A Randomized, Phase 2, Open-Label, Multi-Arm Study of Tislelizumab in Combination With Investigational Agents as First-Line Treatment in Patients With Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

Brief Title:

A Study of Tislelizumab in Combination With Investigational Agents in Participants With Head and Neck Squamous Cell Carcinoma

Protocol Number:	BGB-HNSCC-201
Amendment Number:	Amendment 2 Global
Investigational Medicinal Product:	Tislelizumab (BGB-A317) and other investigational agents
Regulatory Agency Identification Number(s):	EU CT Number: 2023-503418-63-00, NCT Number: NCT05909904
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive 3rd Floor San Mateo, CA 94404 USA
Approval Date:	*See electronic signature*
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INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Randomized, Phase 2, Open-Label, Multi-Arm Study of Tislelizumab in Combination With Investigational Agents as First-Line Treatment in Patients With Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

Protocol Identifier: BGB-HNSCC-201

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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DOCUMENT HISTORY

Amendment Version Number	Approval Date	Global/Region	Type of Protocol Amendment
Protocol Amendment 1.0	19 April 2023	Global	Substantial
Original Protocol	24 February 2023	Global	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

This Protocol Amendment 2.0 replaces Protocol Amendment 1.0 and regional amendment Protocol Amendment 1.1.1 (EU). This amendment is considered substantial based on the criteria set forth in Regulation (EU) No 536/2014 of the European Parliament and the Council of the EU.

The primary purpose of Amendment 2 is to provide directives to close out the study and harmonize content from regional amendments. The changes made in this amendment are described in the table below. Editorial and formatting changes are not included in this summary.

The Summary of Changes for Protocol Amendment 1.0 is available as a standalone document, which is available upon request.

Section Number and Title	Summary of Change	Brief Rationale for Change	Included in Regional Amendment
Section 2.1 Study Objectives and Endpoints; Section 9.1.2 Analysis Sets; Section 9.5 Immunogenicity Analyses (deleted section)	Removed secondary objective and endpoint of immunogenicity (ADA)	• Simplification of study reporting based on preliminary data and absence of specific concerns on immunogenicity • To reflect the removal of secondary objective and endpoint of immunogenicity	No
Section 3.6 Survival Follow-up Section 3.9.1 Continued Access to Study Drug During the Extended investigational product (IP) Access Period (new section), Section 7.6 Pharmacokinetic Testing Section 7.7 Biomarkers Section 8.6.2.1	• Specified when follow-up will occur • Added details on safety, tumor and response evaluations, pharmacokinetic (PK), biomarker sample collection, and data collection and management; removed reference to antidrug antibody (ADA) testing • Qualified SAE parameters for timeframes, documentation, and reporting • Clarified electronic case report form (eCRF) data collection parameters and patient	• During the Extended IP Access period: ○ To provide guidance for patients, including for those patients continuing to benefit from study drug ○ To specify that no data will be	No

Section Number and Title	Summary of Change	Brief Rationale for Change	Included in Regional Amendment
Prompt Reporting of Serious Adverse Events (SAEs) Section 14.1.1 Data Entry in the Electronic Case Report Form Section 14.1.3 Data Management/Coding Appendix 1 Schedule of Assessments	management of clinical source documents	collected in the eCRF ○ To provide guidance on the collection and maintenance of clinical source documents and how SAEs should be reported	
Section 3.9 End of Study	• Added a reason for the study to terminate early Added details for patients benefitting from treatment to continue on treatment	To provide patients the possibility of receiving further treatment after, in the opinion of the investigator, those patients have benefitted from treatment	No
Section 4.2 Exclusion Criteria	Added Criterion #27 excluding vulnerable adults	Updated as per request from the health authorities	Yes
Section 9.7.1 Futility Interim Monitoring	Clarified that a noninformative prior such as Beta (0.5, 0.5) for ORR will be used to calculate the Bayesian posterior probability for the futility interim analysis on the difference in ORR between an experimental arm and the reference arm.	Updated for clarification as per request from the health authorities	Yes
Section 13.4 Patient and Data Confidentiality	Added the scientific rationale for collection of ethnicity and race data during the study	Updated for clarification as per request from the health authorities	Yes
Appendix 1 Footnote q; Appendix 2	Added that: • local laboratory assessments of thyroid function would be	To provide guidance for patient care	No

Section Number and Title	Summary of Change	Brief Rationale for Change	Included in Regional Amendment
Clinical Laboratory Assessments; Appendix 15 EXPERIMENTAL ARM 1; 4.Dosage and Administration Table 3	performed at specific time increments • Total T3 (TT3) is acceptable in case free triiodothyronine analysis is not available		
Appendix 7 INFUSION-RELATED REACTIONS, HYPERSENSITIVITY REACTIONS AND IMMUNE-MEDIATED ADVERSE EVENTS: EVALUATION AND MANAGEMENT	Indicated that treatment must be permanently discontinued in case of Grade 3 ocular toxicity.	Updated as per request from the health authorities	Yes
Appendix 8 MANAGEMENT OF NON-IMMUNE-MEDIATED ADVERSE EVENTS	Revised to permanently discontinue study treatment when non-hematologic Grade 4 event occurs	Updated in response to EU HA request	Yes
Appendix 11 Pregnancy Reporting Period	Qualified pregnancy reporting periods	To provide guidance for all experimental arms	No
Appendix 15 EXPERIMENTAL ARM 1: TISLELIZUMAB+BGB-A425	•Shortened Sections and / added directive to refer to the Investigator's Brochure in Sections 1.2.4 (Prior Clinical Experience With BGB A425), 1.2.4.1 (Safety Assessment of BGB-A425), and 1.2.4.2 (Efficacy Assessment of BGB-A425) •Removed patient monitoring parameters for specific infusions during treatment cycles	To refer the reader to the current Investigator's Brochure for detailed information	No
Appendix 16 EXPERIMENTAL ARM	•Shortened Sections and / added directive to refer to the	To refer the reader to the current	No

Section Number and Title	Summary of Change	Brief Rationale for Change	Included in Regional Amendment
2: TISLELIZUMAB+ LBL-007	Investigator's Brochure in Sections 1.2.4 (Prior Clinical Experience With LBL-007), 1.2.4.1 (Safety Assessment of LBL-007), and 1.2.4.2 (Efficacy Assessment of LBL-007) • Removed patient monitoring parameters for specific infusions during treatment cycles	Investigator's Brochure for detailed information	
Title page and Protocol Amendment Summary of Changes	Followed latest company template	New template was developed to streamline this document type	No

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SYNOPSIS

Study Title	A Randomized, Phase 2, Open-Label, Multi-Arm Study of Tislelizumab in Combination With Investigational Agents as First-Line Treatment in Patients With Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma
Brief Study Title	A Study of Tislelizumab in Combination With Investigational Agents in Participants With Head and Neck Squamous Cell Carcinoma
Brief Summary	The purpose of this study is to evaluate the efficacy and safety of tislelizumab and tislelizumab in combination with investigational agent(s) in first-line recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) with programmed cell death protein ligand-1 (PD-L1) positive expression of Combined Positive Score (CPS) of ⩾ 1, in recurrent or metastatic head and neck squamous cell carcinoma. Study details include: • The study duration will be up to 2 years, plus follow-up up to 30 days (± 7 days) after the last dose of the study drug(s). • The treatment duration will be up to 2 years.
Sponsor	BeiGene, Ltd.
Amendment Version	2
Regulatory Agency Identifier Number (s)	EU CT Number: 2023-503418-63-00
Rationale	Local recurrence or distant metastasis is common in patients with HNSCC, affecting approximately 20% of patients with early-stage disease and 50% of those with locally advanced disease. Previous studies have established the predictive value of PD-L1 expression in tumor region for evaluating efficacy of anti-programmed cell death protein-1 (PD-1) and anti-PD-L1 therapy in patients with R/M HNSCC (Herbst et al 2014). Anti-PD-L1 therapy, depending on tumor PD-L1 expression, either alone or in combination with chemotherapy, has shown improvement in overall survival and replaced chemotherapy alone as the standard of care (SOC) in the treatment for patients with R/M HNSCC with a PD-L1 CPS ⩾ 1 based on Keynote-048 study (Burtness et al 2019). While targeting PD-1 alone has demonstrated a benefit for durable response and overall survival (OS), it is evident that not all patients treated with single-agent PD-1 therapy experience a durable response or prolonged survival. This is supported by data showing that even in patients with enriched PD-L1 expression (CPS ⩾ 20), the response rate in the first-line setting is only 23%. The addition of chemotherapy to immune checkpoint inhibitors improves survival compared with cetuximab plus chemotherapy, but it is also associated with an increased toxicity burden (Burtness et al 2019**).** **Accumulating data and** recent clinical studies suggest that combination therapies using agents that can target different biological pathways can overcome resistance to PD-1/PD-L1 therapy (eg, bypassing immunological escape mechanisms or increasing tumor immunogenicity) and could improve anticancer activity (Nowicki et al 2018). Therefore, identifying and combining novel agents that can synergize with and improve the efficacy of anti-PD-1 therapy would be beneficial for patients with R/M HNSCC without introducing chemotherapy-related toxicity. This Phase 2, randomized study will assess whether the addition of investigational agent(s) targeting different biologic pathways to tislelizumab has the potential to improve and/or extend the therapeutic benefit of anti-PD-1 therapy in patients with R/M HNSCC with PD-L1 CPS ⩾ 1.
Objectives and Endpoints	

Objective	Endpoint
Primary: To assess the antitumor activity of tislelizumab plus investigational agent(s)	**Primary:** Confirmed objective response rate (ORR) as assessed by the investigators per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1
Secondary: • To further assess the antitumor activity of tislelizumab plus investigational agent(s) • To assess the safety and tolerability of tislelizumab plus investigational agent(s) • To assess overall survival (OS)	**Secondary:** • Progression-free survival (PFS), duration of response (DOR), clinical benefit rate (CBR), and disease control rate (DCR) as assessed by the investigator per RECIST v1.1 • The incidence and severity of adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) in reference arm (tislelizumab alone) and experimental arms (tislelizumab plus investigational agent[s]) • OS

Study Design:	This is a randomized, open-label, multicenter, Phase 2, multi-arm study designed to evaluate the efficacy and safety of tislelizumab and tislelizumab in combination with investigational agent(s) in first-line R/M HNSCC with PD-L1 positive expression of CPS $\geqslant$ 1. Patients will be randomized to receive either tislelizumab + investigational agent(s) (experimental arm[s]) or tislelizumab monotherapy (reference arm). The initial randomization ratio between each of the experimental arms and the common reference arm will be 1:1. Randomization in each treatment arm will be stratified based on PD-L1 expression (1 to 19 versus $\geqslant$ 20). A 1:1 randomization ratio is initially applied to each of the experimental arms and the common reference arm. The randomization ratio may be modified to account for emerging safety data, efficacy data, and feasibility considerations. Treatments in each Arm will be administered as follows: • Reference arm: tislelizumab • Experimental arm(s): tislelizumab + investigational agent(s) The details regarding specific treatment regimens/requirements for investigational agents are provided in each investigational agent-specific appendix. Study treatments in all arms will be administered for up to 2 years until disease progression, intolerable toxicity, withdrawal of informed consent, or another discontinuation criterion is met, whichever occurs first. Tumor response will be assessed by investigators using standard RECIST v1.1 criteria. Tumor imaging (computed tomography [CT] with or without contrast and/or magnetic resonance imaging [MRI]) must be performed within 28 days before randomization/enrollment. On-study tumor assessments will occur every 6 weeks (± 7 days) from randomization for the first 52 weeks and then every 12 weeks (± 7 days) thereafter. Tumor assessments should continue until disease progression, as determined by the investigator. Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient experiences disease progression, dies, withdraws consent, is lost to follow-up, or until the study terminates, whichever occurs first. Safety will be assessed throughout the study by monitoring AEs/serious adverse events (SAEs) (toxicity grades assigned per NCI-CTCAE v 5.0 and laboratory results. Vital signs, physical examinations, ECOG Performance Status changes,

	electrocardiogram (ECG) results, and other examinations will also be used for safety assessments. An independent Safety Oversight Committee that is composed of members who are otherwise not directly associated with the study will be established to assess safety periodically throughout this study. This committee may recommend actions including discontinuation or modification for a specific investigational agent due to safety concerns. A futility monitoring will be performed during the course of the study to evaluate the clinical activity of any treatment arm. An Extended Investigational Product (IP) Access Period (starts when Protocol Amendment 2.0 becomes effective) will be included to provide continued access to study treatment after the sponsor's completion of the main study objectives. At the time of initiation of the Extended IP Access Period, any patient on treatment and, in the opinion of the investigator, who continues to benefit from study drug(s), will be offered the option to continue treatment until the current supply of IP is unavailable, any discontinuation criterion is met, or until the patient receives the maximum of 2 years of study drug(s), whichever occurs first. During the Extended IP Access Period, patient management and monitoring, including tumor and response evaluations, safety assessments, study drug modifications, and follow-up will be concordant with the protocol or per the investigator's discretion based on local or institutional guidelines. No further data will be collected by the sponsor in eCRFs. However, as a part of patient management, the investigator must collect and maintain patient clinical source documents per the requirements of local institutions. All SAEs should still be reported to the sponsor safety database through paper forms. Samples for PK, ADA, and biomarker assessments will not be collected during the Extended IP Access Period.
Description of Patients:	**Main Inclusion Criteria** • Adult patients (≥ 18 years of age or of acceptable age according to local regulations, at the time of voluntarily signing of informed consent) with histologically or cytologically confirmed R/M HNSCC that is considered incurable by local therapies. • The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx. • Patients must agree to provide archival tumor tissue from screening or be willing to undergo fresh tumor biopsy. • Patients must have evaluable tumor PD-L1 expression determined locally or centrally. • At least 1 measurable lesion as defined per RECIST v1.1. • ECOG Performance Status of 0 or 1. • Adequate hematologic and organ function. **Main Exclusion Criteria** • Recurrent or metastatic carcinoma of the nasopharynx (any histology). • Has disease that is suitable for local therapy administered with curative intent. • Prior therapy with an anti-PD-1, anti-PD-L1, anti-programmed cell death ligand-2 (PD-L2), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), anti-lymphocyte activation gene-3 (LAG-3), or any other antibody or drug specifically targeting T-cell co-stimulatory or immune checkpoint pathways.
Number of Patients	The total number of patients depends on the number of experimental arms and the timing when they are added to the study.

