Management of imAEs in Patients with Pre-Existing Renal Dysfunction

Patients with renal dysfunction (estimated GFR ≥ 30 mL/min/1.73 m^2 by CKD-EPI equation) may be enrolled into the study. Therefore, the following algorithm is proposed for the use of steroid treatment in the management of imAEs in patients with normal as well as pre-existing mild or moderate renal dysfunction:

- If the serum creatinine (ie, estimated GFR) is normal at baseline, refer to Appendix 8 for diagnosis and management of patients with imAE related abnormal renal laboratory values.
- If the serum creatinine is Grade 1 at baseline and increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 2 after starting treatment with study drug(s), refer to Appendix 8 for diagnosis and management of patients with abnormal renal laboratory values. Check the estimated GFR using Appendix 7 and the estimated GFR calculator link. In the setting of a Grade 2 serum creatinine increase only, study treatment can continue unless the serum creatinine increases by at least 50% from the baseline value OR the estimated GFR falls below 20 mL/min/1.73 m2.
- If the serum creatinine is Grade 2 at baseline (RCC patients only) and increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 3 after starting treatment with study drug(s), refer to Appendix 8 for diagnosis and management of patients with abnormal renal laboratory values. In the setting of a Grade 3 serum creatinine increase only, study treatment will be held until serum creatinine improves to baseline and treatment may resume only after discussion with the medical monitor.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Details of the statistical analyses will be included in a separate Statistical Analysis Plan.

In general, data from the Phase 1 and Phase 2 safety lead-in will be summarized by dose level and schedule; while data from the Phase 2 dose expansion will be summarized by cohort, unless otherwise specified.

9.1. Statistical Analysis

9.1.1. Randomization Methods

Not applicable.

9.1.2. Analysis Sets

The Safety Analysis Set includes all patients who received at least 1 dose of study drug(s). It will be the population for the safety and efficacy analyses.

The Evaluable Analysis Set includes all dosed patients who have evaluable disease at baseline, and at least 1 evaluable postbaseline tumor response assessment unless any clinical PD or death occurred before the first scheduled postbaseline tumor assessment. It will be used for efficacy analysis only.

The DLT Evaluable Analysis Set for Phase 1 includes patients who received at least 80% each of the assigned dose of BGB-A425 on Cycle 1 Day 1 and tislelizumab on Cycle 1 Day 8 (+2 days) and remained on study during the DLT observation period and had sufficient safety evaluation or patients who experienced a DLT within the DLT observation period. For safety lead-in in Phase 2 with Cohort A and Cohort B, DLT Evaluable Analysis Set includes patients who received at least 80% each of the assigned dose of study drug(s) in the combination treatments.

The PK Analysis Set includes all patients who received at least 1 dose of study drug(s) and have at least 1 derivable PK parameter. Subgroup analysis may be carried out based on requirement from local health authorities.

9.1.3. Patient Disposition

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

Major 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 in the Safety Analysis Set using descriptive statistics. Continuous variables include age, weight, time since initial cancer

diagnosis, and time since advanced/metastatic disease diagnosis; categorical variables include gender, ECOG, race, TNM staging, number of prior system therapies received, and tumor type. Other disease specific parameters might be summarized in the relevant cohort for Phase 2.

9.1.5. Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical 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 protocol. Prior medications will be defined as medications that stopped before the day of first dose of 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 Safety Follow-up Visit). A listing of prior and concomitant medications will be included in the clinical study report for this protocol.

9.2. Efficacy Analyses

Efficacy endpoints will be based upon investigator derived tumor assessments per RECIST v1.1. The following efficacy endpoints will be analyzed and summarized in order to evaluate the antitumor activities of all combination treatments:

- ORR is defined as the proportion of patients who had confirmed CR or PR assessed by investigator.
- DOR is defined as the time from the first determination of an objective response, until the first documentation of progression or death, whichever comes first.
- DCR is defined as the proportion of patients with BOR (as defined in Appendix 9 for RECIST v1.1) of a CR, PR, and stable disease. It will be summarized similarly as ORR.
- PFS is defined as the time from the date of the first dose of study drug(s) to the date of the first documentation of disease progression assessed by investigator or death, whichever occurs first.
- OS is defined as time from the first dose of study drug(s) to the date of death due to any cause.

9.2.1. Secondary Efficacy Analysis in Phase 1 and Phase 2 (Safety Lead-in)

ORR, DOR, and DCR will be determined from investigator derived tumor assessments per RECIST v1.1.

ORR and DCR will be summarized by dose cohort, along with their 95% confidence interval in the Safety and Evaluable Analysis Sets.

9.2.2. Primary Efficacy Analysis in Phase 2 (Dose Expansion)

ORR and its 95% confidence interval will be summarized in the Safety and Evaluable Analysis Sets. ORR in Phase 2 dose expansion will be presented by tumor expansion cohort.

9.2.3. Secondary Efficacy Analysis in Phase 2 (Dose Expansion)

PFS, DOR, and DCR will be summarized by tumor expansion cohort.

PFS and DOR will be estimated using the Kaplan-Meier method. The median PFS and the cumulative probability of PFS and event-free rate for DOR at every 3 months will be calculated and presented with 2-sided 95% CIs. PFS censoring rule will follow FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007).

DOR censoring rule will be implemented similarly as PFS, and analysis will be limited in the responders.

DCR will be analyzed similarly to ORR in the Safety and Evaluable Analysis Sets.

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

9.2.4. Exploratory Efficacy Analysis

OS will be analyzed similarly as described for PFS (Section 9.2.3) in all treated patients.

Correlations between drug exposure and response (efficacy and safety endpoints) will also be assessed.

Additionally, the following will be evaluated as appropriate: exploratory biomarkers from patient derived tumor tissue(s) and blood (or blood derivatives) samples obtained before, during and/or after the combination treatments. Candidate biomarkers may include, but are not limited to, PD-1, TIM-3, and LAG-3 RO and immune cell subpopulation in peripheral blood cells, concentrations of cytokine and soluble proteins in plasma or serum, ctDNA analysis in peripheral blood, PD-L1, TIM-3, LAG-3, and ligands expression, TIL assessment, gene expression profiling, and tumor mutation analysis in tumor tissue.

9.3. Safety Analyses

Safety will be determined by the spontaneous reporting of AEs 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 the NCI-CTCAE v5.0. The incidence of DLT events and TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class and preferred term. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs.

Safety data will be summarized in the Safety Analysis Set, and by study phase.

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 (mg), dose intensity, and relative dose intensity.

The number (percentage) of patients requiring dose interruption, dose delay, and drug discontinuation because of AEs will be summarized for each study drug. Reasons of the above dose modification 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 Medical Dictionary for Regulatory Activities. Adverse events will be coded to Medical Dictionary for Regulatory Activities (version 18.1 or higher) lower level term, preferred term and primary system organ class.

DLT will be summarized at each dose cohort in Phase 1 and Phase 2 (safety lead-in).

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 up to 30 days following study drug discontinuation or initiation of new anticancer therapy, whichever comes first. The TEAE classification also applies to imAEs that are recorded up to 90 days after discontinuation from tislelizumab, regardless of whether or not the patient starts a new anticancer therapy.

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.

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

9.3.3. Laboratory Analyses

Clinical laboratory (eg, hematology, serum chemistry, coagulation, 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 included in the clinical study report for this protocol. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline visit.

Laboratory parameters that are graded in 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, calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

9.3.4. Vital Signs

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

9.3.5. Ophthalmologic Examination

Ophthalmologic examination results will be listed by patient.

9.4. Pharmacokinetic Analysis

Noncompartmental analysis will be carried out in patients with serial BGB-A425 and LBL-007 serum concentrations. PK parameters such as C_{max}, C_{min}, T_{max}, $t_{1/2}$, $AUC_{0\text{-}21d}$, CL, and Vz may be derived and summarized with descriptive statistics, including means, medians, ranges, and standard deviations, as appropriate. BGB-A425, LBL-007, and tislelizumab serum concentration by time may be summarized in patients with sparse PK collection.

Population PK analysis may be carried out if supported by data.

Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data.

9.5. Immunogenicity Analyses

Samples to assess anti-BGB-A425-antibodies, anti-LBL-007-antibodies as well as anti-tislelizumab antibodies will be collected only in patients who receive the treatment and in sites that are able to adequately perform sampling, handling, and processing outlined in the laboratory manual.

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

9.6. Other Exploratory Analyses

Summary statistics will be provided for pharmacodynamic biomarkers, including but not limited to immune cell subtypes in the blood and/or tumor tissue. An exploratory analysis on a potential correlation of these pharmacodynamic biomarkers with the dose, safety, and antitumor 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 response, such as efficacy.

9.7. Sample Size Consideration

The study plans to enroll approximately 178 to 358 patients:

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

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

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

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

- Cohort 1: HNSCC - BGB-A425 + Tislelizumab
- Cohort 2: NSCLC - BGB-A425 + Tislelizumab
- Cohort 3: RCC - BGB-A425 + Tislelizumab
- Cohort 4: HNSCC - BGB-A425 + LBL-007 + Tislelizumab
- Cohort 5: NSCLC - BGB-A425 + LBL-007 + Tislelizumab
- Cohort 6: HNSCC - LBL-007 + Tislelizumab
- Cohort 7: NSCLC - LBL-007 + Tislelizumab

There will be approximately 40 evaluable patients planned per cohort (up to 280 evaluable patients in total). For each cohort, the “success” is defined as posterior probability of true ORR greater than historical ORR, which is > 0.75; where historical ORRs from representative populations for HNSCC, NSCLC, and RCC are 15%, 20%, and 25%, respectively.

A two-stage design is implemented in which Bayesian predictive probability of success (PPoS) based on unconfirmed response rate will be used at the interim analysis after approximately 20 evaluable patients in a cohort have completed at least 1 tumor assessment. The use of response without confirmation requirement is to allow timely evaluation of preliminary efficacy results. If the PPoS is > 0. 5 for a given cohort, enrollment of that cohort will continue to approximately 40 evaluable patients. If the PPoS is < 0.05 for a given cohort, enrollment may stop due to futility. If the PPoS is between 0.05 and 0.5, additional efficacy endpoints (eg, PFS, DOR) will be evaluated. The final decision to stop enrollment or terminate the cohorts early will be based on the totality of available data, such as additional efficacy endpoints, all available safety information, biomarker data, and internal and external emergent data..

Given the criteria described above, HNSCC patients will be populated based on whether ≥ 4 responders are observed in the first 20 evaluable patients of each cohort, enrollment will be allowed to proceed to approximately 40 evaluable patients, or if ≤ 1 responder out of the first 20

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

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

Because the treatment landscape is rapidly evolving, the most current standard of care for a representative line of therapy, and patient population for which sufficient historical data is available, will be used in the calculation of predictive probability. As such, the analysis thresholds for additional enrollment may be modified accordingly.

9.8. Interim Analyses

Refer to Section 9.7 for Phase 2 interim analyses.

10. STUDY COMMITTEES

10.1. Safety Monitoring Committee

An SMC will be established to review the safety and efficacy data for this study. The SMC will be composed of representatives from the sponsor, including the medical monitor as the SMC lead, product safety physician, biostatistician, and other members as appropriate, and investigators from enrolling sites for the cohort(s) under discussion. The SMC will review all available safety, efficacy, PK, and exploratory data.

The SMC may also be called upon by the sponsor on an ad hoc basis where applicable to the conduct of the study.

For Phase 1 dose escalation, an SMC meeting will be held after completion of the DLT period of the last patient enrolled in each dosing cohort. The SMC will review all available safety data to evaluate a dosing decision (ie, dose escalation, dose de-escalation, and cohort expansion or suspension), in line with the 3 + 3 design rules as outlined in Section 3.1. Safety data from prior cohorts may also be presented. The decision to escalate the dose and the determination of the MTD/MAD will be based on the cohort safety reviews. The SMC will decide on the DLTs relevant for the treatment and will decide by consensus on dose escalation, dose de-escalation, or suspension of enrollment based on safety and/or PK data.

Before moving to the next dose level, the SMC will review all safety data available to determine whether recruitment to the next cohort should be initiated. The SMC will determine when no further dose escalation is appropriate. The SMC will meet for cohort safety reviews after all patients in a dosing cohort have completed the first treatment cycle and after completing the DLT period . All available safety data will also be provided for patients who discontinue prior to this time. Safety data from prior cohorts may also be presented. The decision to escalate dose and the determination of the MTD/MAD will be based on the cohort safety reviews. The SMC will decide on DLTs relevant for the treatment and will decide by consensus on dose escalation, dose de-escalation, or suspension of enrollment based on safety and/or on PK data. Additionally, the SMC will review any protocol deviations that may have impacted evaluation of potential DLT.

All voting members of the SMC will determine the key recommendations, including dose escalation, dose modification, and dose selection for Phase 1 dose escalation cohorts. Final recommendations will be made by consensus voting. Response from all SMC members, or their designees, shall be required for each escalation/review. Adequate time for review of results will be given to SMC members (approximately 1 to 2 business days). Enrollment in subsequent dose levels will be put “on hold” during each review period, pending the decision of the SMC.

The SMC decision points may fall into one of the categories detailed below:

- Escalate to a higher dose
- Recruit additional patients into existing dose level
- Explore any other dose levels; an intermediate, not predefined, previously evaluated, or not previously evaluated dose level below MTD/MAD
- Stop escalation and investigate lower dose(s)

Decisions will be made using the criteria defined within the protocol (see Section 3.5). The

SMC will make recommendations on dose escalation, dose modification, and dose selection for Phase 1 and Phase 2 safety lead-in.

For Phase 2 dose expansion, routine offline safety reviews will be conducted on a quarterly basis (or less frequently) depending on the recruitment rate or the number of active patients on treatment. The clinical data summary will be circulated to all SMC members.

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 may 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 International Conference on Harmonisation Good Clinical Practice 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 frequency of the monitoring visits should align with the expectations as outlined by the sponsor during the site initiation visit.

The investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

11.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene 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 to representatives of a regulatory agency or BeiGene 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 or 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 Good Clinical Practice 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/her time and the time of his/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. This includes acknowledgment of 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 BeiGene and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, if allowed, 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 BeiGene requirements. At the end of the study, following 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 BeiGene's requirements for disposal, arrangements will be made between the site and BeiGene or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed 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 in full conformance with the International Conference on Harmonisation E6 guideline for Good Clinical Practice 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 individual. The study will also comply with the requirements of the International Conference on Harmonisation E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

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 to the IRB/IEC by the principal investigator and 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.

The principal 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 IRB/IEC. Investigators may receive written Investigational New Drug 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 trial.

13.3. Informed Consent

The sponsor's sample Prescreening and Screening ICFs will be provided to each site. If applicable, they 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 legal representative (only outside Europe, when permitted by local laws) before his or her participation in the study. Moreover, any applicable supplementary ICFs will be provided for patients to sign and date when applicable. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to 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 be re-consented to the most current version of the Screening ICFs (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. Reconsenting of the Prescreening ICF is not required for any patients. For any updated or revised Screening 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 Screening ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legal representative (only outside Europe, when permitted by local laws). 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 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 lab).

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 United States Food and Drug Administration (US FDA), the China National Medical Products Administration (China NMPA), the European Medicines Agency (EMA), 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 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 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 clinical investigators with BeiGene 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 Collection

Data required by the protocol will be entered into an electronic data capture (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 investigator or designee as identified on Form FDA 1572 must sign the completed casebooks to attest to their accuracy, authenticity, and completeness.

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

14.1.2. Data Management/Coding

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

Standard procedures (including following data review guidelines, computerized validation to produce queries and maintenance of an audit file which includes all database modifications) will be followed to support accurate data collection, maintain confidentiality, and to avoid unauthorized access, disclosure, dissemination, alteration or loss of information and personal data processed. Data will be reviewed for outliers, logic, data inconsistencies and completeness.

During the course of 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.

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 giving due consideration to data protection and medical confidentiality.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using the Medical Dictionary for Regulatory Activities.

14.2. Data Integrity and In-house Blinding

Because of the open-label design of the study, access to the unblinded patient level clinical data in the EDC system will only be assigned to predefined study personnel. Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias, or share such outputs from the EDC system with other functions/persons who do not have access to the EDC. If relevant, the central imaging vendor will perform the central imaging review without knowledge of treatment

assignment. Although the trial 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 one of the following 2 categories: 1) investigator's study file, and 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, informed consent, 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 (although not be limited to) documents such as the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

Following 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, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure 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 or 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 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 BeiGene to store these in sealed containers outside of 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 outside of the site.

14.4. Protocol Deviations

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

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

14.5. Publication and Data Sharing Policy

A clinical study report will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the International Conference on Harmonisation 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 regulator guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the trial. The data generated in this clinical trial 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 or stricter local criteria (International Committee of Medical Journal Editors 2016).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor prior to 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 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
- Resolve and close all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of PK samples to assay laboratories

In addition, the sponsor reserves the right to suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance. 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 prior to it taking 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, and 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 IEC/IRB promptly and provide the reason for the suspension or termination.

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

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

Information Disclosure and Inventions

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) is the sole property of the sponsor.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which 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) will be kept 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:

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

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

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16. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

APPENDIX 1A. PHASE 1 SCHEDULE OF ASSESSMENTS

Phase 1 Assessment	Screening[1]	Treatment Cycles									Safety Follow-up[3]			Efficacy Follow-up[4]
		Cycle 1 (28 Days)				Cycle 2 (21 Days)			≥ Cycle 3 (Every 21 Days)	EOT Visit[2]				
Visit Day	**-28 to -1**	**1**	**8**	**15**	**21**	**1**	**8**	**15**	**1**	**0 to 7 Days**	**+30 days**	**+60 Days**	**+90 Days**	
Visit Window			**+ 2**	**± 2**	**± 2**		**± 2**	**± 2**	**± 3**		**± 7**	**± 14**	**± 14**	
Informed consent	x													
Inclusion/exclusion criteria	x													
Demographics/ medical history/ prior medications[5]	x													
Vital signs/ height and weight[6]	x	x[6]	x[6]	x	x	x[6]	x	x	x[6]	x	x			
Physical examination[7]	x	x	x	x	x	x	x	x	x	x	x			
ECOG Performance Status	x	x				x			x	x	x			
12-lead triplicate ECG[8]	x	Predose and 6 hours post study drug(s) infusion on Day 1 of Cycle 1 and 5								x	x			
Optical coherence tomography (or equivalent diagnostic test) and visual acuity tests[9]	x								C4 then every 15 wks (± 7 days)	x[10]	x[10]			

Phase 1 Assessment	Screening[1]	Treatment Cycles									Safety Follow-up[3]			Efficacy Follow-up[4]
		Cycle 1 (28 Days)				Cycle 2 (21 Days)			≥ Cycle 3 (Every 21 Days)	EOT Visit[2]				
Visit Day	**-28 to -1**	**1**	**8**	**15**	**21**	**1**	**8**	**15**	**1**	**0 to 7 Days**	**+30 days**	**+60 Days**	**+90 Days**	
Visit Window			**+ 2**	**± 2**	**± 2**		**± 2**	**± 2**	**± 3**		**± 7**	**± 14**	**± 14**	
Adverse events[11]	x	x	x	x[12]	x[12]	x	x[12]	x[12]	x	x	x	x	x	
Concomitant medications/ procedures	x	x	x	x[12]	x[12]	x	x[12]	x[12]	x	x	x	x	x	
Hematology[13]	x[13]	x[13]	x[13]	x	x	x[13]	x	x	x[13]	x[2]	x			
Serum chemistry[13]	x[13]	x[13]	x[13]	x	x	x[13]	x	x	x[13]	x[2]	x			
Coagulation parameters [13,]	x[13]	x[13]	As clinically indicated[13]							x[2]	x			
Urinalysis[13]	x[13]	As clinically indicated												
CK and CK-MB[14]	x	x	x[14]	x	x	x[14]	x	x	x[14]	x[2]	x			
Pregnancy test[15]	x[15]	x[15]				x[15]			x[15]	x	x			
Thyroid function[16]	x[16]					x[16]			Even # Cycles[16]		x			
HBV/HCV tests[17]	x[17]	Every 4 cycles starting at C5 in HCC patients with detectable HBV DNA at screening or as clinically indicated in all patients[17]								x[17]	x[17]			
Pulmonary function tests[18]	x[18]	As clinically indicated												
Blood biomarkers	x[19]	Refer to Biomarker Table, Appendix 1H												
PD receptor occupancy[20]		Refer to Biomarker Table, Appendix 1H												
Tumor assessment[21]	x	In the first 52 weeks, every 6 weeks. Every 12 weeks thereafter[21]								x[2]				x

Phase 1 Assessment	Screening[1]	Treatment Cycles									Safety Follow-up[3]			Efficacy Follow-up[4]
		Cycle 1 (28 Days)				Cycle 2 (21 Days)			≥ Cycle 3 (Every 21 Days)	EOT Visit[2]				
Visit Day	**-28 to -1**	**1**	**8**	**15**	**21**	**1**	**8**	**15**	**1**	**0 to 7 Days**	**+30 days**	**+60 Days**	**+90 Days**	
Visit Window			**+ 2**	**± 2**	**± 2**		**± 2**	**± 2**	**± 3**		**± 7**	**± 14**	**± 14**	
Archival or fresh tumor tissue[22]	x	Refer to Biomarker Table, Appendix 1H												
BGB-A425 administration[23]		x				x[23]			x[23]					
Tislelizumab administration[24]			x[24]			x			x					

Abbreviations: AE, adverse event; CK-MB, creatine kinase-cardiac muscle isoenzyme; C, cycle; CT, computed tomography; D, day; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; FFPE, formalin-fixed paraffin embedded; FT3, free triiodothyronine; FT4, free thyroxine; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICF, informed consent form; imAE, immune-mediated AE; IRB, Institutional Review Board; IV, intravenous; MRI, magnetic resonance imaging; ^{18}F-NaF PET, 18F-sodium fluoride position emission tomography; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; OCT, optical coherence tomography; PD-1, programmed cell death protein-1; RECIST, Response Evaluation Criteria in Solid Tumors; RNA, ribonucleic acid; SAE, serious adverse event; TSH, thyroid stimulating hormone; wks, weeks; v, version.

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

1. Written informed consent is required prior to performing any study-specific tests or procedures. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to enrollment may be used for screening assessments rather than repeating such tests unless otherwise noted (eg, hematology, serum chemistry, etc.). The ICF signature defines the start of the Screening Period.
2. The EOT Visit is conducted within 7 days from the date the investigator determines that BGB-A425/tislelizumab will no longer be used. If specified laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT Visit, tests need not be repeated. Tumor assessment is not required at the EOT Visit provided that fewer than 6 weeks have passed since the last assessment.
3. The Safety Follow-up Visit is required to be conducted 30 days (± 7 days) after the last dose of either of the study drugs, or before the initiation of a new anticancer treatment, whichever occurs first. In addition, telephone contacts and/or clinic visits with patients must be conducted to assess imAEs (serious and nonserious), anticancer therapy, and concomitant medications/procedures where appropriate (ie, associated with an imAE etc) at 60 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. The EOT Visit may also be used as the Safety Follow-up Visit, provided that it occurred 30 days (± 7 days) after the last study treatment. If the EOT Visit and Safety Follow-up Visit are combined, all individual study assessments for both visits will need to be completed.
4. Efficacy Follow-Up: Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original tumor plan (ie, every 6 weeks (± 7 days) during the first 52 weeks and every 12 weeks (± 7 days) thereafter) until the

patient experiences disease progression, withdraws consent, dies, or until the study terminates, whichever occurs first. The first tumor assessment will be performed 6 weeks (± 7 days) after the first administration of the study drugs.