Study Drug/Treatments	Treatments in each arm will be administered as follows: • Reference arm: tislelizumab 200 mg intravenously once every 3 weeks • Experimental arm(s): tislelizumab 200 mg intravenously once every 3 weeks + investigational agent(s) Study treatments in all arms will be administered for up to 2 years.
Ethical Considerations	This study will be conducted by the investigator and the study center in full conformance with the guidelines for Good Clinical Practice (International Council for Harmonisation [ICH] E6) and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the patient. The study will also comply with the Definitions and Standards for Expedited Reporting (ICH E2A). 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 been approved and is currently being marketed in China for the treatment of several cancer types including nasopharyngeal carcinoma (NPC). Based on the data from clinical studies, tislelizumab has been safe and well tolerated when used in combination with other anticancer therapies. **Tislelizumab Monotherapy** Blockade of the PD-1 pathway has demonstrated strong antitumor efficacy either alone or in combination with SOC across multiple cancer indications. Based on the evaluation of available data in 3220 patients with multiple human malignancies (2173 patients treated with monotherapy and 1047 patients treated with chemotherapy combination) as of the data cutoff date (20 July 2022), the benefit-risk assessment for tislelizumab is considered favorable. The safety profile of tislelizumab is consistent with known class effects of anti-PD-1 antibodies (eg, pembrolizumab) and includes mostly mild and moderate AEs. Very few $\geqslant$ Grade 3 immune-mediated AEs (4.3%) were observed with tislelizumab, and they have been generally reversible and manageable. **Tislelizumab in Combination With Investigational Agents** There is the risk of observing augmented safety signals (both immune and non-immune mediated) caused by the addition of investigational agent(s). A safety monitoring plan has therefore been established to monitor, diagnose, and manage immune-mediated and other AEs. Details regarding benefit-risk assessment for the novel treatment combination with an investigational agent are provided in the investigational agent-specific appendices. The benefit-risk assessment of the study treatment, based on available data, is considered favorable.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
5-FU	5-fluorouracil
AASLD	American Association for the Study of Liver Disease
ADA	antidrug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADL	activities of daily living
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ASCO	American Society for Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BGB-A317	tislelizumab
bTMB	blood tumor mutation burden
CBR	clinical benefit rate
CDC	complement-dependent cytotoxicity
CL	central clearance
CNS	central nervous system
CPS	combined positive score
CR	complete response
CT	computed tomography
ctDNA	circulating tumor DNA
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	End-of-Treatment (Visit)
ESMO	European Society for Medical Oncology
FcγR	gamma fragment crystallizable region (Fc) receptors
FDA	Food and Drug Administration

Abbreviation	Definition
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GEP	gene expression profiling
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation
ICIs	immune checkpoint inhibitors
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IHC	immunohistochemistry
imAE	immune-mediated adverse event
IP	investigational product
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LAG-3	lymphocyte activation gene-3
MedDRA	Medical Dictionary for Regulatory Activities
MoA	mechanism of action
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer (cells)
NMPA	National Medical Products Administration
NPC	nasopharyngeal carcinoma

Abbreviation	Definition
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein ligand-1
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RSI	Reference Safety Information
R/M	recurrent/metastatic
SAE	serious adverse event
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphoctyes
TIM-3	mucin-domain containing-3
TMB	tumor mutation burden
$t_{1/2}$	terminal half-life
ULN	upper limit of normal
US(A)	United States (of America)
V_2	peripheral volume 2
V_3	peripheral volume 3
V_c	central volume of distribution
WHO	World Health Organization

1. INTRODUCTION

1.1. Background Information on Head and Neck Squamous Cell Carcinoma and Unmet Clinical Needs

1.1.1. Background Information on Head and Neck Squamous Cell Carcinoma

HNSCCs encompass a heterogenous group of tumors rising from mucosal epithelia of the oral cavity, pharynx, and larynx. HNSCC is the most common malignancy in the head and neck and the seventh leading cancer by incidence worldwide, with 700,000 new cases and 350,000 deaths in 2018 (Bray et al 2018). The incidence of HNSCC continues to rise and is anticipated to rise by 30% (1.08 million new cases annually) by 2030 (Bray et al 2018). HNSCCs are prevalent in Southeast Asia, Australia, USA, and Western Europe. High risk of HNSCC is most widely associated with geographic regions with populations who are known to have high tobacco use or alcohol consumption. (Johnson et al 2020). Additionally, tumors that arise in the oropharynx are increasingly linked to HPV infection, with more favorable prognosis observed in HPV-positive HNSCCs than HPV-negative HNSCCs. The primary oncogenic HPV strains are HPV16 (83% to 86% of HPV-positive HNSCCs), HPV33 (3.3% to 7.3%), HPV35 (2.2% to 4%), and HPV18 (< 2%) (Castellsague et al 2016; Cancer Genome Atlas Network 2015; Gillison et al 2015; Michaud et al 2014). Men are significantly more likely to develop HNSCC than women with an incidence ratio ranging from 2:1 to 4:1 (Ferlay et al 2015).

At diagnosis, approximately 30% to 40% of patients present with stage I or II disease (early stage) (Pfister et al 2014). About 60% of patients with HNSCC have Stage III & IV (locoregional or locally advanced) disease. Most patients with locally advanced disease present with a high risk of recurrence, and approximately 10% of patients with HNSCC present with metastatic disease. In general, early-stage patients with HNSCC are treated with surgery or radiation and have 5-year survival rates of approximately 70% to 90% (Fasano et al 2021). Locally advanced disease requires multimodality treatment that combines surgery, radiation, and systemic treatment with platinum-based chemotherapy or anti-*EGFR* targeted therapy with cetuximab (Argiris et al 2017). However, most of these patients eventually relapse with either locoregional recurrence or metastatic disease or both (Fasano et al 2021). Although locoregional control has been improved due to treatment with radiochemotherapy compared to radiotherapy-alone, the failure rate at distant organs remains high (mean survival time after diagnosis of distant metastases of 7.5 months; Wiegand et al 2015). The prognosis is poor for R/M HNSCC, with a median duration of around 1 year of OS.

1.1.2. Current Treatment Options for Patients With Recurrent or Metastatic HNSCC

Local recurrence or distant metastasis is common in HNSCC, affecting approximately 20% of patients with early-stage disease and 50% of those with locally advanced disease (Fasano et al 2021).

Among patients with R/M HNSCC, the principle modalities are surgery, radiotherapy and systemic therapy. For patients with no surgery or radiotherapy options, systemic therapy will be recommended. The choice of systemic therapy should be individualized based on patient characteristics (eg, performance score, goals of therapy). Treatments with cisplatin, carboplatin, paclitaxel, docetaxel, 5-FU, and their various combinations have been evaluated in the past

decades, with better overall response rate demonstrated in the combination of cisplatin and 5-FU. While the addition of cetuximab to the chemotherapy doublet of platinum/5-FU increased the OS significantly in the EXTREME trial (10.1 versus 7.4 months, p = 0.04) (Vermorken et al 2008). EXTREME regimen (cetuximab plus a platinum and 5-FU) is the only Category 1 evidence-supported combination regimen recommended by NCCN. Cetuximab plus docetaxel and platinum regimen, platinum, 5-FU, cetuximab, paclitaxel or their combinations are considered as alternative treatments by NCCN as well (NCCN 2023).

Anti-PD-1/PD-L) therapy, depending on tumor PD-L1 expression, either alone or in combination with chemotherapy has shown improvement in overall survival and replaced chemotherapy alone as the SOC in the treatment for locally recurrent disease (without surgical or radiation treatment options) and/or metastatic disease in the first-line setting (NCCN 2023; ESMO 2020).

Immunotherapies are designed to enhance the immune system activity of eradicating cancerous cells. ICIs are a widely effective class of immunotherapies that block inhibitory immune checkpoint pathways in order to reactivate immune responses against cancer. Analysis of tissue samples from patients with HNSCC shows a highly immunogenic tumor microenvironment (Mandal et al 2016; Wang HC et al 2019). HNSCC shows a relatively high TMB and immune infiltration, which suggests a potential to achieve therapeutic efficacy from cancer immunotherapy.

Anti-PD-1 therapy has emerged as an effective treatment for patients with tumors expressing varying degrees of PD-L1 (Hanna et al 2017). Anti-PD-1 and anti-PD-L1 therapies target the programmed death receptor pathway of T lymphocytes; this checkpoint has been found to be activated in cancers allowing tumors to evade the host immune system. Since HNSCC is considered a highly immunogenic tumor type with approximately 85% patients expressing PD-L1 CPS ≥ 1 (Burtness et al 2019), anti-PD-1 antibodies have shown clinical benefit such as extended survival in responding patients with HNSCC which led to approval of anti-PD-1/PD-L1 therapies (Burtness et al 2019).

Two ICIs, pembrolizumab and nivolumab, are recommended treatment options for patients with R/M HNSCC who have progressed on or following platinum-based chemotherapy (NCCN 2023). This recommendation is supported by the results of two trials, Keynote-012 (Seiwert et al 2016) and CheckMate 141 (Ferris et al 2018).

In 2019, US FDA approved pembrolizumab as first-line therapy for the treatment of patients with R/M HNSCC based on Keynote-048 trial, in which pembrolizumab monotherapy compared with the EXTREME regimen (cetuximab plus a platinum and 5-FU) demonstrated a significantly prolonged median OS in patients with a CPS ≥ 20 (14.9 versus 10.7 months, respectively; HR 0.61 [95% CI: 0.45 to 0.83]), as well as in those with a CPS ≥ 1 (12.3 versus 10.3 months, respectively; HR 0.78 [95% CI: 0.64 to 0.96]). Pembrolizumab plus platinum-based chemotherapy significantly prolonged OS in the total patient population compared with the

EXTREME regimen (13.0 versus 10.7 months, respectively; HR 0.77 [95% CI: 0.63 to 0.93]) (Burtness et al 2019).

Table 1: Efficacy Data of 1L Treatment SOC in Recurrent or Metastatic HNSCC

Study	Regimen	Setting	mOS (month)	mPFS (month)	ORR (%)	mDOR (month)
Keynote-048 (Burtness et al 2019)	Pembrolizumab Mono (CPS ≥ 20)	1L	14.9	3.4	23	22.6
	Pembrolizumab Mono (CPS ≥ 1)	1L	12.3	3.2	19	23.4
	Pembrolizumab plus platinum/5-FU	1L	13.0	4.9	36	6.7
	Cetuximab plus Platinum/5-FU (EXTREME regimen)	1L	10.7	5.1	36	4.3

Abbreviations: 1L, first-line; 5-FU, 5- fluorouracil; CPS, combined positive score; HNSCC, head and neck squamous cell carcinoma; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; SOC, standard of care.