5. Includes history of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Information on radiographic studies performed prior to study entry may be collected for review by the investigator.
6. Height assessment is required only at screening. Vital signs collected on study include temperature, pulse rate, respiratory rate, and blood pressure. In the first cycle, vital signs will be collected at the following 3 timepoints: 1) within 60 minutes before infusion of each drug; 2) during infusion; 3) within 30 minutes after the infusion of the study drugs. In the subsequent cycles, vital signs will be collected within 60 minutes before infusion of each drug. If clinically indicated, 2 additional vital signs will be collected: during infusion and 30 minutes after each infusion. If several timepoints are overlapping, then only 1 timepoint is needed.
7. Refer to Section 7.5.2 for details regarding physical examination assessment requirements for screening and subsequent timepoints. Additionally, investigators should solicit patients for information regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit. For any change in vision, referral to an appropriate specialist will be made for further management guidance.
8. The triplicate ECG recordings will be performed at screening; predose and 6 hours post study drug (s) infusions on Day 1 of Cycles 1 and 5; EOT Visit; 30-day Safety Follow-up Visit, and when clinically indicated. Patients should be resting for at least 10 minutes in a semi-recumbent supine position prior to each ECG collection. When coinciding with blood draws, ECG assessment should be performed prior to blood draws.
9. Eye examination, visual acuity test, and optical coherence tomography (OCT; or equivalent diagnostic test for retinal examination) captured prior to obtaining written informed consent but within 28 days of enrollment, may be used rather than repeating tests at screening. Eye examination, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed at the Screening Visit, Cycle 4 Day 1 (± 7 days) and every 15 weeks (± 7 days) thereafter.
10. The ophthalmologic assessments including eye examination, visual acuity test, and OCT (or equivalent diagnostic test) should only be performed once at either the EOT or during Safety Follow-up, within 30 days of study treatment end.
11. The AEs and laboratory abnormalities will be graded per NCI-CTCAE version 5.0. All AEs will also be evaluated for seriousness. After the ICF has been signed, but prior to the administration of study drug, only SAEs should be reported. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study drugs or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of study drugs, regardless of whether or not the patient starts a new anticancer therapy. The investigator should report any SAEs that are assessed as related to study drug treatments at any time after treatment discontinuation.
12. Review of AEs and concomitant medications/procedures may be conducted by telephone on Cycle 1 Days 15 and 21 and Cycle 2 Days 8 and 15 if patient is unable to come to the clinic.
13. Central laboratory assessments will be conducted for serum chemistry, hematology, and coagulation while urinalysis will be performed locally as outlined in Appendix 2. Investigators may use results from local laboratories for assessing eligibility, safety monitoring, and dosing decision(s) but central laboratory assessments must still be collected for the timepoints outlined in the table above where applicable. Hematology and serum chemistry (data collected as specified in Appendix 2) will be performed weekly for the first 2 Cycles and then at the beginning of each subsequent cycle. After Cycle 1 Day 1, results are to be reviewed within 72 hours before study drug administration, where applicable. Urinalysis and/or coagulation lab(s) to be conducted during the treatment period only if clinically warranted. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.
14. CK and CK-MB will be performed by a central laboratory in addition to the local study site laboratory if immediate results are required. The test will be evaluated at screening; weekly for the first 2 Cycles, followed by Day 1 of each cycle thereafter; EOT Visit; 30-day Safety Follow-up Visit, and when clinically indicated. Except for Cycle 1 Day 1, results are to be reviewed within 72 hours before study drug administration where applicable. If your laboratory does not perform CK-MB testing, serum troponins (troponin I and/or T) measurements should be performed instead; if only either troponin is

assessed per local standards that same test should be evaluated throughout. If significant abnormalities are detected, please evaluate the affected patients for possible myocarditis/myositis per institutional guidelines, including additional serum CK/CK-MB, serum troponin levels, ECG, etc.

15. Urine pregnancy test (local laboratory) (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days before enrollment. A negative pregnancy test (by urine or blood) must be completed and recorded on the same day before the administration of study drug at each cycle. A serum pregnancy test (central laboratory) must be performed if the urine pregnancy test is positive or equivocal.
16. Analysis of FT3, FT4, and TSH will be performed by a central laboratory in addition to the local study site laboratory if immediate results are required. Thyroid function tests will be performed at screening and Day 1 every 2 cycles starting at Cycle 2 (ie, Day 1 of Cycles 2, 4, 6, 8 etc.) and 30-day Safety Follow-up Visit. Results are to be reviewed within 72 hours before study drug administration where applicable.
17. Testing will be performed by a central laboratory in addition to the local study site laboratory if immediate results are required at screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA). Testing at screening is mandatory for patients with HCC. Additionally, for HCC patients who have detectable HBV DNA at screening, the respective viral load test will be performed every 4 cycles starting at Cycle 5 (ie, Day 1 of Cycle 5, 9, 13, etc), EOT Visit, and 30-day Safety Follow-up Visit. In patients without HCC, samples for hepatitis serology and viral load will be collected at screening and may be tested if patients have hepatic AE (≥ Grade 3) during the study and as clinically indicated.
18. Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer will have pulmonary function testing which may include, but is not limited to, spirometry and assessment of diffusion capacity done during the Screening Period to assist the determination of suitability on the study and as clinically indicated while on study.
19. Blood biomarker: Refer to Appendix 1H.
20. PD receptor occupancy assay: Refer to Appendix 1H.
21. Radiological images captured as standard of care prior to obtaining written informed consent and within 28 days of enrollment may be used rather than repeating tests. All measurable and evaluable lesions are required to be assessed and documented at the Screening Visit. An MRI (or CT scan if MRI is contraindicated or not readily available) of the head may be required at screening based on clinical judgement; bone scan or ^{18}F-NaF PET is required if clinically indicated. The same radiographic procedure must be used throughout the study for each patient. The investigator must review radiograph results before dosing at the next cycle. Patients will undergo tumor assessments approximately every 6 weeks (± 7 days) during the first 52 weeks and every 12 weeks (± 7 days) thereafter (based on RECIST v1.1 assessment). The investigator may perform additional scans or more frequent assessments if clinically indicated. Patients who continue BGB-A425/tislelizumab beyond initial radiographic disease progression must have a follow-up scan 4 to 12 weeks from the date of initial documentation of disease progression before discontinuing BGB-A425/tislelizumab treatment. See Section 7.6 for more information.
22. Archival or fresh tumor tissue: Refer to Appendix 1H.
23. BGB-A425 will be given IV on Cycle 1 Day 1, Cycle 2 Day 1 and once every 21 days thereafter (see Section 5.3 for details). If tislelizumab is delayed beyond Cycle 1 Day 8 (+2 days), the dose level of BGB-A425 will be reduced starting on Cycle 2 Day 1 (Section 5.6). Note: BGB-A425 must always be prepared and administered separately from any other systemic medication including tislelizumab. When BGB-A425 infusion coincides with tislelizumab, BGB-A425 infusion must always occur after infusion of tislelizumab has completed. Refer to Section 5.6 regarding dose delays and/or modifications.
24. Tislelizumab will be given IV on Cycle 1 Day 8, Cycle 2 Day 1 and once every 21 days thereafter for the remainder of treatment (see Section 5.3 for details). If tislelizumab is delayed beyond Cycle 1 Day 8 (+2 days), it will not be administered in Cycle 1 (Section 5.6). Note: Tislelizumab must always be prepared and administered separately from any other systemic medication including BGB-A425. When tislelizumab infusion coincides with BGB-A425, BGB-A425 infusion must always occur after infusion of tislelizumab has completed. Refer to Section 5.6 and Section 7.6 regarding dose delays.

APPENDIX 1B. PHASE 2 SAFETY LEAD-IN SCHEDULE OF ASSESSMENTS

Phase 2 Safety Lead-In Assessment	Screening[1]	Treatment Cycles					Safety Follow-up[3]				Efficacy Follow-up[4]
		Cycle 1-2 (Every 21 Days)			≥ Cycle 3 (Every 21 Days)	End of Treatment Visit[2]					
Visit Day	**-28 to ~ -1**	**1***	**8**	**15**	**1**	**0 to 7 Days**	**+30 Days**	**+60 Days**	**+90 Days**	**+120 Days [15]**	
Visit Window			**± 2**	**± 2**	**± 3**		**± 7**	**± 14**	**± 14**	**± 14**	
Screening informed consent	x										
Inclusion/exclusion criteria	x										
Demographics/medical history/prior medications[5]	x										
Height[6]	x										
Weight and vital signs[6]	x	x	x	x	x	x	x				
Physical examination[7]	x	x			x	x	x				
ECOG Performance Status	x	x			x	x	x				
12-lead triplicate ECG[8]	x	As clinically indicated				x	x				
Optical coherence tomography (or equivalent diagnostic test) and visual acuity tests[9]	x				C4 then every 15 wks (± 7 days) or 5 cycles from C1D1	x[10]	x[10]				
Adverse events[11]	x	x	x[12]	x[12]	x	x	x	x	x		
Concomitant medications/ procedures	x	x	x[12]	x[12]	x	x	x	x	x		
Hematology[13]	x	x	x	x	x	x	x				
Serum chemistry[13]	x	x	x	x	x	x	x				
Coagulation parameters[13]	x	As clinically indicated				x	x				
Urinalysis[13]	x	As clinically indicated									
CK and CK-MB[14]	x	x	x	x	x	x	x				
Pregnancy test[15]	x	x			x	x	x			x	

Phase 2 Safety Lead-In Assessment	Screening[1]	Treatment Cycles					Safety Follow-up[3]				Efficacy Follow-up[4]
		Cycle 1-2 (Every 21 Days)			≥ Cycle 3 (Every 21 Days)	End of Treatment Visit[2]					
Visit Day	**-28 to ~ -1**	**1***	**8**	**15**	**1**	**0 to 7 Days**	**+30 Days**	**+60 Days**	**+90 Days**	**+120 Days [15]**	
Visit Window			**± 2**	**± 2**	**± 3**		**± 7**	**± 14**	**± 14**	**± 14**	
Thyroid function[16]	x				C3 and every 3 Cycles		x				
Cortisol testing[17]	x				C3 and every 3 Cycles		x				
HBV/HCV tests[18]	x	Every 4 cycles starting at C5 in patients with detectable HBV DNA at screening or as clinically indicated in all patients					x				
Pulmonary function tests[19]	x	As clinically indicated									
Blood biomarkers[20]	x	Refer to Biomarker Table, Appendix 1I									
Tumor assessment[21]	x	In the first 52 weeks, every 6 weeks. Every 12 weeks thereafter[20]				x					x
Archival or fresh tumor tissue[22]	x	Refer to Biomarker Table, Appendix 1I									
BGB-A425 administration[23]		x			x						
Tislelizumab administration[24]		x			x						
LBL-007 administration[25]		x			x						
Survival status											

Abbreviations: AE, adverse event; C, cycle; D, day; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; FFPE, formalin-fixed paraffin embedded; FT3, free triiodothyronine; FT4, free thyroxine; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; ICF, informed consent form; imAE, immune-mediated AE; IV, intravenous; MRI, magnetic resonance imaging; ^{18}F-NaF PET, 18F-sodium fluoride position emission tomography; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; OCT, optical coherence tomography; PD, pharmacodynamic; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; RNA, ribonucleic acid; SAE, serious adverse event; TSH, thyroid stimulating hormone; wks, weeks; v, version.

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

*If needed, some safety laboratory procedures including chemistry, hematology, coagulation, ECOG, and physical examination for C1D1 and C2D1 can be done 1-2 days before dosing.

1. In Phase 2 (safety lead-in), the Screening ICF is required prior to performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to enrollment may be used for Screening assessments rather than

repeating such tests unless otherwise noted (eg, hematology, serum chemistry, etc.). The ICF signature defines the start of the Screening Period. Refer to Section 7.1 and Section 7.2 for more information on the Prescreening and Screening Visits.

2. The EOT Visit is conducted when the investigator determines that any of the study drugs (ie, LBL-007, BGB-A425, and tislelizumab) will no longer be used. If specified laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT Visit, tests need not be repeated. Tumor assessment is not required at the EOT Visit provided that fewer than 6 weeks have passed since the last assessment.
3. The Safety Follow-up Visit is required to be conducted 30 days (± 7 days) after the last dose of any of the study drugs (ie, LBL-007, BGB-A425, and tislelizumab), or before the initiation of a new anticancer treatment, whichever occurs first. In addition, telephone contacts and/or clinic visits with patients must be conducted to assess imAEs (serious and nonserious), anticancer therapy, and concomitant medications/procedures where appropriate (ie, associated with an imAE etc) at 60 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. The EOT Visit may also be used as the Safety Follow-up Visit, provided that it occurred 30 days (± 7 days) after the last study treatment. If the EOT Visit and Safety Follow-up Visit are combined, all individual study assessments for both visits will need to be completed.
4. Efficacy Follow-Up: Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original tumor plan (ie, every 6 weeks [± 7 days] during the first 52 weeks and every 12 weeks [± 7 days] thereafter) until the patient experiences disease progression, withdraws consent, dies, or until the study terminates, whichever occurs first. The first tumor assessment will be performed 6 weeks (± 7 days) after the first administration of the study drugs.
5. Includes history of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Information on radiographic studies performed prior to study entry may be collected for review by the investigator.
6. Height assessment is only required for screening. Vital signs collected on study include temperature, pulse rate, respiratory rate, and blood pressure. The patient's vital signs are required to be recorded within 60 minutes before and 30 minutes after the first infusion of study drug(s) (LBL-007). For subsequent infusions (tislelizumab or tislelizumab and BGB-A425), vital signs will be collected within 60 minutes before infusion of each study drug and if clinically indicated, and 30 minutes after each study drug infusion. If several timepoints are overlapping, then only 1 timepoint is needed.
7. Refer to Section 7.5.2 for details regarding physical examination assessment requirements for screening and subsequent timepoints. Additionally, investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit. For any change in vision, referral to an appropriate specialist will be made for further management guidance.
8. The triplicate ECG recordings will be obtained during screening, the 30-day Safety Follow-up Visit, and as clinically indicated. Assessments that occur on the same day as study drug administration should occur approximately 30 minutes after study drug(s) infusion. Patients should be resting for at least 10 minutes in a semi-recumbent supine position prior to each ECG collection.
9. Eye examination, visual acuity test, and optical coherence tomography (OCT; or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of enrollment may be used rather than repeating tests. Eye examination, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed at the Screening Visit. Patients will undergo repeat assessments approximately every 15 weeks or 5 Cycles (± 7 days) thereafter.
10. The ophthalmologic assessments by an ophthalmologist including eye examination, visual acuity test, and OCT (or equivalent diagnostic test) should only be performed once at either the EOT or during the 30-day Safety Follow-up.
11. The AEs and laboratory abnormalities will be graded per NCI-CTCAE version 5.0. All AEs will also be evaluated for seriousness. After the Prescreening ICF has been signed, but prior to the administration of study drug, only SAEs should be reported. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study drugs or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of study drugs, regardless of whether or not the patient starts a new anticancer therapy. The investigator should report any SAEs that are assessed as related to study drug treatments, at any time after treatment discontinuation.
12. Review of AEs and concomitant medications/procedures may be conducted by telephone on Days 8 and 15 if patient is unable to come to the clinic.

13. Local laboratory assessments will be conducted for serum chemistry, hematology, coagulation and urinalysis as outlined in Appendix 2. Hematology and serum chemistry (data collected as specified in Appendix 2) will be performed at screening, and weekly for Cycle 1 and 2 followed by Day 1 of each subsequent cycle, EOT Visit, 30-day Safety Follow-up Visit, and when clinically indicated. After Cycle 1 Day 1, results are to be reviewed within 72 hours before study drug administration, where applicable. Coagulation assessment is required at screening, EOT Visit, and 30-day Safety Follow-up Visit as well as during the treatment period but only if clinically warranted. Urinalysis assessment is required at screening only and otherwise performed when clinically warranted. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities. If screening safety laboratory tests including chemistry, hematology, and coagulation are completed within 7 days prior to C1D1, then no additional blood will be collected for safety laboratory tests.
14. CK and CK-MB testing will be performed locally. The test will be evaluated at screening; weekly for the first 2 Cycles, followed by Day 1 of each cycle thereafter; EOT Visit; 30-day Safety Follow-up Visit, and when clinically indicated. Except for Cycle 1 Day 1, results are to be reviewed within 72 hours before study drug administration where applicable. If your laboratory does not perform CK-MB testing, serum troponins (troponin I and/or T) measurements should be performed instead; if only either troponin is assessed per local standards that same test should be evaluated throughout. If significant abnormalities are detected, please evaluate the affected patients for possible myocarditis/myositis per institutional guidelines, including additional serum CK/CK-MB, serum troponin levels, ECG, etc.
15. Urine pregnancy test (local laboratory) (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to enrollment. A negative pregnancy test (by urine or blood) must be completed and recorded on the same day before the administration of study drug at each cycle. An additional pregnancy test must be performed for women of childbearing potential at approximately 120 days after the last dose of study treatment. A serum pregnancy test (local laboratory) must be performed if the urine pregnancy test is positive or equivocal.
16. Analysis of FT3, FT4, and TSH will be performed locally. Thyroid function tests will be performed at screening and every 3 cycles (ie, Day 1 of Cycles 3, 6, 9, etc.), and at the Safety Follow-up Visit. Results are to be reviewed within 72 hours before study drug administration, where applicable.
17. Cortisol blood test will be performed at screening and every 3 cycles (ie, Day 1 of Cycles 3, 6, 9, etc), and at the Safety Follow-up Visit according to local guidelines.
18. HBV/HCV testing will be performed locally at screening and the 30-day Safety Follow-up Visit (only if positive at screening) and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody, hepatitis B core antibody, and HCV antibody). In case of positive HBsAg or positive HCV antibody results, these tests will be followed by viral load assessment (HBV DNA and HCV RNA). Viral load assessment (HBV DNA and HCV RNA) may be performed at the same time as HBV/HCV serology at investigator's discretion in line with the clinical history of the patient. Patients who have detectable HBV DNA at screening but remain eligible for enrollment will have their respective viral load tested every 4 cycles. Testing should also be performed as needed for any patient during treatment where clinically indicated.
19. Patients who are suspected or known to have serious/severe respiratory conditions, exhibit significant respiratory symptoms unrelated to the underlying cancer, or patients with NSCLC enrolled in Phase 2 will have pulmonary function testing which may include, but is not limited to, spirometry and assessment of diffusion capacity done during the Screening Period to assist the determination of suitability on the study. Pulmonary function testing may also be required during treatment if clinically indicated.
20. Blood biomarkers: Refer to Appendix 11.
21. Radiological images captured as standard of care prior to obtaining written informed consent and within 56 days of enrollment may be used rather than repeating tests. All measurable and evaluable lesions are required to be assessed and documented at the Screening Visit. The required radiographic procedure for Phase 2 (safety lead-in and dose expansion) during the screening and the treatment is detailed in Section 7.6. The investigator must review radiograph results before dosing at the next cycle. Patients will undergo tumor assessments approximately every 6 weeks (± 7 days) from the first administration of the study drugs during the first 52 weeks and every 12 weeks (± 7 days) thereafter. The investigator may perform additional scans or more frequent assessments if clinically indicated. Tumor response will be assessed per RECIST v1.1. Patients who continue the combination treatment as assigned beyond initial

radiographic disease progression per RECIST v1.1 must have a follow-up scan 4 to 12 weeks from the date of initial documentation of disease progression before discontinuing the assigned treatment (Section 7.6).

22. Archival or fresh tumor tissue: Refer to Appendix 1I.
23. BGB-A425 will be infused IV on Cycle 1 Day 1 and once every 21 days thereafter (see Section 5.3 for details) in Cohort B. Note: BGB-A425 must always be prepared and administered separately from any other systemic medication including tislelizumab and LBL-007. When BGB-A425 infusion coincides with tislelizumab, BGB-A425 infusion must always occur after infusion of tislelizumab has completed. When BGB-A425 infusion coincides with LBL-007, BGB-A425 infusion must always occur after infusion of LBL-007 has completed.
24. Tislelizumab will be infused IV on Cycle 1 Day 1 and once every 21 days thereafter (see Section 5.3 for details) in Cohort A and Cohort B. Note: Tislelizumab must always be prepared and administered separately from any other systemic medication including BGB-A425 and LBL-007. When tislelizumab infusion coincides with BGB-A425, BGB-A425 infusion must always occur after infusion of tislelizumab has completed. When tislelizumab infusion coincides with LBL-007, tislelizumab infusion must always occur after infusion of LBL-007 has completed.
25. LBL-007 will be infused IV on Cycle 1 Day 1 and once every 21 days thereafter (see Section 5.3 for details) in Cohort A and Cohort B. Note: LBL-007 must always be prepared and administered separately from any other systemic medication including BGB-A425 and tislelizumab. When LBL-007 infusion coincides with BGB-A425, BGB-A425 infusion must always occur after infusion of LBL-007 has completed. When LBL-007 infusion coincides with tislelizumab, tislelizumab infusion must always occur after infusion of LBL-007 has completed.

APPENDIX 1C. PHASE 2 DOSE EXPANSION SCHEDULE OF ASSESSMENTS

Phase 2 Dose Expansion Assessment	Prescreening[1]	Screening[1]	Treatment Cycles						Safety Follow-up[3]				Efficacy Follow-up[4]	Survival Follow-up[27]
			Cycle 1 (Every 21 Days)			Cycle 2	≥ Cycle 3 (Every 21 Days)	End of Treatment Visit[2]						
Visit Day	**-56 to ~ -28**	**-28 to ~ -1**	**1***	**8**	**15**	**1**	**1**	**0 to 7 Days**	**+30 Days**	**+60 Days**	**+90 Days**	**+120 Days [15]**		
Visit Window				**± 2**	**± 2**	**± 3**	**± 3**		**± 7**	**± 14**	**± 14**	**± 14**		
Prescreening informed consent	x													
Screening informed consent		x												
Inclusion/ exclusion criteria		x												
Demographics/ medical history/ prior medications[5]		x												
Height[6]		x												
Weight and vital signs[6]		x	x	x	x	x	x	x	x					
Physical examination[7]		x	x			x	x	x	x					
ECOG Performance Status		x	x			x	x	x	x					
12-lead triplicate ECG[8]		x	As clinically indicated						x					
Optical coherence tomography (or equivalent diagnostic test) and visual acuity tests[9]		x					C4 then every 15 weeks (± 7 days) or 5 cycles from C1D1	x[10]	x[10]					
Adverse events[11]	x	x	x	x[12]	x[12]	x	x	x	x	x	x			

Phase 2 Dose Expansion Assessment	Prescreening[1]	Screening[1]	Treatment Cycles						Safety Follow-up[3]				Efficacy Follow-up[4]	Survival Follow-up[27]
			Cycle 1 (Every 21 Days)			Cycle 2	≥ Cycle 3 (Every 21 Days)	End of Treatment Visit[2]						
Visit Day	**-56 to ~ -28**	**-28 to ~ -1**	**1***	**8**	**15**	**1**	**1**	**0 to 7 Days**	**+30 Days**	**+60 Days**	**+90 Days**	**+120 Days [15]**		
Visit Window				**± 2**	**± 2**	**± 3**	**± 3**		**± 7**	**± 14**	**± 14**	**± 14**		
Concomitant medications/ procedures		x	x	x[12]	x[12]	x	x	x	x	x	x			
Hematology[13]		x	x	x	x	x	x	x	x					
Serum chemistry[13]		x	x	x	x	x	x	x	x					
Coagulation parameters[13]		x	As clinically indicated					x	x					
Urinalysis[13]		x				As clinically indicated								
CK and CK-MB[14]		x	x	x	x	x	x	x	x					
Pregnancy test[15]		x	x			x	x	x	x	x	x	x		
Thyroid function[16]		x					C3 and every 3 cycles		x					
Cortisol testing [17]		x					C3 and every 3 cycles		x					
HBV/HCV tests[18]		x				Every 4 cycles starting at C5 in patients with detectable HBV DNA at screening or as clinically indicated in all patients			x					
Pulmonary function tests[19]		x	As clinically indicated											
Blood biomarkers[20]		x				Refer to Biomarker Table, Appendix 1J								
Tumor assessment[21]		x				In the first 52 weeks, every 6 weeks. Every 12 weeks thereafter[20]		x					x	

Phase 2 Dose Expansion Assessment	Prescreening[1]	Screening[1]	Treatment Cycles						Safety Follow-up[3]				Efficacy Follow-up[4]	Survival Follow-up[27]
			Cycle 1 (Every 21 Days)			Cycle 2	≥ Cycle 3 (Every 21 Days)	End of Treatment Visit[2]						
Visit Day	**-56 to ~ -28**	**-28 to ~ -1**	**1***	**8**	**15**	**1**	**1**	**0 to 7 Days**	**+30 Days**	**+60 Days**	**+90 Days**	**+120 Days [15]**		
Visit Window				**± 2**	**± 2**	**± 3**	**± 3**		**± 7**	**± 14**	**± 14**	**± 14**		
Archival or fresh tumor tissue[22]	x	x					Refer to Biomarker Table, Appendix 1J							
PD-L1 test[23]	x													
BGB-A425 administration[24]			x			x	x							
Tislelizumab administration[25]			x			x	x							
LBL-007 administration[26]			x			x	x							
Survival status														x

Abbreviations: AE, adverse event; C, cycle; D, day; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; FFPE, formalin-fixed paraffin embedded; FT3, free triiodothyronine; FT4, free thyroxine; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; ICF, informed consent form; imAE, immune-mediated AE; IV, intravenous; MRI, magnetic resonance imaging; ^{18}F-NaF PET, 18F-sodium fluoride position emission tomography; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; OCT, optical coherence tomography; PD, pharmacodynamic; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein-ligand 1; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; RNA, ribonucleic acid; SAE, serious adverse event; TSH, thyroid stimulating hormone; wks, weeks; v, version.