1.1.3. Unmet Medical Need

While targeting PD-1 alone has been successful in demonstrating a benefit in the durable response and OS, it is evident that not all patients who are treated with single-agent PD-1 therapy experience a durable response or prolonged survival. This is supported by the data that even in the patients with PD-L1 expression of CPS ≥ 20, the response rate in the first-line setting is only 23%. The addition of chemotherapy to ICIs has certainly improved the overall survival compared with cetuximab plus chemotherapy but it is associated with an increased toxicity burden (Burtness et al 2019). Accumulating clinical data suggest that combination therapy using agents that can target different biological pathways can overcome resistance to PD-1/PD-L1 therapy (eg, bypassing immunological escape mechanisms or increasing tumor immunogenicity) and improve anti-cancer activity (Nowicki et al 2018). Additionally, studies like Checkmate 651 support the rationale that combining immunotherapy without chemotherapy can improve efficacy outcomes without adding chemotherapy comparing to SOC (EXTREME regimen) (Argiris et al 2021). Therefore, identifying and combining novel agents that can synergize with and improve the efficacy of anti-PD-1 therapy would be beneficial for patients with R/M HNSCC without adding chemotherapy-related toxicity.

1.2. Background Information on Tislelizumab

As of 19 April 2023, Tislelizumab has been approved in China for multiple indications, including the treatment of the following patients:

- Patients with relapsed or refractory classical Hodgkin lymphoma who received at least two lines of systemic chemotherapy regimens
- Patients with locally advanced or metastatic urothelial carcinoma with PD-L1 high expression whose disease progressed during or following platinum-containing

chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

- Patients with HCC who have been previously treated with at least one systemic therapy
- Patients with unresectable, locally advanced or metastatic squamous NSCLC (first-line treatment in combination with paclitaxel plus carboplatin or paclitaxel for injection [albumin bound] plus carboplatin)
- Patients with unresectable, locally advanced or metastatic nonsquamous NSCLC, with *EGFR* genomic tumor aberrations negative and *ALK* genomic tumor negative (first-line treatment in combination with pemetrexed and platinum chemotherapy)
- Adult patients with locally advanced or metastatic nonsquamous NSCLC, with *EGFR* genomic tumor aberrations negative and *ALK* genomic tumor negative, that has progressed after or did not tolerate prior platinum-based chemotherapy and adult patients with locally advanced or metastatic squamous NSCLC, with *EGFR* and *ALK* negative or unknown, that has progressed after or did not tolerate prior platinum-based chemotherapy
- Adult patients with advanced unresectable or metastatic microsatellite instability-high or mismatch repair deficient solid tumors:
  - patients with advanced colorectal cancer who have been treated with fluoropyrimidine, oxaliplatin, and irinotecan
  - patients with other advanced solid tumors who develop disease progression after prior treatment and have no satisfactory alternative treatment options
- Patients with locally advanced or metastatic esophageal squamous cell carcinoma who have disease progression following or are intolerant to first-line standard chemotherapy
- Patients with R/M NPC (first-line treatment in combination with gemcitabine and cisplatin)

Refer to the most recent edition of the Tislelizumab Investigator's Brochure for additional background.

1.2.1. Pharmacology

Tislelizumab (also known as BGB-A317) is a humanized, IgG4-variant monoclonal antibody 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 and affinity (dissociation constant [K_D] = 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, tislelizumab was observed to consistently and dose-dependently enhance the functional activity of human T cells and pre-activated primary peripheral blood mononuclear cells. Tislelizumab has demonstrated in vivo antitumor activity in several allogeneic xenograft models, in which peripheral blood mononuclear cells were co-injected with human cancer cells

(A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

Tislelizumab is an IgG4-variant antibody to FcγRs such as FcγRI and FcγRIIIA, and has very low binding affinity to complement 1q, a subunit of complement 1. In vitro assays with tislelizumab suggest either low or no ADCC, ADCP, or CDC effects in humans (Zhang et al 2018). Tislelizumab was specifically engineered to minimize these potential mechanisms of T-cell clearance. Preserving T cells may slow tumor resistance to anti-PD-1 therapy.

1.2.2. Toxicology

The nonclinical toxicity and toxicokinetic profile of tislelizumab was characterized in single dose studies in mice and cynomolgus monkeys and in a repeated-dose study in cynomolgus monkeys dosed once every 2 weeks for 13 weeks. Tissue cross-reactivity in normal human and cynomolgus monkey frozen tissues was also evaluated. The pivotal studies were conducted in accordance with Good Laboratory Practice regulations. The single-dose regimens spanned from the intended human dose to 10-fold higher than the maximum of the intended human dose, and the repeated-dose regimens spanned to 3-fold higher than the maximum of the intended human dose. Cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

Overall, no apparent toxicity was noted in mice or monkey toxicity studies. No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in a human whole-blood assay. 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 or effect on the systemic exposure. The no-observed-adverse-effect level of tislelizumab in the 13-week monkey toxicity study was considered to be 30 mg/kg. The toxicity profile of tislelizumab is considered adequate to support the current study. For more detailed information on the toxicity of tislelizumab, refer to the most recent edition of the Tislelizumab Investigator's Brochure.

1.2.3. Clinical Pharmacology

Tislelizumab exhibited a dose-proportional increase in exposure over the entire dose range (0.5 to 10 mg/kg) tested in BGB-A317_Study_001. A population PK analysis was performed based on 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 mechanisms. No time-varying clearance was observed in tislelizumab PK. The typical estimates of CL, V_c, and V_2 and V_3, respectively, were 0.153 L/day, 3.05 L, 1.27 L, and 2.10 L, respectively, with interindividual variability in CL (26.3%), V_c (16.7%), V_2 (74.7%), and V_3 (99.9%). The $t_{1/2}$ was estimated to be approximately 23.8 days. The accumulation ratios are estimated to be 2.14 and 2.49 for area under the serum concentration-time curve at steady state and minimum concentration at steady-state, respectively. Steady state is expected to be reached in approximately 12 weeks.

The population PK analyses demonstrated that race, baseline AST, ALT, bilirubin, lactate dehydrogenase, estimated glomerular filtration rate, ECOG Performance Status, and the sum of products of perpendicular diameters of classical Hodgkin lymphoma did not have statistically

significant influences on tislelizumab PK. Baseline body weight, tumor size of solid tumors, albumin level, 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 relatively small compared to the overall range estimated for the PK exposures and hence are not considered clinically meaningful. For more detailed information on the clinical pharmacology of tislelizumab, refer to the most recent edition of the Tislelizumab Investigator's Brochure.

1.2.4. Prior Clinical Experience With Tislelizumab

For more detailed information on the safety and efficacy of tislelizumab when given as monotherapy or in combination with chemotherapy, refer to the most recent edition of the Tislelizumab Investigator's Brochure.

1.2.4.1. Safety Assessment of Tislelizumab

The overall safety experience with tislelizumab, as a monotherapy or in combination with chemotherapy, is based on experience in 3220 patients (2173 patients treated with monotherapy and 1047 patients treated with chemotherapy combination) in clinical studies as of the data cutoff date of 20 July 2022.

The safety profile of tislelizumab is consistent with that observed with other PD-1 inhibitors when given as single-agent or in combination with chemotherapy.

1.2.4.1.1. Pooled Safety Assessment of Tislelizumab Monotherapy Studies

As of 20 July 2022, 1992 patients with solid tumors have been treated with tislelizumab monotherapy in 7 monotherapy studies.

A pooled monotherapy analysis was conducted to provide a comprehensive review of the safety profile of tislelizumab.

Across the 7 monotherapy studies in solid tumors, the safety profile was well tolerated and generally consistent between studies. While approximately 96% of patients experienced a TEAE of any causality in the monotherapy setting, the frequency of treatment-related events of any grade in the solid tumor studies (N = 1992) was 70.2%. Most AEs were Grade 1 or 2 in the pooled solid tumor studies, and most ≥ Grade 3 TEAEs were assessed as unrelated to tislelizumab. Treatment-related events of ≥ Grade 3 were reported in 13.5% of patients. AEs were generally reversable and manageable. The rate of treatment-emergent SAEs was 35.7%. Treatment-related treatment-emergent SAEs were notably lower, with a rate of 9.9%. A total of 11.5% of patients experienced ≥ 1 TEAE leading to tislelizumab discontinuation and 5.1% experienced ≥ 1 treatment-related TEAE leading to tislelizumab discontinuation.

Immune-mediated adverse events of any grade were reported in 16.3% of patients, while ≥ Grade 3 imAEs were reported in 4.3% of patients. These imAEs have well-established algorithms for treatment and are considered manageable.

Out of 1992 patients with solid tumors treated with tislelizumab monotherapy, 7.1% of patients experienced TEAEs leading to death and 1.0% of patients experienced ≥ 1 tislelizumab-related TEAE leading to death.

The safety profile for single-agent tislelizumab is manageable and consistent to that observed with other PD-1 inhibitors in solid tumors.

1.2.4.2. Efficacy Assessment of Tislelizumab

Efficacy data are available from 4 monotherapy studies and 1 combination therapy study. Among the 4 monotherapy studies, 2 Phase 1 monotherapy studies in patients with solid tumors were completed, including Study BGB-A317_Study_001 (data cutoff date 20 May 2019) and Study BGB-A317-102 (data cutoff date 01 December 2018), and 2 Phase 3 monotherapy studies were ongoing, including Study BGB-A317-302 in ESCC patients (data cutoff date 01 December 2020), Study BGB-A317-303 in NSCLC patients (data cutoff date 15 July 2021). One combination therapy Study BGB-A317-309 was in patients with R/M NPC (initial analysis with data cutoff date 26 March 2021; updated analysis with data cutoff date 30 September 2021).

Refer to the Tislelizumab Investigator's Brochure for more detailed information on efficacy data for tislelizumab when given as monotherapy or in combination therapies.

1.2.4.2.1. Efficacy Assessment of Tislelizumab Monotherapy in Solid Tumors

BGB-A317_Study_001 was a Phase 1a/1b study consisting of a dose-escalation phase (1a) and a dose-expansion phase (1b) designed to establish the MTD and dosing schedule, determine the RP2D, and investigate the preliminary efficacy of tislelizumab in previously treated patients with select tumor types, including HNSCC.

The RP2D and schedule for tislelizumab were determined to be 200 mg administered once every 3 weeks. Across all disease cohorts (N = 451), 6 patients (1.3%) experienced a CR and 54 patients (12.0%) had a confirmed PR, yielding an ORR of 13.3%. Stable disease was observed in 141 patients (31.3%). The DCR was 44.6% (95% CI: 39.92% to 49.29%), and the CBR was 25.9% (95% CI: 21.96% to 30.25%). Among the 20 patients with HNSCC enrolled in the study, the ORR was observed to be 15.0% (95% CI: 3.21% to 37.89%) (Desai et al 2020).

Study BGB-A317-302 is a randomized, controlled, open-label, global Phase 3 study comparing the efficacy and safety of tislelizumab versus chemotherapy (paclitaxel, docetaxel, or irinotecan) as second-line treatment in patients with advanced unresectable/metastatic esophageal squamous cell carcinoma. A total of 512 patients were randomized in the study (256 patients in each arm). There was a statistically significant and clinically meaningful improvement in OS for the tislelizumab arm compared with the chemotherapy arm in the ITT Analysis Set. The stratified hazard ratio from the Cox regression model was 0.70 (95% CI: 0.57 to 0.85; 1 sided p = 0.0001 via stratified log-rank test). The median OS was 8.6 months (95% CI: 7.5 to 10.4 months) in the tislelizumab arm and 6.3 months (95% CI: 5.3 to 7.0 months) in the chemotherapy arm (Shen et al 2022).

Study BGB-A317-102 was a nonrandomized, Phase 1/2 study of tislelizumab monotherapy evaluating the activity and safety of tislelizumab at the RP2D and schedule of 200 mg given once every 3 weeks in previously treated Chinese patients with select advanced solid tumors, including NPC. Tislelizumab (200 mg once every 3 weeks) demonstrated preliminary antitumor activity across multiple tumor types. Of the presented indications, ORR was ≥ 15% in NPC (43%), microsatellite instability-high/mismatch repair deficient solid tumors (19%), NSCLC (18%), gastric cancer (17%), HCC (17%), and melanoma (15%). The median DOR was only mature for NPC cohort, which had a DOR of 8.3 months (range 3.9 months to not estimable)

with a median follow-up of 4.8 months. In the PD-L1$^+$ NPC cohort (n = 16), the ORR was 50% (95% CI: 24.7% to 75.3%). In the PD-L1$^-$ NPC cohort (n = 4), the ORR was 25% (95% CI: 0.6% to 80.6%) (Shen et al 2020).

Study BGB-A317-303 is a randomized, Phase 3 study evaluating tislelizumab monotherapy versus docetaxel in patients with locally advanced or metastatic NSCLC (squamous or nonsquamous) that progressed on a prior platinum-containing regimen. As of the data cutoff date of 15 July 2021, a total of 805 patients were randomized to the Tislelizumab Arm (535 patients) or Docetaxel Arm (270 patients). The final analysis showed that, tislelizumab continued to have OS benefit versus docetaxel (median OS = 16.9 months [95% CI: 15.2 to 19.1 months] versus 11.9 months [95% CI: 9.6 to 13.5 months], respectively; HR = 0.66 [95% CI: 0.56 to 0.79]) in ITT population. In the PD-L1 tumor expression ≥ 25% population, tislelizumab has a statistically significant and clinically meaningful OS benefit versus docetaxel (median OS = 19.3 months [95% CI: 16.5 to 22.6 months] versus 11.5 months [95% CI: 8.2 to 13.5 months], respectively; HR = 0.53 [95% CI: 0.40 to 0.70], p < 0.0001). (Zhou et al 2023).

1.2.4.2.2. Efficacy Assessment of Tislelizumab in Combination With Chemotherapy in R/M Nasopharyngeal Carcinoma

Study BGB-A317-309 (RATIONALE-309) is a Phase 3, multicenter, randomized-controlled, double-blinded study evaluating the efficacy and safety of tislelizumab in combination with gemcitabine and cisplatin as first-line treatment for R/M NPC. The primary endpoint was PFS assessed by IRC. A total of 263 patients were randomized to receive tislelizumab combined with gemcitabine and cisplatin (n = 131) or placebo combined with gemcitabine and cisplatin (n = 132). At the initial analysis (data cutoff date 26 March 2021) (Yang et al 2021), significantly longer PFS by IRC was observed in the tislelizumab + chemotherapy arm versus the placebo + chemotherapy arm (HR = 0.52; 95% CI: 0.38 to 0.73; p < 0.0001). Higher IRC-assessed ORR and longer IRC-assessed DOR were also observed in the tislelizumab + chemotherapy arm (69.5%; 8.5 months) versus the placebo + chemotherapy arm (55.3%; 6.1 months). At the updated analysis (data cutoff date 30 September 2021) (Zhang et al 2022), longer PFS by IRC was observed in the tislelizumab + chemotherapy arm (9.6 months) versus the placebo + chemotherapy arm (7.4 months; HR = 0.50; 95% CI: 0.37 to 0.68). With a median follow-up time of 15.5 months at the updated analysis, the median OS was not reached in the tislelizumab + chemotherapy arm and was 23.0 months for the placebo + chemotherapy arm. Based on clinical data from the RATIONALE 309 study, tislelizumab in combination with gemcitabine and cisplatin was approved in China as a first-line treatment for patients with R/M NPC.

1.3. Background Information on Investigational Agents

The background information on investigational agents is provided in the investigational agent-specific appendix.

1.4. Study Rationale

1.4.1. Rationale for Study and Patient Population

This study will enroll first-line R/M patients with HNSCC with PD-L1 positive expression CPS ≥ 1.

Previous studies have established the predictive value of PD-L1 expression in tumor region for evaluating efficacy of anti-PD-1 and anti-PD-L1 therapy in R/M HNSCC (Herbst et al 2014). Anti-PD-1 antibody monotherapy is the new SOC for recurrent or metastasis HNSCC in patients with a PD-L1 CPS ≥ 1 based on Keynote-048 study (Burtness et al 2019). US FDA and the European Commission approved pembrolizumab as a single agent for patients whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test in 2019 (Keytruda [pembrolizumab] US prescribing information 2022, Keytruda [pembrolizumab] European Union [EU] summary of product characteristics 2020). Existing data suggests that high PD-L1 expression may be associated with better response from a PD-1 inhibitor in HNSCC. Therefore, in line with current SOC, only patients with PD-L1 positive expression (PD-L1 CPS ≥ 1) will be included in this study.

While targeting PD-1 alone has been successful in demonstrating a benefit in the response rate and OS, data from Keynote-048 trial indicates that overall responses occurred in approximately 20% of patients treated with pembrolizumab monotherapy. Differential responses are not uncommon with ICIs, as several factors play a role in response, including the degree of tumor lymphocyte infiltration, expression of the immune checkpoint proteins, and availability of neoantigens and others (Topalian et al 2016). The selection of patients who will benefit from such treatment, the identification of the most suitable treatment regimens, and the reduction of immunosuppression in non-responding patients with head and neck cancer will be vital for the future treatment of the disease. Therefore, identifying novel targeted agents that can synergize with and improve the efficacy of anti-PD-1 therapy would be beneficial to patients with R/M HNSCC.

The BGB-HNSCC-201 study is an umbrella study designed to establish proof of concept for multiple novel investigational agents in a randomized setting, in combination with a single-agent PD-1 inhibitor (tislelizumab), based on the PD-L1 expression. This Phase 2, randomized study will assess whether the addition of the investigational agent(s) targeting different biologic pathways to tislelizumab has the potential to improve and/or extend the therapeutic benefit of anti-PD-1 therapy in patients with R/M HNSCC with PD-L1 CPS ≥ 1.

1.4.2. Rationale for Tislelizumab Monotherapy and in Combination- with Investigational Agent(s) as First-Line Treatment in Patients With Recurrent or Metastatic HNSCC

In HNSCC, PD-L1 expression is relatively high, with PD-L1 positivity rates of approximately 85% (Burtness et al 2019), and is associated with poor survival. Analysis of tissue samples from patients with HNSCC shows a highly immunogenic tumor microenvironment (Mandal et al 2016). An analysis of 280 different tumors also showed that HNSCCs are among the most highly immune-infiltrated cancer types among other phenotypes indicative of an inflamed tumor.

Results from treatment with ICIs such as anti-PD-1/PD-L1 antibodies in patients with solid tumors have paved the way to a new era of cancer immunotherapy, leading to a paradigm shift in cancer treatment. In 2019, the US FDA and the European Commission approved pembrolizumab monotherapy as a first-line treatment for patients with HNSCC whose tumors express PD-L1 (CPS ≥ 1) (Keytruda [pembrolizumab] US prescribing information 2022, Keytruda [pembrolizumab] EU summary of product characteristics 2020). This revolutionized the treatment landscape for HNSCC by bringing immunotherapy into the first-line setting. The patients who were treated with pembrolizumab had a longer median OS; however, the benefits of ORR and PFS were limited. This is supported by the data that even in the patients with PD-L1 expression of CPS ≥ 20, the response rate in the first-line setting is only 23% (Burtness et al 2019). The addition of chemotherapy to ICIs has improved ORR, but it is associated with an increased toxicity burden. Therefore, identifying novel targeted agents that can synergize with and improve the efficacy of ICIs would be beneficial to patients with R/M HNSCC without chemotherapy-related toxicity.

Cancer cells have been found to have intrinsic mechanisms bypassing every step in the cancer immunity cycle to evade anticancer immunity. Across the cancer-immunity cycle, diverse mechanisms of immune escape have been reported, including defective cancer antigen presentation, immune checkpoint mediated exhaustion, decreased sensitivity to immune killing, and enriched immunosuppressive cells/cytokines (Gao et al 2017; Huang et al 2016; Koyama et al 2016; Shayan et al 2016; Topalian et al 2015; Zhu et al 2021). Several preclinical studies have shown that immunotherapy combinations may bring an additional synergistic effect, such as PD-1/PD-L1 in combination with T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain or LAG-3 (Zhu et al 2021). Overcoming the pathways of tumor immune escape may provide a mechanism justification to explore different kinds of immunotherapies or combinations and to improve the outcome. Combination therapies are currently being extensively explored in emerging clinical studies to target multiple defects along the immunity cycle and cancer intrinsic alterations to improve the anticancer efficacy.

Tislelizumab is being developed for the treatment of several types of human malignancies. Tislelizumab has been approved and is currently being marketed in China for the treatment of several cancer types including NPC (see Section 1.2.4.2.2). Results from two studies, BGB-A317_Study_001 and Study BGB-A317-102, revealed that single-agent tislelizumab was generally well tolerated and had antitumor activity in patients with advanced refractory solid tumors, including HNSCC and NPC (Shen et al 2020). In addition, data from Study BGB-A317-303 (RATIONALE 303), a Phase 3, open-label, multicenter, randomized study evaluating the efficacy and safety of tislelizumab monotherapy versus docetaxel as a second- or third-line treatment for patients with locally advanced or metastatic NSCLC of squamous or nonsquamous histology, showed a statistically significant and clinically meaningful improvement in OS with tislelizumab treatment in the ITT Analysis Set (Zhou et al 2023). In the ITT Analysis Set, the ORR among tislelizumab-treated patients was 22.6%, compared with 7.1% in patients receiving docetaxel (Zhou et al 2023). This response rate with tislelizumab monotherapy compares favorably with that of pembrolizumab in a similar patient population (Garon et al 2015). Based on available data with tislelizumab monotherapy, tislelizumab appears comparable to other anti-PD-1 inhibitors, including pembrolizumab, in terms of safety and anti-tumor activity in patients with advanced solid tumors.

Based on the information above, this study will evaluate efficacy and safety for tislelizumab as a single-agent PD-1 (reference arm) and in combination with investigational agent(s) (experimental arm) to identify novel combination therapies that could improve response rates and clinical benefit for patients with R/M HNSCC with PD-L1 CPS ≥ 1.

1.4.3. Rationale for Selection of Tislelizumab Dose

The dosage of 200 mg intravenously once every 3 weeks was selected based on safety, efficacy, and PK assessments in the first-in-human study BGB-A317_Study_001. A wide range of dosages were investigated in this study, including 2 mg/kg or 5 mg/kg on schedules of once every 2 weeks or once every 3 weeks. For the once-every-3-weeks schedule, a fixed dose of 200 mg was also investigated, and was ultimately selected for the following reasons:

- All dosages tested, including 200 mg once every 3 weeks, were tolerated. The maximum tolerated dose was not reached with dosages up to 10 mg/kg once every 2 weeks. The observed serum concentration after 200 mg dosing was within the range seen after 2 mg/kg and 5 mg/kg dosing.
- Preliminary clinical activity was observed at this dosage.
- Exposure-response relationships were flat for ORR and safety endpoints across a variety of tumor types (data from studies BGB-A317_Study_001, BGB-A317-102, and BGB-A317-203). In addition, no clinically significant covariates were identified in population PK analysis.
- Compared with doses based on patient weight, a fixed dose simplifies dose administration and reduces the chance of medical errors.
- Compared with a once-every-2-weeks schedule, a once-every-3-weeks schedule allows for more convenient integration with common chemotherapeutic regimens and increases patient convenience.

The 200-mg once-every-3-week dosing schedule of tislelizumab has also been approved by the China NMPA in multiple indications.

1.4.4. Rationale for Investigational Agents

The rationale for the use of investigational agents in the treatment of R/M HNSCC and their dose selection is provided in the investigational agent-specific appendix.

1.4.5. Biomarker Strategy Rationale

Biomarker analyses will be performed to explore pharmacodynamics of tislelizumab alone or in combination with other investigational agents, as well as the association of biomarkers with patient prognosis, response, and potential resistance to the treatment.

PD-L1 is expressed in tumor cells and tumor-infiltrating immune cells, and its expression levels were shown to correlate with the clinical efficacy of anti-PD-1 treatment in patients with R/M HNSCC. Anti-PD-1 monotherapies have been approved by the US FDA for first-line treatment of patients with HNSCC with PD-L1 expression CPS ≥ 1 based on Keynote-048 study (Burtness et al 2019). Patients with HNSCC with tumors exhibiting PD-L1 CPS ≥ 20 and CPS ≥ 1 derived significant benefit from treatment with pembrolizumab (anti-PD-1 antibody),

compared with the EXTREME chemotherapy regimen (mOS 14.9 months versus 10.7 months, HR 0.61 for CPS ≥ 20 population; 12.3 months versus 10.3 months, HR 0.78 for CPS ≥ 1 population), suggesting PD-L1 could be a predictive biomarker of response for the first-line R/M HNSCC.

In this study, PD-L1 expression will be used to guide patient selection and stratification. Additional investigational agent-specific protein and/or ligands expression will be assessed by immunohistochemistry or multiplexed immunohistochemistry or immunofluorescence to evaluate their association with efficacy.

Accumulating evidence from mouse models and human patients with cancer has demonstrated the importance of the immune system in recognizing and eliminating transformed malignant cells, as well as the contradictory role in promoting tumor progression by immune system (Yang 2015). Multiple immunotherapy strategies have been proposed to harness the immune system to battle cancer, including activating antitumor effector cells and/or removing immunosuppressive components. In this study, pharmacodynamics will be studied mainly focusing on phenotype changes of immune cells (including effector T cells, Tregs, NK cells, myeloid cells, etc) in the peripheral blood and tumor microenvironment before, during, and/or after treatment based on mechanisms of action of each investigational agent.

Proteins like cytokines/chemokines and soluble proteins released from tumor and immune cells, will also be investigated before, during and/or after treatment as they may serve as possible predictive biomarkers and/or pharmacodynamic biomarkers that may help to explore the depth of response and understanding of MoA(s).