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

*If needed, some safety laboratory procedures including chemistry, hematology, coagulation, ECOG, and physical examination for C1D1 and C2D1 can be done 1-2 days before dosing.

1. In Phase 2 (dose expansion only), the Prescreening Period is 56 days before the first dose of study drug(s). A longer Prescreening Period may be granted on a case-by-case basis following discussion and written approval from the sponsor. The purpose of the Prescreening Period is to allow time for confirmation of the PD-L1 test for HNSCC and NSCLC patients only. A Prescreening ICF is required for HNSCC and NSCLC patients in Phase 2 (dose expansion only). RCC patients are not required to sign a Prescreening ICF. Patients with HNSCC and NSCLC who sign the Prescreening ICF and are confirmed PD-L1 positive may be allowed into the Screening Period. All RCC patients are allowed into screening.
   The Screening ICF is then required prior to performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to enrollment may be used for Prescreening or Screening assessments rather than repeating such tests unless otherwise noted (eg, hematology, serum chemistry, etc.). The ICF signature defines the start of the Prescreening and Screening Period. Refer to Section 7.1 and Section 7.2 for more information on the Prescreening and Screening Visits.

2. The EOT Visit is conducted when the investigator determines that any of the study drugs (ie, LBL-007, BGB-A425, and tislelizumab) will no longer be used. If specified laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT Visit, tests need not be repeated. Tumor assessment is not required at the EOT Visit provided that fewer than 6 weeks have passed since the last assessment.
3. The Safety Follow-up Visit is required to be conducted 30 days (± 7 days) after the last dose of any of the study drugs (ie, LBL-007, BGB-A425, and tislelizumab), or before the initiation of a new anticancer treatment, whichever occurs first. In addition, telephone contacts and/or clinic visits with patients must be conducted to assess imAEs (serious and nonserious), anticancer therapy, and concomitant medications/procedures where appropriate (ie, associated with an imAE etc) at 60 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. The EOT Visit may also be used as the Safety Follow-up Visit, provided that it occurred 30 days (± 7 days) after the last study treatment. If the EOT Visit and Safety Follow-up Visit are combined, all individual study assessments for both visits will need to be completed.
4. Efficacy Follow-Up: Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original tumor plan (ie, every 6 weeks (± 7 days) during the first 52 weeks and every 12 weeks (± 7 days) thereafter) until the patient experiences disease progression, withdraws consent, dies, or until the study terminates, whichever occurs first. The first tumor assessment will be performed 6 weeks (± 7 days) after the first administration of the study drugs.
5. Includes history of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Information on radiographic studies performed prior to study entry may be collected for review by the investigator.
6. Height assessment is only required for screening. Vital signs collected on study include temperature, pulse rate, respiratory rate, and blood pressure. For Cohorts 1 to 3, the patient's vital signs are required to be recorded within 60 minutes before and 30 minutes after the first infusion of study drug(s) (tislelizumab). For subsequent infusions of BGB-A425, vital signs will be collected within 60 minutes before infusion of each study drug and if clinically indicated, and 30 minutes after each study drug infusion. For Cohorts 4-7, the patient's vital signs are required to be recorded within 60 minutes before and 30 minutes after the first infusion of study drug(s) (LBL-007). For subsequent infusions (tislelizumab or tislelizumab and BGB-A425), vital signs will be collected within 60 minutes before infusion of each study drug and if clinically indicated, and 30 minutes after each study drug infusion. If several timepoints are overlapping, then only 1 timepoint is needed.
7. Refer to Section 7.5.2 for details regarding physical examination assessment requirements for screening and subsequent timepoints. Additionally, investigators should solicit patients for information regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit. For any change in vision, referral to an appropriate specialist will be made for further management guidance.
8. The triplicate ECG recordings will be obtained during screening, the 30-day Safety Follow-up Visit, and as clinically indicated. Assessments that occur on the same day as study drug administration should occur approximately 30 minutes following study drug(s) infusion. Patients should be resting for at least 10 minutes in a semirecumbent supine position prior to each ECG collection.
9. Eye examination, visual acuity test, and optical coherence tomography (OCT; or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of enrollment may be used rather than repeating tests. Eye examination, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed at the Screening Visit. Patients will undergo repeat assessments approximately every 15 weeks or 5 Cycles (± 7 days) thereafter.
10. The ophthalmologic assessments by an ophthalmologist including eye examination, visual acuity test, and OCT (or equivalent diagnostic test) should only be performed once at either the EOT or during the 30-day Safety Follow-up.
11. The AEs and laboratory abnormalities will be graded per NCI-CTCAE Version 5.0. All AEs will also be evaluated for seriousness. After the Prescreening ICF has been signed, but prior to the administration of study drug, only SAEs should be reported. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study drugs or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of study drugs, regardless of whether or not the patient starts a new anticancer therapy. The investigator should report any SAEs that are assessed as related to study drug treatments, at any time after treatment discontinuation.

12. Review of AEs and concomitant medications/procedures may be conducted by telephone on Days 8 and 15 if patient is unable to make it to the clinic.
13. Local laboratory assessments will be conducted for serum chemistry, hematology, coagulation and urinalysis as outlined in Appendix 2. Hematology and serum chemistry (data collected as specified in Appendix 2) will be performed at screening, and weekly for Cycle 1 and 2 followed by Day 1 of each subsequent cycle, EOT Visit, 30-day Safety Follow-up Visit, and when clinically indicated. After Cycle 1 Day 1, results are to be reviewed within 72 hours before study drug administration, where applicable. Coagulation assessment is required at screening, EOT Visit, and 30-day Safety Follow-up Visit as well as during the treatment period but only if clinically warranted. Urinalysis assessment required at screening only and otherwise performed when clinically warranted. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities. If screening safety laboratory tests including chemistry, hematology, and coagulation are completed within 7 days prior to C1D1, then no additional blood will be collected for safety laboratory tests.
14. CK and CK-MB will be performed locally. The test will be evaluated at screening; weekly for the first 2 Cycles, followed by Day 1 of each cycle thereafter; EOT Visit; 30-day Safety Follow-up Visit, and when clinically indicated. Except for Cycle 1 Day 1, results are to be reviewed within 72 hours before study drug administration where applicable. If your laboratory does not perform CK-MB testing, serum troponins (troponin I and/or T) measurements should be performed instead; if only either troponin is assessed per local standards that same test should be evaluated throughout. If significant abnormalities are detected, please evaluate the affected patients for possible myocarditis/myositis per institutional guidelines, including additional serum CK/CK-MB, serum troponin levels, ECG, etc.
15. Urine pregnancy test (local laboratory) (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to enrollment. A negative pregnancy test (by urine or blood) must be completed and recorded on the same day before the administration of study drug at each cycle. An additional pregnancy test must be performed for women of childbearing potential at approximately 120 days after the last dose of study treatment. A serum pregnancy test (local laboratory) must be performed if the urine pregnancy test is positive or equivocal.
16. Analysis of FT3, FT4, and TSH will be performed locally. Thyroid function tests will be performed at screening and every 3 cycles (ie, Day 1 of Cycles 3, 6, 9, etc), and at the Safety Follow-up Visit. Results are to be reviewed within 72 hours before study drug administration, where applicable.
17. Cortisol blood test will be performed at screening and every 3 cycles (ie, Day 1 of Cycles 3, 6, 9, etc), and at the Safety Follow-up Visit according to local guidelines.
18. HBV/HCV testing will be performed locally at screening and the 30-day Safety Follow-up Visit (only if positive at screening) and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody, hepatitis B core antibody, and HCV antibody). In case of positive HBsAg or positive HCV antibody results, these tests will be followed by viral load assessment (HBV DNA and HCV RNA). Viral load assessment (HBV DNA and HCV RNA) may be performed at the same time as HBV/HCV serology at investigator's discretion in line with the clinical history of the patient. Patients who have detectable HBV DNA at screening but remain eligible for enrollment will have their respective viral load tested every 4 cycles. Testing should also be performed as needed for any patient during treatment where clinically indicated.
19. Patients who are suspected or known to have serious/severe respiratory conditions, exhibit significant respiratory symptoms unrelated to the underlying cancer, or patients with NSCLC enrolled in Phase 2 will have pulmonary function testing which may include, but is not limited to, spirometry and assessment of diffusion capacity done during the Screening Period to assist the determination of suitability on the study. Pulmonary function testing may also be required during treatment if clinically indicated.
20. Blood biomarkers: Refer to Appendix 1J.
21. Radiological images captured as standard of care prior to obtaining written informed consent and within 56 days of enrollment may be used rather than repeating tests. All measurable and evaluable lesions are required to be assessed and documented at the Screening Visit. The required radiographic procedure for Phase 2 (safety lead-in and dose expansion) during the screening and the treatment is detailed in Section 7.6. The investigator must review radiograph results before dosing at the next cycle, and provide measurements and response assessment based on RECIST v1.1 criteria, before the next cycle. Patients will undergo tumor assessments approximately every 6 weeks (± 7 days) from the first administration of the study drugs during the first

52 weeks and every 12 weeks (± 7 days) thereafter (the date of each further scan is based on the actual date of the last scan). The investigator may perform additional scans or more frequent assessments if clinically indicated. Tumor response will be assessed per RECIST v1.1. Patients who continue the combination treatment as assigned beyond initial radiographic disease progression per RECIST v1.1 must have a follow-up scan 4 to 12 weeks from the date of initial documentation of disease progression before discontinuing the assigned treatment. For patients with confirmed PD, they can continue the treatment as assigned, under the conditions outlined in Section 7.6.

22. Archival or fresh tumor tissue: Refer to Appendix 1J.
23. During the prescreening period, HNSCC and NSCLC patients will undergo PD-L1 positivity confirmation with either central analysis or local documented results. If a central analysis is used, PD-L1 CPS ≥ 1 or TPS ≥ 1% by IHC 22C3 pharmDx assay is acceptable for HNSCC and NSCLC patients, respectively. If local testing is used, PD-L1 (CPS ≥ 1) by IHC 22C3 pharmDx assay (preferred) or PD-L1 (CPS ≥ 1, vCPS or TAP ≥ 1%) by VENTANA PD-L1 (SP263) are acceptable for HNSCC patients (Note: PD-L1 positivity determined by PD-L1 IHC 22C3 pharmDx assay will be used for HNSCC patients in the EU); PD-L1 (TPS or TC ≥ 1%) by IHC 22C3 or 28-8 pharmDx or VENTANA PD-L1 (SP263) assay are acceptable for NSCLC patients (Note: If PD-L1 IHC 28-8 assay is to be used for determining PD-L1 positivity, it will be used for nonsquamous NSCLC patients only in the EU). This requires tissue samples obtained recently within 2 years. For patients who have known PD-L1 positivity, a historically documented result is acceptable for PD-L1 positivity confirmation by specified PD-L1 assay at the prescreening phase. Tissue obtained within 2 years or fresh biopsy is required prior to the patient commencing first drug administration on C1D1. It is highly recommended to provide the same tissue that was tested for the local PD-L1 assay. If a patient has more than 1 archival tumor tissue, the most recent one is preferred. Positivity confirmation of the PD-L1 test must be obtained before HNSCC and NSCLC patients are allowed to continue to screening. The PD-L1 test is not required for RCC patients as part of prescreening or screening. The PD-L1 status of all cohorts will also be retrospectively evaluated by VENTANA PD-L1 (SP263) assay.
24. BGB-A425 will be infused IV on Cycle 1 Day 1 and once every 21 days thereafter (see Section 5.3 for details) in Cohorts 1 to 5. Note: BGB-A425 must always be prepared and administered separately from any other systemic medication including tislelizumab and LBL-007. When BGB-A425 infusion coincides with tislelizumab, BGB-A425 infusion must always occur after infusion of tislelizumab has completed. When BGB-A425 infusion coincides with LBL-007, BGB-A425 infusion must always occur after infusion of LBL-007 has completed.
25. Tislelizumab will be infused IV on Cycle 1 Day 1 and once every 21 days thereafter (see Section 5.3 for details) in Cohorts 1 to 7. Note: Tislelizumab must always be prepared and administered separately from any other systemic medication including BGB-A425 and LBL-007. When tislelizumab infusion coincides with BGB-A425, BGB-A425 infusion must always occur after infusion of tislelizumab has completed. When tislelizumab infusion coincides with LBL-007, tislelizumab infusion must always occur after infusion of LBL-007 has completed.
26. LBL-007 will be infused IV on Cycle 1 Day 1 and once every 21 days thereafter (see Section 5.3 for details) in Cohorts 4 to 7. Note: LBL-007 must always be prepared and administered separately from any other systemic medication including BGB-A425 and tislelizumab. When LBL-007 infusion coincides with BGB-A425, BGB-A425 infusion must always occur after infusion of LBL-007 has completed. When LBL-007 infusion coincides with tislelizumab, tislelizumab infusion must always occur after infusion of LBL-007 has completed.
27. Survival Follow-up: Patients will be followed for survival and further anticancer therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits, including follow up of any ongoing AE, approximately every 3 months (every 90 days ± 14 days) after the 90 days Safety Follow-up phone call and/or clinic visit (at the expected date), or after the 120 days Safety Follow-up Visit for women of childbearing potential, or as directed by the sponsor until death, withdrawal of consent, loss to follow-up, or end of study.