In addition to immune phenotyping, gene expression profile analysis offers an opportunity to dissect the tumor microenvironment, a crucial mediator of cancer progression and therapeutic outcome. Biomarkers such as TMB (Cristescu et al 2018) may reflect tumor-intrinsic neoantigen generation and the capability to evoke the immune response. In the Phase 2 Keynote-495 study, high T-cell-inflamed gene signature and high TMB subgroup demonstrated highest response in different pembrolizumab combinations, including pembrolizumab with anti-LAG-3 combination (Gutierrez et al 2021). Therefore, the relationship between the clinical response to tislelizumab and combinations with gene expression profiling and tumor mutation analysis in tumor tissue will be studied to explore potential predictive biomarkers and resistance mechanism.

More recently, ctDNA derived from peripheral blood has shown incredible potential as a highly sensitive and specific cancer biomarker. Particularly, studies of the anti-PD-L1 antibody durvalumab in patients with NSCLC or urothelial carcinoma revealed a correlation between quantitative variations in ctDNA levels and tumor response or patient outcome (Kuziora et al 2017). Therefore, ctDNA of blood samples will be analyzed in this study to provide valuable information on several aspects of exploratory biomarkers, such as prognosis, detection of theranostic mutations, predictive biomarkers, early detection of treatment efficacy or disease relapse, and potential mechanisms of resistance (Cabel et al 2018).

1.5. Benefit-Risk Assessment

Tislelizumab has been approved and is currently being marketed in China for the treatment of several cancer types including for the first-line treatment of R/M NPC. Based on the data from

clinical studies, tislelizumab has been safe and well tolerated when used in combination with other anticancer therapies.

Blockade of the PD-1 pathway has demonstrated strong antitumor efficacy either alone or in combination with SOC across multiple cancer indications. Based on the evaluation of available data in 3220 patients with multiple human malignancies (2173 patients treated with monotherapy and 1047 patients treated with chemotherapy combination) as of the data cutoff date (20 July 2022), the benefit-risk assessment for tislelizumab is considered favorable. The safety profile is consistent with known class effects of anti-PD-1 antibodies and includes mostly mild and moderate AEs. Very few Grade 3 or Grade 4 imAEs have been observed, and they have been generally reversible and manageable with study drug interruption and/or corticosteroid treatment. Therefore, existing data supports the assessment that the efficacy and safety profile of tislelizumab as monotherapy and as backbone therapy in novel combinations. For further information on the safety profile of tislelizumab, see the Tislelizumab Investigator's Brochure.

The BGB-HNSCC-201 study will evaluate the efficacy and safety of the tislelizumab alone and of tislelizumab-based immunotherapy combinations as first-line treatment in patients with R/M HNSCC. Preliminary anti-tumor activity and favorable safety and tolerability for tislelizumab and tislelizumab-based immunotherapy combination has been observed in patients with HNSCC (Section 1.2.4). Based on general assessment, the sponsor believes tislelizumab-based immunotherapy combination with novel agents may provide clinical benefit by enhancing the tumor response and reducing disease recurrence.

The risk of observing augmented safety signals, as has been shown for other anti-PD-1-based immune-oncology combinations remains. Therefore, to ensure enhanced safety monitoring and minimize potential risk of imAEs related to immuno-oncology combinations, a safety monitoring plan derived from the ESMO and ASCO has been established to identify, evaluate, and manage imAEs. Additional details regarding safety assessment and risk mitigation is provided in Section 7.4 and Section 8.

The benefit-risk assessment, based on available tislelizumab data, is considered favorable.

The design of the current study aims to minimize potential risks to patients, and specifies the rules and procedures to add tislelizumab-based combination arms as follows:

- A rationale for potential synergistic activity of the novel candidate agent in combination with tislelizumab or other PD-1/PD-L1 antibody based on its MoA and supported by nonclinical or clinical evidence at the concept level
- Preliminary evidence of clinical activity of the novel agent in combination with tislelizumab or other PD-1/PD-L1 antibody in certain solid tumor settings
- An established preliminarily, recommended combination dose for the novel agent in combination with tislelizumab with an acceptable safety profile for the target population in this study.
- Requirement of a protocol amendment and respective health authority and local IRB/IEC approvals prior to implementing any new experimental arm
- Updated ICF with relevant information on the new tislelizumab-based combination arms

The benefit-risk assessment for the novel treatment combination with an investigational agent is provided in the respective appendix.

1.6. Study Conduct

This study will be conducted in compliance with the protocol approved by the IRB or IEC and in accordance with GCP standards and the applicable regulatory requirements (eg, Regulation [EU] No. 536/2014).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives and Endpoints

Table 2: Objectives and Endpoints

Primary:	
Objectives	**Endpoints**
To assess the antitumor activity of tislelizumab plus investigational agent(s)	Confirmed objective response rate (ORR) as assessed by the investigators per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1
Secondary:	
Objectives	**Endpoints**
To further assess the antitumor activity of tislelizumab plus investigational agent(s)	Progression-free survival (PFS), duration of response (DOR), clinical benefit rate (CBR), and disease control rate (DCR) as assessed by the investigators per RECIST v1.1
To assess the safety and tolerability of tislelizumab plus investigational agent(s)	The incidence and severity of adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) in reference arm (tislelizumab alone) and experimental arms (tislelizumab plus investigational agent[s])
To assess overall survival (OS)	OS
Exploratory:	
Objectives	**Endpoints**
To characterize the pharmacokinetics (PK) of tislelizumab and investigational agent(s) given in combination with tislelizumab	Plasma or serum concentrations of tislelizumab and investigational agents at specified timepoints
To assess time to the first objective tumor response	Time to response (TTR) (ie, time to the first objective response) as assessed by the investigators per RECIST v1.1

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, programmed cell death ligand-1 (PD-L1), investigational agent-specific protein and/or ligands expression, tumor-infiltrating immune cells, gene expression profiling, tumor mutation analysis and HPV positive or negative status in tumor tissue, immunophenotyping in peripheral blood cells, concentrations of cytokine/chemokine and soluble proteins in plasma and/or serum, circulating tumor DNA (ctDNA)/blood tumor mutational burden (bTMB)/mutation profile in peripheral blood.

3. STUDY DESIGN

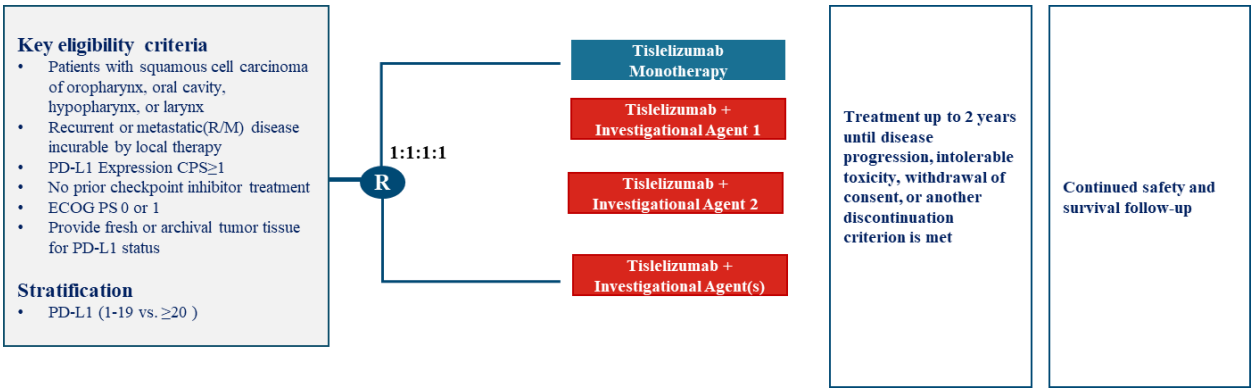
3.1. Summary of Study Design

This is a randomized, open-label, multicenter, Phase 2, multi-arm study designed to evaluate the efficacy and safety of tislelizumab and tislelizumab in combination with investigational agent(s) in first-line R/M HNSCC with PD-L1 positive expression CPS ≥ 1. Patients will be randomized to receive either tislelizumab + investigational agent(s) (experimental arm[s]) or tislelizumab monotherapy (reference arm). The initial randomization ratio between each of the experimental arms and the common reference arm will be 1:1.

Randomization in each treatment arm will be stratified based on PD-L1 expression (CPS 1 to 19 versus ≥ 20). A 1:1 randomization ratio is initially applied to each of the experimental arms and the common reference arm. The randomization ratio may be modified to account for emerging safety data, efficacy data, and feasibility considerations. The total number of patients depends on the number of experimental arms and the timing when they are added to the study.

The study design schematic is presented below.

Figure 1: Study Schema



Abbreviations: CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-L1, programmed cell death protein ligand-1; R/M, recurrent or metastatic; R, randomization.

Treatments in each arm will be administered as follows:

- Reference arm: tislelizumab
- Experimental arm(s): tislelizumab + investigational agent(s)

The details regarding specific treatment regimens/requirements for investigational agents are provided in each appendix.

Study treatments in all arms will be administered for up to 2 years until disease progression, intolerable toxicity, withdrawal of informed consent, or another discontinuation criterion is met, whichever occurs first.

Tumor response will be assessed by the investigators using standard RECIST v1.1 criteria. Tumor imaging must be performed within 28 days before randomization/enrollment. On-study tumor assessments will occur every 6 weeks (± 7 days) from randomization for the first 52 weeks and then every 12 weeks (± 7 days) thereafter. See Section 7.5 for more details.

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per NCI-CTCAE v5.0) and laboratory results. Vital signs, physical examinations, ECOG Performance Status changes, ECG results, and other examinations will also be used for safety assessments.

An independent Safety Oversight Committee that is composed of members who are otherwise not directly associated with the study will be established to assess the safety periodically throughout this study. This committee may recommend actions including discontinuation or modification for a specific investigational agent due to safety concerns.

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

3.2. Screening Period

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

Patients are required to provide archival tumor tissues (FFPE blocks or approximately 15 freshly cut unstained slides) for prospective analysis of PD-L1 expression (if local PD-L1 data are not available or in mainland China, in screening period) and for retrospective analysis of exploratory biomarkers (before Cycle 1 Day 1). Archival tissue collected within 6 months from screening is strongly preferred. However, archival tissue collected within 2 years is acceptable. Refer to Section 7.1 for more details.

3.3. Treatment Phase

After completing all screening activities, eligible patients will be randomized at a ratio of 1:1 to each of the experimental arms and the reference arm, respectively.

- Reference arm: tislelizumab 200 mg intravenously once every 3 weeks
- Experimental arm(s): tislelizumab 200 mg intravenously once every 3 weeks + investigational agent(s)

Details for treatment administration, investigational agent cycles, and on-treatment procedures to be performed are provided in investigational agent-specific appendix.

Study treatments in all arms will be administered for up to 2 years until disease progression, intolerable toxicity, withdrawal of informed consent, or another discontinuation criterion is met, whichever occurs first (see Section 3.4).

Tumor assessments are required to be performed on schedule, regardless of whether study treatment has been administered or held (ie, the patient's schedule should not be adjusted for delays in cycles). Tumor response will be assessed by the investigators using standard RECIST v1.1 criteria. Tumor imaging (CT with or without contrast and/or MRI) must be performed within 28 days before randomization/enrollment. On-study tumor assessments will occur every 6 weeks (± 7 days) from randomization for the first 52 weeks and then every 12 weeks (± 7 days) thereafter. Tumor assessments should continue until disease progression occurs, as determined

by the investigators. Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient experiences disease progression, dies, withdraws consent, is lost to follow-up, or until the study terminates, whichever occurs first. See Section 7.5 for details.

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per NCI-CTCAE v5.0 and laboratory results. Vital signs, physical examinations, ECOG Performance Status changes, ECG results, and other examinations will also be used for safety assessments. Safety assessments are further detailed in Section 7.4 and investigational agent-specific appendix.

3.4. 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 study treatment for reasons other than disease progression should be followed for assessments of antitumor activity (Section 7.5), safety (Section 7.4) and survival (Section 3.6), if possible.

The primary reason for discontinuation from the study treatment should be documented on the appropriate eCRF. Patients may discontinue study treatment for reasons that include but are not limited to the following:

- Disease progression assessed by the investigator per RECIST v1.1
- AE(s)
- Patient decision
- Pregnancy
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she were to continue the study treatment
- Use of any concurrent systemic anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other country) herbal medicine and Chinese (or other country) patent medicines] for the treatment of cancer)
- Patient noncompliance
  Investigative site staff should first counsel patients who are significantly noncompliant (eg, missing 2 treatment cycles) on the importance of study drug compliance and drug accountability. The investigator may discontinue patients from treatment who are consistently noncompliant.
- Completion of planned treatment(s)

Patients who discontinue study treatment before disease progression will continue to undergo tumor assessments as outlined in Section 7.5.

3.5. End-of-Treatment and Safety Follow-up Visit

Patients who discontinue from study treatment for any reason will be asked to return to the clinic for an EOT Visit, which is required to be conducted within 7 days after the investigator decides to permanently discontinue study treatment or before the initiation of a new anticancer treatment, whichever occurs first. A Safety Follow-up Visit is required to occur 30 days (± 7 days) after the last dose of study drug(s) or before the initiation of a new anticancer treatment, whichever occurs first, unless the time window overlaps with the time window of the EOT Visit. The Safety Follow-up Visit may be a telephone call or an on-site visit if laboratory assessments are necessary. See Appendix 1 for assessments to be performed at the EOT Visit and the Safety Follow-up Visit.

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

For women of childbearing potential, an additional visit to perform a pregnancy test should be conducted at qualified local laboratories following the longest contraception requirement. See Appendix 11 for more details.

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

3.6. Survival Follow-up

Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months after the EOT/Safety Follow-up Visit until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up. See Section 3.9.

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

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

- Patient withdrawal of consent from study treatment and follow-up
- Noncompliance
- Death
- Lost to follow-up (at minimum, 3 contact attempts must be made and documented in the source documents)
- Patient completion of all study assessments

3.8. Criteria for Pausing Enrollment or Early Termination of Experimental Arm(s)

The sponsor may pause further enrollment or terminate any of the experimental arm(s) at any time based on criteria provided in Section 9.7.

3.9. End of Study

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

The sponsor has the right to terminate this study or any of the experimental arms 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
- A rollover study becomes available

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

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the IRB/IEC of the early termination of the study.

3.9.1. Continued Access to Study Drug During the Extended IP Access Period

The Extended IP Access Period was established to provide continued access to study treatment after the sponsor's completion of the main study objectives. The Extended IP Access Period will begin when Protocol Amendment 2.0 becomes effective. At the time of initiation of the Extended IP Access Period, any patient on treatment and, in the opinion of the investigator, who continues to benefit from study drug(s), will be offered the option to continue treatment until the current supply of IP is unavailable, any discontinuation criterion specified in Section 3.4 is met, or until the patient receives the maximum of 2 years of study drug(s), whichever occurs first. Patients who enter the Extended IP Access Period will re-sign the informed consent form.

During the Extended IP Access Period, patient management and monitoring, including tumor and response evaluations, safety assessments, study drug modifications, and follow-up will be concordant with the protocol or per the investigator's discretion based on local or institutional guidelines. No further data will be collected by the sponsor in eCRFs. However, as a part of patient management, the investigator must collect and maintain patient clinical source documents per the requirements of local institutions. All SAEs should still be reported to the sponsor safety database through paper forms per requirements and timelines described in Section 8.6.2. Samples for PK, ADA, and biomarker assessments will not be collected during the Extended IP Access Period.

4. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The patients enrolled in the randomization phase must meet all the common and investigational agent-specific eligibility criteria for treatment with the investigational agent combination. If a patient does not meet the eligibility criteria for one of the investigational agents in the study, randomization/enrollment will be allowed to one of the other available eligible treatment arms. The sponsor will not grant any eligibility waivers.

If applicable, additional inclusion/exclusion criteria for a specific experimental arm will be presented in the investigational agent-specific appendix. In addition to the inclusion and exclusion criteria in the protocol body, investigational agent-specific inclusion and exclusion criteria should be met based on patient assignment.

4.1. Inclusion Criteria

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

1. Patient must sign a written ICF and understand and agree to comply with the requirements of the study and the schedule of assessments.
2. Adult patients (≥ 18 years of age or of acceptable age according to local regulations, at the time of voluntarily signing of informed consent) with histologically or cytologically confirmed R/M HNSCC that is considered incurable by local therapies
   a. The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx.
   b. Subjects should not have had prior systemic therapy administered in the R/M setting. Systemic therapy which was completed prior to randomization/enrollment if given as part of multimodal treatment for locally or locoregionally advanced disease is allowed.
3. Patients must have positive PD-L1 expression (CPS ≥ 1) as determined by a local laboratory (using PD-L1 IHC 22C3 pharmDx assay) or by 22C3 pharmDx assay in central testing on archival tumor tissue or fresh biopsy. Patients with unknown or low (CPS < 1) PD-L1 expression will not be eligible for this study.

   Note: For study sites in mainland China, PD-L1 expression (CPS ≥ 1) will be determined by a central laboratory.
4. Agreement to provide archival tumor tissue (FFPE block containing tumor [preferred] or approximately 15 freshly cut unstained slides). Archival tissue collected within 6 months from screening is strongly preferred. However, archival tissue collected within 2 years is acceptable. In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion is required before Cycle 1 Day 1. Refer to Section 7.7 for additional details.
5. Have at least 1 measurable lesion as defined per RECIST v1.1.

   Note: A lesion in an area subjected to prior locoregional therapy, including previous radiotherapy, is not considered measurable unless there has been demonstrated progression in the lesion since such therapy as defined by RECIST v1.1.
6. ECOG Performance Status of 0 or 1

7. Adequate hematologic and organ function as indicated by the following laboratory values within 7 days of first dose of study drug :
    a. Patients must not have required blood transfusion or growth factor support ≤ 14 days before sample collection at screening for the following:
        i. Absolute neutrophil count ≥ 1.5 x 10^9/L
        ii. Platelets ≥ 75 x 10^9/L
        iii. Hemoglobin ≥ 90 g/L
    b. Estimated creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault equation (Appendix 9).
    c. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilbert syndrome).
    d. AST and ALT ≤ 2.5 x ULN.
8. Women of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of study drug(s). They must also have a negative urine or serum pregnancy test result at screening and ≤ 7 days before first dose. See Appendix 11 for investigational agent-specific requirements.
9. Nonsterile males must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of study drug(s)
    a. A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
    b. Males with known “low sperm counts” (consistent with “subfertility”) are not to be considered sterile for purposes of this study.

4.2. Exclusion Criteria

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

1. Recurrent or metastatic carcinoma of the nasopharynx (any histology), squamous cell carcinoma of unknown primary, squamous cell carcinoma that originated from the skin and salivary gland primary tumor or non-squamous histologies (eg, mucosal melanoma).
2. Has disease that is suitable for local therapy administered with curative intent.
3. Has a life expectancy of less than 3 months and/or has rapidly progressing disease (eg, tumor bleeding, uncontrolled tumor pain) in the opinion of the treating investigator.
4. Prior therapy with an anti-PD-1, anti-PD-L1, PD-L2, T-cell immunoglobulin and TIM-3, LAG-3, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.
5. Has received any Chinese herbal medicine or Chinese patent medicines used to control cancer ≤ 14 days before randomization/enrollment
6. Active leptomeningeal disease or uncontrolled, untreated brain metastasis

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

a. Brain imaging at screening shows no evidence of interim progression, and there is no evidence of new brain metastases
b. Patient is clinically stable for ≥ 2 weeks
c. Brain metastases are not the only site of disease
d. No ongoing requirement for corticosteroids as therapy for CNS disease; off corticosteroids 3 days before randomization/enrollment; anticonvulsants at a stable dose are allowed
e. No stereotactic radiation or whole-brain radiation ≤ 14 days before randomization/enrollment
f. No evidence of leptomeningeal disease

7. Active autoimmune diseases or history of autoimmune diseases that may relapse (Appendix 5)

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

   a. Controlled type 1 diabetes
   b. Hypothyroidism (managed with hormone replacement therapy only)
   c. Celiac disease controlled by diet alone
   d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia)
   e. Any other disease that is not expected to recur in the absence of external triggering factors

8. Any active malignancy ≤ 2 years before randomization/enrollment except for the specific cancer under investigation in this study, those with a negligible risk of metastasis or death, and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, localized prostate cancer, and carcinoma in situ of the cervix or breast)

9. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before randomization/enrollment

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

   a. Adrenal replacement corticosteroid (dose ≤ 10 mg daily of prednisone or equivalent)
   b. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption
   c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy, premedication prior to pemetrexed or paclitaxel) or for the treatment of a nonautoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)

10. With uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before randomization/enrollment

11. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence ≤ 14 days after intervention). Patients with symptomatic pleural

effusion are excluded unless the patient undergoes a therapeutic thoracentesis or has had pleurodesis (> 14 days before randomization/enrollment) with subsequent stable effusions.

12. History of interstitial lung disease, noninfectious pneumonitis, or uncontrolled lung diseases including pulmonary fibrosis, and acute lung diseases.

13. Infection (including tuberculosis infection) requiring systemic (oral or intravenous) antibacterial, antifungal, or antiviral therapy ≤ 14 days before randomization/enrollment, or patients with symptomatic COVID-19 infection. Patients who have recovered from symptomatic COVID-19 infection can be rescreened on this study.

    Note: Antiviral therapy is permitted for patients with chronic infection with HBV or infection with HCV. Patients receiving prophylactic antibiotics (eg, for the prevention of urinary tract infection, chronic obstructive pulmonary disease, or for dental extraction) are eligible.

14. Untreated chronic hepatitis B or chronic HBV carriers with HBV DNA ≥ 500 IU/mL (or ≥ 2500 copies/mL) at screening

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

15. Patients with active hepatitis C

    Note: Patients with a negative HCV antibody test at screening or positive HCV antibody test followed by a negative HCV RNA test at screening are eligible. The HCV RNA test will be performed only for patients testing positive for HCV antibody. Patients receiving antivirals at screening should have been treated for > 2 weeks before randomization/enrollment.

16. Known history of HIV infection

17. Any major surgical procedure ≤ 28 days before randomization/enrollment. Patients must have adequately recovered from the toxicity and/or complications from the intervention before randomization/enrollment.

18. Prior immunodeficiency, allogeneic stem cell transplantation or organ transplantation

19. Any of the following cardiovascular risk factors:

    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before randomization/enrollment
    b. Symptomatic pulmonary embolism ≤ 28 days before randomization/enrollment
    c. Any history of acute myocardial infarction ≤ 6 months before randomization/enrollment
    d. Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 6) ≤ 6 months before randomization/enrollment
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before randomization/enrollment

f. Any history of cerebrovascular accident ≤ 6 months before randomization/enrollment
g. Uncontrolled hypertension that cannot be managed by standard antihypertension medications ≤ 28 days before randomization/enrollment
h. Any episode of syncope or seizure ≤ 28 days before randomization/enrollment

20. A history of severe hypersensitivity reactions to other monoclonal antibodies or has experienced a severe imAE, an imAE that led to treatment discontinuation, or a cardiac or ocular imAE of any grade with prior immunotherapy
21. Has received any chemotherapy, immunotherapy (eg, interleukin, interferon, thymosin, etc) or any investigational therapies ≤ 14 days or ≤ 5 half-lives (whichever is shorter) before randomization/enrollment
22. Was administered a live vaccine ≤ 28 days before randomization/enrollment

    Note: Vaccines for COVID-19 are allowed except for any live vaccine that may be developed. Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
23. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug, will affect the explanation of drug toxicity or AEs, or will result in insufficient or impaired compliance with study conduct
24. Women who are pregnant or are breastfeeding
25. Concurrent participation in another therapeutic clinical study
    Note: Concurrent participation in observational or noninterventional studies is allowed. In addition, patients who have completed active treatment in a clinical study and are in the follow-up period can be enrolled in this study.
26. Patients with toxicities (as a result of prior anticancer therapy) that have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, ≤ Grade 2 neuropathy). Prior radiotherapy must have been completed at least 2 weeks prior to randomization/enrollment.
27. Vulnerable adults who are under legal protection or safeguarded by the courts.

Investigational agent-specific eligibility criteria are provided in the corresponding appendix.

5. STUDY TREATMENT

Details regarding study treatment, including the medicine product approval status, formulation, administration, and dose modification of study drugs, are provided in each investigational agent-specific appendix.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

All prior cancer related treatments, treatments for underlying active medical conditions, and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient ≤ 30 days before Day 1 of Cycle 1 must be recorded in the appropriate eCRF.

6.2. Concomitant Therapy

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

6.2.1. Permitted Concomitant Medications/Procedures

Most concomitant medications and therapies deemed necessary and in keeping with the local standards of medical care at the discretion of the investigator for the supportive care (eg, antiemetics, antidiarrheals, pain medications, and nutritional support) and for a patient's wellbeing are allowed. All concomitant medications will be recorded in the eCRF including all prescriptions, over-the-counter drugs, herbal supplements, and intravenous medications and fluids. If changes (dose, stop, or start) in concomitant medication occur during the study, documentation of drug dosage, frequency, route, date, and reason for use will be recorded in the eCRF. All concomitant medications received ≤ 30 days before Day 1 of Cycle 1 and 30 days after the last infusion or dose of study treatment should be recorded.

Liver function tests should be carefully monitored in patients taking concomitant medications with potential hepatotoxic effects.

6.2.1.1. Systemic Corticosteroids

Systemic corticosteroids for management of imAEs must be tapered gradually (see Appendix 7) and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next study treatment administration. The short-term use of steroids as prophylactic treatments (eg, for patients with allergies to diagnostic imaging contrast dyes) is permitted.