APPENDIX 1D. PHASE 1 AND PHASE 2 SAFETY LEAD-IN PHARMACOKINETIC AND IMMUNOGENICITY SAMPLING SCHEDULE WITH SERIAL SAMPLE COLLECTION

This appendix applies to serial PK and immunogenicity sampling for: 1) BGB-A425 in patients in Phase 1 dose escalation; 2) LBL-007 in patients in Phase 2 safety lead-in.

	Cycle	PK Assessment (Planned CxDx)	ADA Assessment
Treatment Period	1	Predose EOI (Within 30-min after EOI) 6 hrs (± 2 hr) from SOI – C1D1 24 hrs (± 2 hr) from SOI – C1D2 72 hrs (± 2 hr) from SOI – C1D4 168 hrs (± 4 hr) from SOI – C1D8 336 hrs (± 4 hr) from SOI – C1D15 **504 hrs (± 4 hr) from SOI – C1D22	Predose
	2	Predose (-60 min to predose) EOI (Within 30-min after EOI)	Predose
	3	Predose	Predose
	5	Predose EOI (Within 30-min after EOI) 6 hrs (± 2 hr) from SOI – C5D1 24 hrs (± 2 hr) from SOI – C5D2 72 hrs (± 2 hr) from SOI – C5D4 168 hrs (± 4 hr) from SOI – C5D8 336 hrs (± 4 hr) from SOI – C5D15	Predose
	6	Predose – C6D1	Predose
	9	Predose – C9D1	Predose
	13	Predose – C13D1	Predose
	17	Predose – C17D1	Predose
	25*	Predose – C25D1	Predose
Safety Follow-up	(30 days ± 7 days after last dose)		

* No PK/ADA samples need to be collected after the completion of cycle 25, except at the safety follow-up.
** PK assessment at 504 hrs only applies to BGB-A425 not for LBL-007.
Abbreviations: ADA, antidrug antibody; CxDx, Cycle x and Day x; EOI, end of infusion; PK, pharmacokinetic; SOI, start of infusion

Note: Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK and ADA should be from a different site. Window: ± 30 minutes for EOI and ± 60 minutes for all other timepoints unless otherwise specified.

APPENDIX 1E. PHASE 1 AND PHASE 2 SAFETY LEAD-IN PHARMACOKINETIC AND IMMUNOGENICITY SAMPLING WITH SPARSE PK SAMPLE COLLECTION

This appendix applies to sparse PK and immunogenicity sampling for: 1) BGB-A425 in patients in Phase 2 safety lead-in; 2) Tislelizumab in patients in Phase 1 dose escalation and Phase 2 safety lead-in

	Cycle	PK Assessment	ADA Assessment
Treatment Period	1*	Predose EOI (Within 30-min after EOI)	Predose
	2	Predose	Predose
	3	Predose	Predose
	5	Predose EOI (Within 30-min after EOI)	Predose
	6	Predose	Predose
	9	Predose	Predose
	13	Predose	Predose
	17	Predose	Predose
	25**	Predose	Predose
Safety Follow-up	(30 days ± 7 days after last dose)		

* The Cycle 1 Day 8 (+2 days) sample collection must only occur on the day that tislelizumab is given. If Cycle 1 Day 8 (+2 days) tislelizumab administration is not given, samples should not be collected at this timepoint. Please refer to the laboratory manual for additional details.

** No PK/ADA samples need to be collected after the completion of cycle 25, except at the safety follow-up.

Abbreviations: ADA, antidrug antibody; EOI, end of infusion; PK, pharmacokinetic

Note: Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK and ADA should be from a different site. Window: ± 30 minutes for EOI and ± 60 minutes for all other timepoints

APPENDIX 1F. PHASE 2 DOSE EXPANSION PHARMACOKINETIC AND IMMUNOGENICITY SAMPLING FOR BGB-A425, LBL-007, AND TISLELIZUMAB IN PATIENTS WITH SPARSE SAMPLE COLLECTION

This appendix applies to sparse PK and immunogenicity sampling for: 1) BGB-A425 in patients in Phase 2 dose expansion; 2) LBL-007 in patients in Phase 2 dose expansion; 3) Tislelizumab in patients in Phase 2 dose expansion.

	Cycle	PK Assessment*	ADA Assessment
Treatment Period	1	Predose[#] EOI (Within 30-min after EOI)	Predose
	2	Predose	Predose
	5	Predose EOI (Within 30-min after EOI)	Predose
	6	Predose	Predose
	9	Predose	Predose
	13	Predose	Predose
	17	Predose	Predose
	25*	Predose	Predose
Safety Follow-up	(30 days ± 7 days after last dose)		

***** No PK/ADA samples need to be collected after completion of cycle 25, except at the safety follow-up.
[#] "Predose" in this table refers to a timeframe before the administration of the first study drug in the combination treatments.
Abbreviations: ADA, antidrug antibody; EOI, end of infusion; PK, pharmacokinetic
Note: Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK and ADA should be from a different site. For the patients with poor venous access, blood collection from a vein in the leg or foot will be suggested.
Window: ± 30 minutes for EOI and ± 60 minutes for all other timepoints.

APPENDIX 1G. PHASE 2 DOSE EXPANSION PHARMACOKINETIC AND IMMUNOGENICITY SAMPLING FOR BGB-A425 IN PATIENTS WITH SERIAL SAMPLE COLLECTION

This appendix applies to PK and immunogenicity sampling for BGB-A425 only in Cohorts 1, 2, 3 of Phase 2 dose expansion in approximately 15 patients enrolled, with 10 patients from South Korea and 5 patients from Australia. These patients will also be collected for sparse immunogenetic samples for tislelizumab (as described in Appendix 1F).

	Cycle	PK Assessment (Planned CxDx)	ADA Assessment**
Treatment Period	1	Predose[#] EOI (Within 30-min after EOI) 6 hrs (± 2 hr) from SOI – C1D1 24 hrs (± 2 hr) from SOI – C1D2 72 hrs (± 2 hr) from SOI – C1D4 168 hrs (± 4 hr) from SOI – C1D8 336 hrs (± 4 hr) from SOI – C1D15	Predose
	2	Predose End of infusion (Within 30-min after EOI)	Predose
	5	Predose EOI (Within 30-min after EOI) 6 hrs (± 2 hr) from SOI – C5D1 24 hrs (± 2 hr) from SOI – C5D2 72 hrs (± 2 hr) from SOI – C5D4 168 hrs (± 4 hr) from SOI – C5D8 336 hrs (± 4 hr) from SOI – C5D15	Predose
	6	Predose – C6D1	Predose
	9	Predose – C9D1	Predose
	13	Predose – C13D1	Predose
	17	Predose – C17D1	Predose
	25*	Predose – C25D1	Predose
Safety Follow-up	(30 days ± 7 days after last dose)		

* No PK/ADA samples need to be collected after the completion of cycle 25, except at the safety follow-up.
[#] "Predose" in this table refers to a timeframe before the administration of the first study drug in the combination treatments.
Abbreviations: ADA, antidrug antibody; CxDx, Cycle x and Day x; EOI, end of infusion; PK, pharmacokinetic; SOI, start of infusion
Note: Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK and ADA should be from a different site. For the patients with poor venous access, blood collection from a vein in the leg or foot will be suggested.
Window: ± 30 minutes for EOI and as noted for all other timepoints

APPENDIX 1H. PHASE 1 BLOOD AND TUMOR TISSUE BIOMARKER ANALYSIS

Biomarker assessment	Screening	Treatment period									
		Cycle 1[1]				Cycle 2	Cycle 3	Cycle 4	Cycle 5	Patients with confirmed PR or CR	EOT Visit
Visit Day	-28 to ~ -1	1	2	8	15	1	1	1	1		0 to 7 days
Immunophenotyping[2]	X	X		X	X	X	X				
Cytokine or soluble proteins in blood[3]		X	X (24 hr±2 hrs post BGB-A425 infusion)	X	X	X	X	X		X	X
PBMC[3]		X	X (24 hr±2 hrs post BGB-A425 infusion)	X	X	X	X	X		X	X
Archival or fresh tumor tissue[4]	X						X				X
BGB-A425/TIM-3 receptor occupancy[5]		X (Predose AND 6 hr ±2 hrs post BGB-A425 infusion)	X (24 hr±2 hrs post BGB-A425 infusion)	X (On the day of visit if tislelizumab not given OR 6 hr ±2 hrs post tislelizumab)	X	X	X		X		
Tislelizumab/PD-1 receptor occupancy[6]		X		X (On the day of visit if tislelizumab not given OR 6 hr±2hrs post tislelizumab)	X	X	X		X		

Abbreviations: CR, complete response; EOT, end of treatment; FFPE, formalin fixed paraffin embedded; hrs, hours; PBMC, peripheral blood mononuclear cells; PR, partial response

1. From the protocol, patients may or may not receive tislelizumab on Cycle 1 Day 8. If a patient receives tislelizumab on Cycle 1 Day 8, then the PD-1 and TIM-3 receptor occupancy sample will be collected 6 hours (±2 hours) post tislelizumab infusion while the other blood samples for biomarker analysis (immunophenotyping, cytokines and soluble protein, PBMC) will be collected before tislelizumab infusion on the same day. If tislelizumab is not given on Cycle 1 Day 8, receptor occupancy samples will be collected together with the blood-based biomarker samples.
2. Blood samples for immunophenotyping will be collected at screening, Cycle 1 Day 1 (predose), Cycle 1 Day 8*, Cycle 1 Day 15, Cycle 2 Day 1 (predose), and Cycle 3 Day 1 (predose). *If tislelizumab is given on Cycle 1 Day 8, the sample should be collected before tislelizumab infusion (see footnote 1). Please refer to the laboratory manual for additional detailed information.
3. Blood samples for cytokine and PBMC analysis will be collected on Cycle 1 Day 1 (predose), Cycle 1 Day 2 (24 hours ± 2 hours post BGB-A425 infusion), Cycle 1 Day 8*, Cycle 1 Day 15, Cycle 2 Day 1 (predose), Cycle 3 Day 1 (predose), Cycle 4 Day 1 (predose), before the next study treatment following confirmation of PR or CR, and End of Treatment Visit for patients who have confirmed when disease progression. *If tislelizumab is given on Cycle 1 Day 8, the sample should be collected before tislelizumab infusion (see footnote 1). Please refer to the laboratory manual for additional detailed information.

4. Archival or fresh tumor tissue: Patients will provide archival tumor tissues (FFPE blocks or approximately 15 freshly cut unstained slides) for biomarker analysis if available. If archival tissue is not available, fresh tumor biopsy is strongly encouraged but not mandatory. An optional biopsy after 2 cycles of treatment (approximately Cycle 3 Day 1) is also strongly encouraged and an optional biopsy is also recommended from patients who have confirmed disease progression. If feasible, post treatment biopsy should be ideally taken from the same tumor lesion as the baseline biopsy/archival tumor tissues. Written patient consent is required for any fresh tumor biopsies.
5. BGB-A425/TIM-3 receptor occupancy assay: Blood will be collected Cycle 1 Day 1 predose and 6 hours (± 2 hours) post BGB-A425 infusion, Cycle 1 Day 2 (24 hours ± 2 hours post BGB-A425 infusion), Cycle 1 Day 8*, Cycle 1 Day 15, Cycle 2 Day 1 (predose), Cycle 3 Day 1 (predose), and Cycle 5 Day 1 (predose). *If tislelizumab is given to the patient on Cycle 1 Day 8, samples should be collected 6 hours (±2 hours) post tislelizumab infusion (see footnote 1). Please refer to laboratory manual for additional details.
6. Tislelizumab/PD-1 receptor occupancy assay: Blood will be collected on Cycle 1 Day 1 (predose), Cycle 1 Day 8*, Cycle 1 Day 15, Cycle 2 Day 1 (predose), Cycle 3 Day 1 (predose), and Cycle 5 Day 1 (predose). *If tislelizumab is given on Cycle 1 Day 8, the sample should be collected at 6 hours (±2 hours) post tislelizumab infusion (see footnote 1). Please refer to laboratory manual for additional details.