6.2.1.2. Hepatitis B Treatment

Patients with active hepatitis B, defined as HBV DNA ≥ 500 IU/mL, at screening must initiate treatment > 2 weeks before randomization/enrollment and continue until 6 months after the last dose of study drug(s). Patients should continue effective antiviral treatment during the study to decrease the risk of viral reactivation.

Tenofovir and entecavir are recommended in the AASLD guidelines because they lack resistance with long-term use (Terrault et al 2016; AASLD/IDSA HCV Guidance Panel 2015). The investigator may use other antiviral agents, if appropriate, following local guidelines. However, interferon-based therapy for hepatitis B is not permitted in this study.

Management of prophylactic antiviral therapy for patients with inactive, treated, and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) is at the discretion of the investigator, as aligned with local guidance. Such medications must be documented in the patient's chart and recorded in the eCRF. Patients receiving antivirals at screening should be treated for > 14 days before randomization/enrollment. Once initiated, antiviral treatment should continue until 6 months after the last dose of study treatment or as permitted by local guidance.

6.2.1.3. Hepatitis C Treatment

Patients with detectable HCV RNA at screening should be referred to hepatologists for consultation on receiving antiviral therapy before they receive study treatment; patients with detectable HCV RNA who are receiving treatment at screening must meet the criterion of negative HCV RNA to be eligible or should remain on continuous, effective antiviral therapy during the study as recommended by their hepatologist or the treating physician following the international or local guidelines as appropriate. Patients given antiviral therapy must not enroll until > 2 weeks after the initiation of such therapy and continue treatment during the study and for 6 months after study treatment discontinuation. Investigators can consider treatment following the AASLD guideline or the local guidelines, as appropriate. However, interferon-based therapy for HCV is not permitted in this study.

6.2.1.4. COVID-19 Vaccines

Vaccines for COVID-19 are allowed except for any live vaccine (ie, live SARS-CoV-2 virus) that may be developed. Attenuated (vector) COVID-19 vaccines are inactivated vaccines and as such, are permitted. It is recommended to avoid COVID-19 vaccination within 72 hours before or after study drug(s) administration during the first 2 treatment cycles and within 24 hours before or after study drug(s) administration thereafter (ie, from Cycle 3 onwards). Vaccinations are considered a concomitant medication and hence should be entered in the eCRF. The specific COVID-19 vaccine should be recorded instead of generic language, eg, mRNA-1273 vaccine (Moderna), BioNTech vaccine (Pfizer), etc.

6.2.1.5. Radiation Therapy

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

- Repeated 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 have been met

Additionally, palliative radiation or other focally ablative therapy for other nontarget sites of the disease is permitted if the investigator determines that it is clinically indicated. The medical monitor should be informed of the on-study radiotherapy. These patients should have a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out progression of disease.

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

6.2.2. Prohibited Concomitant Medications/Procedures

Live vaccines ≤ 28 days before randomization/enrollment and ≤ 60 days after the last dose of study drug(s) are prohibited.

The following medications are prohibited during screening and through the EOT Visit:

- Any concurrent systemic anticancer therapy, including chemotherapy, hormonal therapy, immunotherapy, standard anticancer agents, or investigational anticancer agents
- Herbal remedies for the treatment of cancer or Chinese patent medicines with approval from the China NMPA for use as anticancer treatment (regardless of cancer type) (Appendix 12)
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (eg, hypericin) (Appendix 12)

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

6.2.3. Restricted Concomitant Medications/Procedures

The following medications/procedures are restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE)
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug related AE (per protocol) or for short-term use as prophylactic treatment
- Patients should not abuse alcohol or other drugs during the study.
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored (Appendix 13). lists drugs with potential hepatotoxic effects. Liver function tests should be carefully monitored in patients taking these concomitant medications.
- Radiation therapy is not allowed, except for palliative radiation therapy described in Section 6.2.1.5.
- Surgeries, except:
  - To treat an AE (eg, appendectomy)
  - Curative surgery when, after study treatment, a previously inoperable lesion becomes operable

Additional prohibited/restricted concomitant medications specific to the investigational agent(s) are provided in the investigational agent-specific appendix.

6.3. Potential Interactions Between the Study Drugs and Concomitant Medications

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

7. STUDY ASSESSMENTS AND PROCEDURES

A table of scheduled study assessments is provided in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study. In addition to the common assessments and procedures stated in this section, additional assessment requirements for each experimental arm are provided in the respective agent-specific appendix, if applicable. All assessments must be performed and documented in the medical record for each patient.

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

7.1. Screening

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

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

Only patients with positive PD-L1 (CPS ≥ 1) expression determined by specified PD-L1 IHC testing will be considered eligible. PD-L1 positivity determined from either local documented result (using PD-L1 IHC 22C3 pharmDx assay) or by 22C3 pharmDx assay in central analysis will be acceptable (Note: for study sites in mainland China, PD-L1 expression [CPS ≥ 1] will be determined by a central laboratory). If the patient has more than 1 PD-L1 result available during screening phase, the most recent PD-L1 result should be used for PD-L1 positivity determination.

- For patients who have known PD-L1 positivity, a local documented result is acceptable for PD-L1 positivity confirmation by 22C3 pharmDx assay at the screening phase. An archival tumor tissue or fresh biopsy is required prior the patient commencing first drug administration on Cycle 1 Day 1. Archival tissue collected within 6 months from screening is strongly preferred. However, archival tissue collected within 2 years is acceptable. It is highly recommended to provide the same tissue that was tested for the local PD-L1 assay.
- For patients who are unable to provide a local documented PD-L1 result, or for study sites in mainland China, patients will be required to submit archival tumor tissue or fresh biopsy for PD-L1 positivity determination in a central laboratory. Archival tissue collected within 6 months from screening is strongly preferred. However, archival tissue collected within 2 years is acceptable.

In all of above situations, PD-L1 status will also be retrospectively evaluated on the archival tumor tissues or fresh biopsy samples by 22C3 pharmDx (if local PD-L1 data used for randomization/enrollment), and VENTANA PD-L1 (SP263) assay. Refer to Section 7.7 for more details.

For descriptions of other assessments conducted during screening, see Section 7.4, Section 7.5, and Section 7.7.

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

7.1.1. Informed Consent and Screening Log

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

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

7.1.2. Patient Numbering

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

Patients who are rescreened (see Section 7.1) will be assigned a new patient number. Screening numbers assigned to the same patient within the IRT system will be linked. Rescreening is allowed one time per patient.

7.1.3. Female Patients of Childbearing Potential and Contraception

Childbearing potential is defined as being physiologically capable of becoming pregnant. Refer to Appendix 10 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential".

7.2. Enrollment

7.2.1. Confirmation of Eligibility

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

Sponsor verification of patient eligibility will be managed by way of source data verification in accordance with ICH E6.

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

7.2.2. Enrollment/Randomization

All other patients will be randomized to a treatment arm according to the randomization ratios specified in Section 3 and Section 9.1.1 after enrollment.

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

Study treatment must commence ≤ 2 business days after randomization/enrollment.

7.3. Study Drug Dispensation

Study treatment will be dispensed and administered as described in investigational agent-specific appendix.

7.4. Safety Assessments

In addition to the common safety assessments described in this section, additional requirements for safety assessments for each experimental arm are provided in the respective investigational agent-specific appendix, if applicable.

7.4.1. Vital Signs

See Appendix 1 for vital signs to be collected and the timing of their collection.

Vital signs and weight measurements are required on Day 1 of the first cycle, on Day 1 of each subsequent cycle, and at the EOT Visit. Height measurements are only required at screening.

Vital signs are required to be recorded ≤ 60 minutes before, during, and 30 minutes after the first infusion completed of study drug(s) on Day 1 of Cycle 1. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and if clinically indicated, during and 30 minutes after the infusion.

7.4.2. Physical Examinations

During the Screening Visit, a complete physical examination will be conducted, including evaluations of 1) head, eyes, ears, nose, and 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 eCRF with appropriate disease/condition terms.

Patients should be solicited at every visit for signs of uveitis such as changes in visual acuity or intraocular inflammation (eg, blurred/distorted vision, blind spots, change in color vision, photophobia, tenderness/pain, and eyelid swelling) and referred to an ophthalmologist where slit lamp biomicroscopy should be considered, if warranted, for further evaluation if visual changes are reported. For patients with symptomatic vision changes, dosing of study drug should be held until uveitis can be ruled out by an ophthalmologist.

At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed.

New or worsened clinically significant abnormalities are to be recorded as AEs on the eCRF. Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

7.4.3. Eastern Cooperative Oncology Group Performance Status

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

7.4.4. Laboratory Safety Tests

Local laboratory assessments of serum chemistry, hematology, coagulation, urinalysis, and thyroid function will be conducted as described in Appendix 1. Specific assessments to be performed are listed in Appendix 2.

7.4.4.1. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune checkpoint inhibitors, serum creatinine kinase and creatinine kinase cardiac isoenzyme will be monitored to protect study participants and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 7 for guidelines for the management of suspected immune-mediated myocarditis). Serum troponins may be substituted per local guidelines if used consistently throughout the study.

7.4.5. Electrocardiograms

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 source documents at the site.

When coinciding with blood sample collection at the same timepoint, the ECG assessment should be performed prior to the blood sample collection. Patients should rest in a semirecumbent supine position for ≥ 10 minutes prior to the ECG recording.

7.4.6. Adverse Events

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

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

7.4.7. Hepatitis B and C Testing

Testing will be performed by a local laboratory at screening and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody, hepatitis B core antibody, and HCV antibody). In patients who test positive for HBsAg or HCV antibody, these tests will be followed by a viral load assessment (HBV DNA and HCV RNA).

Inactive HBsAg carriers and patients with treated and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Patients who have detectable HBV DNA at screening will have a viral load test performed every 4 cycles (eg, Day 1 of Cycles 5, 9, 13, etc).

Patients with a negative HCV antibody test at screening or positive HCV antibody test followed by a negative HCV RNA test at screening can be enrolled. The HCV RNA test will be performed only for patients testing positive for HCV antibody. Patients who have detectable HCV RNA at screening will have a viral load test performed every 4 cycles (eg, Day 1 of Cycles 5, 9, 13, etc).

7.5. Tumor and Response Evaluations

Tumor imaging will be performed ≤ 28 days before randomization/enrollment. Radiological images captured as SOC before obtaining informed consent and ≤ 28 days before randomization/enrollment may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed every 6 weeks (± 7 days) from randomization for the first 52 weeks, then every 12 weeks (± 7 days) after 52 weeks based on RECIST v1.1. If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted on the planned schedule.

Screening assessments and each subsequent assessment of the tumor must include CT scans (with oral and/or intravenous contrast, unless contraindicated) or an MRI. In addition to the brain/head, neck, chest, abdomen, pelvis, all known sites of disease should be assessed at baseline. The head (including brain), neck, chest, abdomen, pelvis, and other known or suspected sites of disease must be included in the imaging assessments.

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

- Imaging of the brain (preferably MRI) at baseline is required for all screened patients. Screening evaluations will be performed ≤ 28 days before randomization/enrollment. Subsequent assessments should include the brain (only if brain metastases are detected at screening, or if clinically indicated during the course of the trial).
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a PET/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- Bone scans (technetium-99m) or PET should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans, technetium-99m or PET bone scans should be repeated when a CR is suspected in the target lesion or when progression in bone is suspected.
  - If bone metastases are visualized on the bone scan or PET scan at screening, a confirmatory CT/MRI scan should be performed. If the metastases are confirmed by CT/MRI, then evaluation by CT/MRI should be given preference for subsequent assessments. If the metastases are not confirmed by CT/MRI, then the use of bone scan or CT/MRI for subsequent assessments is at the investigator's discretion.
  - If an increase in the uptake of existing lesions is seen on a bone scan, or the appearance of new osteoblastic bone lesions is seen on an x-ray, CT, or MRI, this should not automatically be considered evidence of progression in an otherwise stable or responding subject. It may in fact be indicative of response to therapy.

  - New areas of uptake seen on a bone scan should not automatically result in diagnosis of progressive disease but should be correlated with other available imaging (eg, CT, MRI, or x-ray).
- At the investigator's discretion, other methods of assessing target lesions and nontarget lesions per RECIST v1.1 may be used. However, CT or MRI should be given preference for assessment of target lesions.

Response will be assessed by the investigator using RECIST v1.1 (see Appendix 4). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

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

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

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

7.6. Pharmacokinetic Testing

Blood samples may be collected for PK characterization of tislelizumab and investigational agents. The serum or plasma (as appropriate) samples may be assayed for tislelizumab and/or investigational agent concentrations using validated bioanalytical methods.

The timing for blood sample collection for PK assessment and ADA testing is specified in the Schedule of Assessments (Appendix 1).

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

Blood samples for PK or ADA analyses will not be collected during the Extended IP Access Period. See Section 3.9.1

7.7. Biomarkers

Shipping, storage, and handling of blood, archival tumor, fresh tumor, and leftover 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 Assessments (Appendix 1) for sample collection timepoints.