APPENDIX 1I. PHASE 2 (SAFETY LEAD-IN) BLOOD AND TUMOR TISSUE BIOMARKER ANALYSIS

Biomarker assessment	Screening	Treatment period								
		Cycle 1				Cycle 2	Cycle 3	Cycle 5	Patients with confirmed PR or CR	EOT Visit
Visit Day	-28 to ~ -1	1	2	8	15	1	1	1		0 to 7 days
LBL-007/LAG-3 receptor occupancy[1]		X (Predose AND 6 hr ±2 hrs post LBL-007 infusion)	X (24 hr±2 hrs post LBL-007 infusion)	X	X	X (Predose)	X (Predose)	X (Predose)		
Cytokine or soluble proteins in blood[2]		X (Predose)	X (24 hr±2 hrs post LBL-007 infusion)	X	X	X (Predose)	X (Predose)			
Immunophenotyping[3]		X (Predose)	X (24 hr±2 hrs post LBL-007 infusion)	X	X	X (Predose)	X (Predose)			
ctDNA analysis[4]		X (Predose)							X	X
Archival or fresh tumor tissue[5]	X						X			X

Abbreviations: CR, complete response; ctDNA, circulating tumor DNA; EOT, end of treatment; FFPE, formalin fixed paraffin embedded; hrs, hours; PBMC, peripheral blood mononuclear cells; PR, partial response

1. LBL-007/LAG-3 receptor occupancy assay: Blood will be collected Cycle 1 Day 1 predose and 6 hours (± 2 hours) post LBL-007 infusion, Cycle 1 Day 2 (24 hours ± 2 hours post LBL-007 infusion), Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1 (predose), Cycle 3 Day 1 (predose), and Cycle 5 Day 1 (predose). Please refer to laboratory manual for additional details.
2. Blood samples for cytokine or soluble protein analysis will be collected on Cycle 1 Day 1 (predose), Cycle 1 Day 2 (24 hours ± 2 hours post LBL-007 infusion), Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1 (predose), Cycle 3 Day 1 (predose). Please refer to the laboratory manual for additional detailed information.
3. Blood samples for immunophenotyping analysis will be collected on Cycle 1 Day 1 (predose), Cycle 1 Day 2 (24 hours ± 2 hours post LBL-007 infusion), Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1 (predose), Cycle 3 Day 1 (predose). Please refer to the laboratory manual for additional detailed information.
4. Blood samples for ctDNA analysis will be collected at Cycle 1 Day 1 (predose), before the next study treatment after confirmation of PR or CR (for patients achieving confirmed PR or CR only), and End of Treatment Visit for patients who have confirmed disease progression. Please refer to the laboratory manual for additional detailed information.
5. Archival or fresh tumor tissue: Patients will provide archival tumor tissues (FFPE blocks or approximately 15 freshly cut unstained slides) for biomarker analysis if available. If archival tissue is not available, fresh tumor biopsy is strongly encouraged but not mandatory. An optional biopsy after 2 cycles of treatment (approximately Cycle 3 Day 1) is also strongly encouraged and an optional biopsy is also recommended from patients who have confirmed disease progression. If feasible, post treatment biopsy should be ideally taken from the same tumor lesion as the baseline biopsy/archival tumor tissues. Written patient consent is required for any fresh tumor biopsies.

APPENDIX 1J. PHASE 2 (DOSE EXPANSION) BLOOD AND TISSUE BIOMARKER ANALYSIS

Biomarker assessment	Prescreening	Screening	Treatment period						
			Cycle 1			Cycle 2	Cycle 3	Patients with confirmed PR or CR	End of Treatment Visit
Visit Day	**-56 to ~ -28**	**-28 to ~ -1**	**1**	**2**	**8**	**1**	**1**		**0 to 7 Days**
LBL-007/LAG-3 receptor occupancy[1]			X (Predose)		X	X (Predose)	X (Predose)		
Cytokine or soluble proteins in blood[2]			X (Predose)	X	X	X (Predose)	X (Predose)		
ctDNA[3]			X (Predose)					X	X
Archival or fresh tumor tissue[4]	X	X					X		X
PD-L1 test[5]	X								

Abbreviations: CR, complete response; ctDNA, circulating tumor DNA; FFPE, formalin fixed paraffin embedded; hrs, hours; PD-L1, programmed cell death protein-ligand 1; PR, partial response.

1. LBL-007/LAG-3 receptor occupancy assay: Blood will be collected Cycle 1 Day 1 (predose), Cycle 1 Day 8, Cycle 2 Day 1 (predose), and Cycle 3 Day 1 (predose). Blood samples for LBL-007/LAG-3 RO assay will be collected only for Cohort 4 to Cohort 7 in expansion phase, approximately 5 patients (in APAC region only) in each cohort. More patients might be added for RO sample collection in case there are missing samples or incorrect collection. Please refer to laboratory manual for additional details.
2. Blood samples for cytokine or soluble protein analysis will be collected on Cycle 1 Day 1 (predose), Cycle 1 Day 2*, Cycle 1 Day 8*, Cycle 2 Day 1 (predose), Cycle 3 Day 1 (predose). Cytokine or soluble proteins analysis is including but not limited to soluble TIM-3, and soluble LAG-3. *Blood samples on Cycle 1 Day 2 will be collected only for Cohort 1 to Cohort 3; blood samples for Cycle 1 Day 2 will be collected for patients who have serial PK visits; blood samples on Cycle 1 Day 8 will be collected only for Cohort 4 to Cohort 7. Please refer to the laboratory manual for additional detailed information.
3. Blood samples for ctDNA analysis will be collected at Cycle 1 Day 1 (predose), before the next study treatment after confirmation of PR or CR (for patients achieving confirmed PR or CR only), and End of Treatment Visit for patients who have confirmed disease progression. Please refer to the laboratory manual for additional detailed information.
4. Archival or fresh tumor tissue: During the prescreening period, HNSCC and NSCLC patients will undergo PD-L1 positivity confirmation with either local documented results or central testing. This includes archival tissue samples obtained within 2 years. For patients who have known PD-L1 positivity, a historically documented result is acceptable for PD-L1 positivity confirmation by specified PD-L1 assay at prescreening phase. Tissue samples obtained within 2 years or fresh biopsy is required prior to the patient commencing first drug administration on C1D1. It is highly recommended to provide the same tissue that was tested for the local PD-L1 assay. If a patient has more than 1 archival tumor tissue, the most recent one is preferred. Patients in all cohorts must provide archival tumor tissue obtained within 2 years or fresh tumor tissues (FFPE blocks or approximately 15 freshly cut unstained slides). If recently obtained tumor tissue is insufficient, a fresh tumor biopsy is mandatory. If qualified tumor tissues were received in the prescreening period then a repeat tumor biopsy does not need to be done. Optional biopsy after 2 cycles of treatment (approximately Cycle 3 Day 1) and at EOT from patients who have

confirmed disease progression is also strongly encouraged. If feasible, post treatment biopsy should be ideally taken from the same tumor lesion as the baseline biopsy/fresh tumor tissues. Written patient consent is required for any fresh tumor biopsies.

5. During the prescreening period, HNSCC and NSCLC patients will undergo PD-L1 positivity confirmation with either local documented results or central testing. If a central analysis is used, PD-L1 CPS ≥ 1 or TPS ≥ 1% by IHC 22C3 pharmDx assay is acceptable for HNSCC and NSCLC patients, respectively. If local testing is used, PD-L1 (CPS ≥ 1) by IHC 22C3 pharmDx assay (preferred) or PD-L1 (CPS ≥ 1, vCPS or TAP ≥ 1%) by VENTANA PD-L1 (SP263) are acceptable for HNSCC patients (Note: PD-L1 positivity determined by PD-L1 IHC 22C3 pharmDx assay will be used for HNSCC patients in the EU); PD-L1 (TPS or TC ≥ 1%) by IHC 22C3 or 28-8 pharmDx or VENTANA PD-L1 (SP263) assay are acceptable for NSCLC patients (Note: If PD-L1 IHC 28-8 assay is to be used for determining PD-L1 positivity, it will be used for nonsquamous NSCLC patients only in the EU). This requires tissue samples obtained recently within 2 years. For patients who have known PD-L1 positivity, a historically documented result is acceptable for PD-L1 positivity confirmation by local documented testing at the prescreening phase. If a patient has more than 1 archival tumor tissue, the most recent one is preferred. Tissue obtained within 2 years or fresh biopsy is required prior to the patient commencing first drug administration on C1D1. Positivity confirmation of the PD-L1 test must be obtained before HNSCC and NSCLC patients are allowed to continue to screening. The PD-L1 test is not required for RCC patients as part of prescreening or screening. The PD-L1 status of all cohorts will also be retrospectively evaluated by VENTANA PD-L1 (SP263) assay.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Clinical Chemistry	Hematology	Coagulation	Urinalysis
Alkaline phosphatase	Hematocrit	Prothrombin time	pH
Alanine aminotransferase	Hemoglobin	Partial thromboplastin time or activated partial thromboplastin time	Specific gravity
Aspartate aminotransferase	Platelet counts	International Normalized Ratio	Glucose
Albumin	WBC count		Protein
Total bilirubin	Neutrophil count		Ketones
Blood urea nitrogen or urea	Lymphocyte count		Blood
Potassium			24-hour protein[b]
Sodium			
Calcium			
Creatinine			
Glucose			
Lactate dehydrogenase			
Total protein			
Testosterone[a]			
Lipase			
Amylase			
Creatine Kinase (CK)			
CK-MB[c]			
Cortisol (blood test)[d]			

Abbreviations: CK-MB, creatine kinase cardiac isoenzyme; pH, negative of the logarithm to base 10 of the activity of the (solvated) hydronium ion; WBC, white blood cell

[a] Testosterone test is only applied for patients with mCRPC. However, the testosterone levels do not need to be checked if the patient has undergone surgical castration for > 4 months. Patients receiving chemical castration should have testosterone levels checked at baseline and confirmed to be in the castrate levels (< 0.5 ng/mL or 1.735 nM).

[b] On routine urinalysis, if urine protein is ≥ 2+ by dipstick, then obtain a 24 hour urine sample for total protein and a random urine sample for total protein and creatinine to determine a protein to creatinine ratio

[c] In the event that CK-MB fractionation is not available, please assess troponin I and/or troponin T instead. If only either troponin is assessed per local standards, that same should be evaluated throughout.

[d] Cortisol testing will be performed only for patients in Phase 2 (safety lead-in and dose expansion).

APPENDIX 3. ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-disease 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

As published by (Oken et al 1982). Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.

APPENDIX 4. PRE-EXISTING IMMUNE DEFICIENCIES ORAUTOIMMUNE DISEASES

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

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

Acute disseminated encephalomyelitis	Addison's 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's disease
Bullous pemphigoid	Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome	Crohn's disease
Dermatomyositis	Dysautonomia
Epidermolysis bullosa acquisita	Gestational pemphigoid
Giant cell arteritis	Goodpasture's syndrome
Granulomatosis with polyangiitis	Graves' disease
Guillain-Barré syndrome	Hashimoto's disease
Immunoglobulin A (IgA) neuropathy	Inflammatory bowel disease
Interstitial cystitis	Kawasaki's disease
Lambert-Eaton myasthenia syndrome	Lupus erythematosus
Lyme disease (chronic)	Mooren's ulcer
Morphea	Multiple sclerosis
Myasthenia gravis	Neuromyotonia
Opsoclonus myoclonus syndrome	Optic neuritis
Ord's thyroiditis	Pemphigus
Pernicious anemia	Polyarteritis nodusa
Polyarthritis	Polyglandular autoimmune syndrome
Primary biliary cirrhosis	Psoriasis
Reiter's syndrome	Rheumatoid arthritis
Sarcoidosis	Sjögren's syndrome
Stiff person syndrome	Takayasu's arteritis
Ulcerative colitis	Vogt-Kovangai-Harada disease

APPENDIX 5. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL", "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical studies include the use of highly effective forms of birth control (Clinical Trials Facilitation and Coordination 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, or 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 barrier method of contraception (eg, condoms with or without spermicide) as well.
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized male 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. See also the definition of sterile male below.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment).
  Note: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, or postovulation 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. If used, this method must be combined with another acceptable method listed above.

Patients using hormonal contraceptives (eg, birth control pills or devices) must use a barrier method of contraception (eg, condoms) as well.

Definition of "Sterile Man"

For the purposes of this study, a sterile man is one for whom azoospermia, in a semen sample, has been demonstrated as definitive evidence of infertility. Men with known "low sperm counts" (consistent with "sub-fertility") are not to be considered sterile for purposes of this study.

Definitions of "Women of Childbearing Potential," "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 a postmenopausal follicle-stimulating hormone 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 a follicle-stimulating hormone measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

Adapted from Clinical Trials Facilitation and Coordination Group 2020.

APPENDIX 6. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity (eg, no shortness of breath when walking, climbing stairs, et cetera).
II	Mild symptoms (eg, mild shortness of breath and/or angina). Slight limitations during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20 to 100 meters). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound.

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 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 7. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In adults, the most widely-used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the Modification of Diet in Renal Disease Study equation. National Kidney Disease Education Program calculators rely on creatinine determinations which are isotope dilution mass spectrometry traceable. All laboratories should be using creatinine methods calibrated to be isotope dilution mass spectrometry traceable.

The CKD-EPI equation calculator should be used when serum creatinine (S_{cr}) reported in mg/dL. This equation is recommended when estimated GFR values above 60 mL/min/1.73 m^2 are desired.

$$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

where:

S_{cr} is serum creatinine in mg/dL,

κ is 0.7 for female patients and 0.9 for male patients,

α is 0.329 for female patients and -0.411 for male patients,

min indicates the minimum of S_{cr}/κ or 1, and

max indicates the maximum of S_{cr}/κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m2 body surface area, which is an accepted average adult surface area.

The online calculator for CKD-EPI can be found here: https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/Pages/gfr-calculators.aspx

1. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

APPENDIX 8. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any imAE are intended as a 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.

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 drug(s) and the AE?
- How did the patient respond to withdrawal of study drug(s)?
- Did the event recur when study drug(s) 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 eCRF should be checked.

Recommended Diagnostic Tests in the Management of Possible Immune-mediated Adverse Events	
Immune-mediated Toxicity	**Diagnostic Evaluation Guideline**
Thyroid Disorders	Scheduled and repeat 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.
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 *D*LCO. 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.

Recommended Diagnostic Tests in the Management of Possible Immune-mediated Adverse Events	
Immune-mediated Toxicity	**Diagnostic Evaluation Guideline**
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, 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 ≥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 (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology 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 rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin I and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, troponin I, and refer to a cardiologist.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; 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.

Treatment 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, with patients is 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 medical monitor
- 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 medical monitor
- Steroid 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

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 to 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 to 1.6 µg/kg/day (for the elderly or those with co-morbidities, 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Hypophysitis	1-2 Mild symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5 to 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. Taper corticosteroids over at least 1 month.	Continue study treatment.
	3-4 Moderate-severe symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV 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 endocrinology advice. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade 2 or less. Discontinuation is usually not necessary.
Pneumonitis	1 Radiographic changes only	Monitor symptoms every 2 to 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.
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2 to 4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		(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.	
Neurological Toxicity	1 Mild symptoms	–	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5 to 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	Initiate treatment with oral prednisolone or IV 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 to 96 hours.	Discontinue study treatment.
Colitis/Diarrhea	1 Mild symptoms: < 3 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.
	2 Moderate symptoms: 4 to 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 steroids over 2 to 4 weeks, consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV 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. If no improvement in 72 hours or symptoms worsen, consider	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Life-threatening symptoms	infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA Grade 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 steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5 to 1 mg/kg/day for 3 days then taper over 2 to 4 weeks. For severe symptoms: IV methylprednisolone 0.5 to 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 IV 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 3X ULN	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		If LFTs are worsening, recheck every 48 to 72 hours until improvement is seen.	worsening until improvement is seen.
	2 ALT or AST 3 to 5X ULN	Recheck LFTs every 48 to 72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5 to 1 mg/kg/day for 3 days then taper over 2 to 4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2 to 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.
	3 ALT or AST 5 to 20X 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 IV (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.	Hold study treatment until improved to baseline Grade; reintroduce only after discussion with the study medical monitor.
	4 ALT or AST > 20X ULN	Initiate IV methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: ▪ If on oral prednisolone, change to pulsed IV methylprednisolone ▪ If on IV, add mycophenolate mofetil (MMF) 500 to 1000 mg twice a day ▪ If worsens on MMF, consider addition of tacrolimus ▪ Duration and dose of steroid required will depend on severity of event		
Nephritis	1 Creatinine 1.5X baseline or > ULN to 1.5X ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5X-3X baseline or > 1.5X-3X ULN	Ensure hydration and review creatinine in 48 to 72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade:

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		If attributed to study drug, initiate oral prednisolone 0.5 to 1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48 to 72 hours.	Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3X baseline or > 3X-6X 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 IV (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 > 6X ULN	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 to 250 mg/dL; 8.9 to 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 to 500 mg/dL; 13.9 to 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.	
Ocular Toxicity	1 Asymptomatic eye exam/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2	Refer patient to an ophthalmologist for assessment	Continue study treatment or hold

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	Anterior uveitis or mild symptoms	and topical corticosteroid treatment. Consider a course of oral steroids.	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 IV (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 IV (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.
	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 worsens, 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 to 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
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 IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improved 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 IV 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 steroids and treat as Grade 2	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 X ULN or worse initiate oral prednisolone 0.5 to 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 IV (methyl)prednisolone and1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks	Hold study treatment until improved to Grade 0-1. Discontinue if any evidence of myocardial involvement
Myocarditis	1 Asymptomatic but abnormal CK-MB, cardiac troponin I or intraventricular conduction delay	Admit to hospital and refer to a cardiologist. Transfer all patients with moderate/severe cardiac symptoms or any increase in cardiac serum markers to the coronary care unit. Initiate oral prednisolone or IV (methyl)prednisolone at 1-2	Hold study treatment until completely resolved or myocarditis has been ruled out.
	2 Symptoms on mild-moderate exertion		Discontinue study treatment unless cardiac involvement

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Severe symptoms with mild exertion	mg/kg/day. Manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1g/day and add MMF, infliximab or anti-thymocyte globulin	has been excluded and symptoms have completely resolved
	4 Life-threatening		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CK, creatine kinase; CK-MB, creatine kinase- cardiac muscle isoenzyme; CHF, congestive heart failure; INR, international normalized ratio; IV, intravenous; LFT, liver function test; MMF, mycophenolate mofetil; 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.

APPENDIX 9. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

The text below was obtained from the following reference:

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;45:228-247.

DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1). 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 non-measurable 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 CT scan (irrespective of scanner type) and 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 examination (when superficial).
- 20 mm by chest Xray (if clearly defined and surrounded by aerated lung).

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.

Non-measurable 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 non-measurable 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 non-measurable.

Bone lesions:

- Bone scan, 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 as 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 as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

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. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that 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 dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 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 short axis ≥10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological 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 reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target 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 non-target lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph node" or "multiple liver metastases").

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. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are accessible 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 trial.
- Chest Xray: Chest CT is preferred over chest Xray, particularly when progression is an important endpoint, since CT is more sensitive than Xray, particularly in identifying new lesions. However, lesions on chest Xray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: 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 slice thickness > 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).
- 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 trials where recurrence following complete response or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in firstline trials in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between 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 PD.

RESPONSE CRITERIA

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): 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 PD, taking as reference the smallest sum diameters while on study.
- 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 complete response criteria are met, since a normal lymph node is defined as having a

short axis of < 10 mm. Case report recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, stable disease and PD, 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 nonnodal) 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 which 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 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 should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When nonnodal 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 Non-target Lesions

While some non-target 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).
- PD: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: the appearance of 1 or more new lesions is also considered progression.)
- Non-CR/Non-PD: Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
- 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 trials when it is not a criterion of trial entry to have measurable disease. The same general concept apply 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 PD 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 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 PD 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 pre-existing 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 trial 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 the patient who has visceral disease at baseline and while on trial has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/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 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 FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in 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 PD 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 PD. 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 PD 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 PD.
- 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-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
Stable disease	Non-PD or not all evaluated	No	Stable disease
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; 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-PD	No	SD (Non-CR/non-PD)
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; SD, stable disease.

Evaluation of Best Overall Response

The best overall response (BOR) is the best response recorded from the start of the study drug treatment until the end of treatment taking into account 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 BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

The BOR is determined once all the data for the patient is known.

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

Best response determination in trials 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 not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero". In trials where confirmation of response is required, repeated 'NE' timepoint assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials 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 trial therapy.

Conditions that define "early progression, early death, and inevaluability" are trial specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is

recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. 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 false positive CR due to 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 at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In nonrandomized trials 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 trials. However, in all other circumstances, ie, in randomized trials (Phase 2 or 3) or trials where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not < 6 weeks).

Duration of Overall Response

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

The duration of overall complete response 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 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 calculation of PD).

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

Note: The duration of response and SD as well as the PFS 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 trials are to be made.

APPENDIX 10. CHILD-PUGH CLASSIFICATION SCORING SYSTEM

The information presented here has been obtained from the Washington University Medical Center, with sources as follows:

Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list. Liver Transl Surg. 1997;3(6):628-637.

Pugh RNH, Murray-Lyon IN, Dawson DL, et al. Transection of the esophagus for bleeding esophageal varices. Brit J Surgery. 1973;60:646-645.

Trey C, Burns DG, and Saunders SJ. Treatment of hepatic coma cornia by exchange blood transfusion. N Engl J Med. 1996;274(9):473-481.

Child-Pugh classification is either Grade A (mild: score 5 to 6 points), B (moderate: from 7 to 9 points), or C (severe: from 10 to 15 points) and is determined by both clinical and biochemical parameters (as shown below).

Clinical/Biochemical Parameter	**Score (Anomaly Severity)**		
	1	**2**	**3**
Hepatic encephalopathy (NCI-CTCAE grade)[a]	0[b]	1[c] or 2[d]	3[e] or 4[f]
Ascites (presence and severity)	None	Mild	Moderate
Total bilirubin (mg/dL)	< 2.0	2.0 to 3.0	> 3.0
Serum albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Prolonged prothrombin time (seconds) or INR[g]	< 4 or < 1.7	4 to 6 or 1.7 to 2.3	> 6 or > 2.3

Abbreviations: INR, international normalized ratio; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events.

a. Trey C, Burns DG, and Saunders SJ. Treatment of hepatic coma cornia by exchange blood transfusion. N Engl J Med. 1996;274(9):473-481.
b. Grade 0: Consciousness, personality, neurological examination, and electrocardiogram are all normal.
c. Grade 1: Restlessness, sleep disorders, irritability/anxiety, hand tremor, writing disorders, 5CPS waves.
d. Grade 2: Lethargy, time barrier, discomfort, asterixis, ataxia, three-phase slow wave.
e. Grade 3: Drowsiness, coma, orientation disorder, over-reflection, stiff/slow wave.
f. Grade 4: Cannot wake up from coma, no independent personality/behavior, irrational, slow 2-3CPS Delta activity.
g. Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keeffe EB, et al. Minimal criteria for placement of adults on the liver transplant waiting list. Liver Transl Surg. 1997;3(6):628-637.

APPENDIX 11. LIST OF HERBAL MEDICINE OR CHINESE PATENT MEDICINES WHICH HAVE EFFECT OF CONTROL CANCER OR BOOST IMMUNITY

The following table lists those medications that require a 14-day wash-out 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
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

Drug Name (Chinese)	Drug Name (English)
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: Pian = tablet, Jiao Nang/Jiaonang = capsule, Ke Li/Keli = granules, Zhue She ye/Zhusheye = injections, Kou Fu Ye/koufuye = oral liquid, Wan = Pill/bolus, He Ji/Heji = mixture, Gao = ointment
Note: This list of Chinese herbal medicines or Chinese patent medicines is provided as an example and is not intended to be all-inclusive.

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