Blood or tissue samples for biomarker analysis will not be collected during the Extended IP Access Period. See Section 3.9.1

7.7.1. Tissue Biomarkers

During the screening period, positive PD-L1 (CPS ≥ 1) expression determined by a local laboratory (using PD-L1 IHC 22C3 pharmDx assay) or by 22C3 pharmDx assay in central testing are required.

For patients who have known PD-L1 positivity, a local documented result is acceptable for PD-L1 positivity confirmed by 22C3 pharmDx assay at the screening phase. For patients unable to provide a local documented PD-L1 result, PD-L1 positivity will be determined in a central laboratory (Note: for study sites in mainland China, PD-L1 expression (CPS ≥ 1) will be determined by a central laboratory).

For all patients, an archival tumor tissue (FFPE block or approximately 15 freshly cut unstained slides) or fresh tissue biopsy (if archival tissue is not available) is required prior to the patient commencing first drug administration on Cycle 1 Day 1. Archival tissue collected within 6 months from screening is strongly preferred. However, archival tissue collected within 2 years is acceptable. 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. PD-L1 status will also be retrospectively evaluated on the archival tumor tissues or fresh biopsy samples by 22C3 pharmDx (if local documented result used for randomization/enrollment), and VENTANA PD-L1 (SP263) assay.

After 2 cycles of treatment (approximately Cycle 3 Day 1), patients will be strongly recommended to provide optional fresh biopsy samples for the evaluation of pharmacodynamic effects, if available. To explore resistance mechanisms, optional biopsies will be taken from accessible tumor sites for treated patients who has disease progresses during the study. Ideally and if feasible, post-treatment biopsies should be taken from the same tumor lesion as the baseline biopsy/fresh tumor tissues.

HPV status will be explored for clinical response/resistance or treatment benefit. Documentation of p16 expression by local testing is sufficient to determine HPV status for patients with oropharyngeal cancer.

Tissue samples obtained as described above will be shipped to a sponsor-designated central laboratory for biomarker testing after local regulatory approval. This may occur after the start of study treatment if necessary. Biomarker analysis in tumor tissues will include but not be limited to, PD-L1 expression, investigational agent-specific protein, and/or ligands expression. In addition, other exploratory biomarkers, such as TIL assessment, GEP, tumor mutation analysis, and HPV status, that are related to response or clinical benefit of investigational agents may also be evaluated. For study sites in mainland China, tumor tissue will be collected to test the expression of PD-L1, target or ligand proteins of investigational agents, tumor-infiltrating immune cells, GEP, tumor mutation profile and HPV status.

Written informed consent is required for any optional fresh tumor biopsy. Tumor tissue should be of good quality based on total and viable tumor content. Fine needle aspiration, brushing, cell pellets from pleural effusion, lavage samples, and bone/bone marrow aspirates are not acceptable.

7.7.2. Blood Biomarkers

Blood samples will be collected at specified times as described in Appendix 1 for the evaluation of biomarkers including but not limited to, immunophenotyping quantification and phenotype change in peripheral blood cells, concentration and dynamic changes of cytokines/chemokines and soluble proteins in plasma and/or serum, and ctDNA/bTMB/mutation profile in peripheral blood. Analysis may include the association between these biomarkers and clinically relevant outcomes including response, resistance, and prognosis. For study sites in mainland China, blood-based biomarkers will be included cytokines/chemokines and soluble proteins, immunophenotyping, and ctDNA/TMB/mutation profiling.

7.8. Visit Windows

All visits must occur within ± 3 days of the scheduled date, unless otherwise noted (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 (Day 1 of each cycle) should be performed before study drug administration unless otherwise noted. Laboratory results should also be reviewed before study drug administration.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled on the nearest feasible date (the visit window is provided in Appendix 1).

A cycle is defined as having a duration of 21 days. Subsequent visits should be conducted according to a new 21-day schedule based on the date of the patient's last treatment of investigational agent(s).

7.9. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the investigator's request and may include assessment of vital signs/focused physical examination, ECOG Performance Status, AE review, review of concomitant medications and procedures, radiographic assessments, physical examination of the liver, spleen, and lymph nodes, review of 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 the investigator's assessment as appropriate, and the results of the diagnostic tests and images 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 Study Treatment

The information on the risks associated with each investigational agent is provided in the investigational agent-specific appendix.

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies and clinical data with investigational agent(s) as well as the nonclinical/clinical data from other immunotherapy combination(s) containing PD-L1/PD-1 inhibitors, were considered. Specifically, patients at risk for developing study-emergent active autoimmune diseases or who have a history of autoimmune diseases that may relapse, patients who have undergone allogeneic stem cell or organ transplantation, and patients who have received a live vaccine ≤ 28 days before randomization are excluded from the study (see Section 4.2 for the full list of exclusion criteria).

8.2.2. Safety Monitoring Plan

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

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

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

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

8.3. Adverse Events

8.3.1. Definitions and Reporting

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to the study treatment 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
- Detection or diagnosis of a new condition after study treatment administration, even though the condition may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment 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. There may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers must be blinded or redacted on the copies of the medical records prior to submission to the sponsor.

8.3.2. Assessment of Severity

The investigator will assess the severity of each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon 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 ADL
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

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

8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study treatment and the occurrence of each AE or SAE, using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the administration of study treatment should be considered and investigated. The investigator should consult the Investigator's Brochure of each study drug in the determination of his/her assessment.

There may be situations when an SAE has occurred and the investigator only has limited information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses causality for every SAE before transmitting the SAE report to the sponsor, because the causality assessment is one of the criteria used in determining regulatory reporting requirements. After considering follow-up information, the investigator may subsequently change his/her opinion of causality and may amend the SAE report accordingly.

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

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

8.3.4. Follow-up of Adverse Events

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

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

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

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

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

8.3.5. Laboratory Test Abnormalities

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

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

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

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

8.4. Definition of a Serious Adverse Event

A 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 that hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization
  Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency department for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
- Results in disability/incapacity
  Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are **not** considered to be SAEs:

- Hospitalization for elective treatment of a 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 SUSAR is a serious adverse reaction that is both unexpected (ie, not present in the product's RSI) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with that noted in the corresponding Investigator's Brochure for the respective investigational agent(s).

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

8.6.1. Adverse Event Recording Period

After informed consent has been signed but before the administration of the study treatment, only SAEs should be reported.

After initiation of study treatment, all AEs and SAEs, regardless of relationship to the study treatment, will be reported until either 30 days after the last dose of study drug(s) or until initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be recorded until 90 days after the last dose of study drug(s), regardless of whether the patient starts a new anticancer therapy. SAEs assessed as related to the study treatment that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

AEs and SAEs should be as outlined in Table 3. For the follow-up period for AEs, see Section 8.3.4. For the definition of TEAEs, see Section 9.3.2.

Table 3: Guidance for Duration of Recording New or Worsening Adverse Events in All Treatment Arms

Event type	Record new or worsening events that occur during this period	
	Begin	**End**
SAEs (not treatment-related)	Signing of informed consent	Up to 30 days after the last dose of study drug(s), initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Treatment-related SAEs	Signing of informed consent	Patient death, withdrawal of consent, or loss to follow-up, whichever occurs first
Nonserious AEs due to progressive disease	Do not record (see Section 8.6.4)	
Nonserious AEs other than those due to progressive disease	First dose of study treatment	Up to 30 days after the last dose of study drug(s), initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Immune-mediated AEs (serious or nonserious)	First dose of study treatment	Up to 90 days after last dose of study drug(s) (regardless of initiation of new anticancer therapy), death, withdrawal of consent, or loss to follow-up, whichever occurs first

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

8.6.2. Reporting Serious Adverse Events

8.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (≤ 24 hours after determination) to the sponsor or designee as described in Table 4.

Table 4: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor

	Timeframe for sending initial/follow-up report [a]	**Documentation method**	**Reporting method**
All SAEs before the Extended IP Access Period begins	≤ 24 hours after first knowledge of the SAE	SAE report	Electronic submission of SAE form to portal [b]
All SAEs during the Extended IP Access Period from patients with continuous access to study treatment	≤ 24 hours after first knowledge of the SAE	SAE report	Paper SAE form

Abbreviations: AE, adverse event; IP, investigational product; SAE, serious adverse event.

a. Report follow-up information that is clinically relevant and pertains to the SAE, which includes but is not limited to the following: Update to the SAE, new additional SAE, outcome, seriousness criteria, investigator-assessed causality, event start date/date of onset, date of death, relationship to each study drug. Follow-up information will also be reported, as per the discretion of the investigator if the new or updated information changes the medical assessment of the case.

b. SAE reports should be submitted to the sponsor safety database electronically from within the electronic data capture system. If the electronic submission is not available for any reason, a paper SAE form should be submitted by email or fax.

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he or she is to report the information to the sponsor ≤ 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 or she must not wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

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

The sponsor will provide contact information for SAE receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

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

The investigator, or 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 SUSARs (as defined in Section 8.5), will be submitted to all applicable regulatory authorities and investigators for investigational agent studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated responsible person is required to promptly notify his/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 patients about AEs by asking the following standard questions:

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

8.6.4. Disease Progression

Disease progression, which is expected in this study population and is measured as an efficacy endpoint, should not be recorded as an AE term. Similarly, nonserious AEs that are clearly consistent with the pattern of progression of the underlying disease and are considered unequivocally due to disease progression should not be recorded. However, if there is any uncertainty as to whether a nonserious AE is due to disease progression, it should be recorded as an AE. All SAEs and deaths, regardless of relatedness to disease progression, should be recorded and reported (see Section 8.6.2).

8.6.5. Deaths

When a patient dies, if the only information available is that the death occurred and the cause of death is unknown, then the death is reported as an AE, eg, "death NOS." In all other cases, death is captured as an outcome.

8.6.6. Pregnancies

The pregnancy reporting period for each investigational agent is in Appendix 11. If a female patient or the female partner of a male patient becomes pregnant during the pregnancy reporting period, a pregnancy report form must be submitted to the sponsor. The pregnancy report is a type of SAE report and must follow the same prompt reporting guidelines described in Section 8.6.2.1. The outcome of the pregnancy, including any premature termination of the pregnancy will also be reported to the sponsor.

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

Patients who become pregnant must immediately discontinue treatment (see Section 3.7). For patients who are no longer pregnant, resumption of treatment may be discussed with the medical monitor.

In addition to the common stipulations with respect to pregnancy in this section, additional requirements for the treatment with a particular agent are provided in the investigational agent-specific appendix, if applicable.

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

The sponsor will promptly assess all SAEs against cumulative study treatment 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 RSI in the Investigator's Brochure of each study drug.

8.6.8. Assessing and Recording Immune-Mediated Adverse Events

Treatment with anti-PD-1 therapy and ICIs can cause autoimmune disorders. All AEs considered by the investigator to be immune-mediated (see Section 8.7.2) should be classified as imAEs and identified as such in the eCRF adverse event page.

8.6.9. Recording Infusion-Related Reactions

The signs and symptoms of an infusion-related reaction should be recorded as the adverse terms for those individual signs and symptoms. In assessing whether an AE is infusion related, note that the symptoms of infusion-related reactions may include but may not be limited to 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, or cardiogenic shock. Each individual sign and symptom of an infusion reaction should be recorded as a separate AE in the eCRF and identified as an infusion-related reaction. Refer to the eCRF completion guidelines for details.

8.7. Adverse Events of Special Interest

Infusion-related reactions, severe hypersensitivity reactions, and imAEs according to the NCI-CTCAE v5.0 criteria are outlined below. In addition to the common statements with respect to AE of special interest presented in this section, additional requirements regarding AEs of interest for each particular agent are provided in the investigational agent-specific appendix, if applicable.

8.7.1. Infusion-Related Reactions and Hypersensitivity Reactions

Patients should be closely monitored during and after study drug administration for infusion-related reactions and hypersensitivity reactions. See each investigational agent specific appendix for the monitoring periods required. Immediate access to an intensive care unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids,

antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions. See Appendix 7 for the management of infusion-related reactions and hypersensitivity reactions as well as treatment modifications.

8.7.2. Immune-Mediated Adverse Events

In this study, imAEs are of special interest. Potential imAEs are listed in Table 5 below. All AEs similar to those listed in the table should be evaluated in patients receiving the study agent(s) to determine whether the AE is immune-mediated. The investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic, toxin, disease progression, or other neoplastic causes) with appropriate diagnostic tests that may include but may not be limited to serologic, immunologic, and histologic (biopsy) data (see Appendix 7). If alternative causes have been ruled out and the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy, and it is consistent with an immune-mediated MoA, the imAE indicator in the eCRF AE page should be checked. Recommendations for managing imAEs are detailed in Appendix 7.

Table 5: Examples of Immune-Mediated Adverse Events

Body system affected	Events
Skin (mild-common)	pruritus or maculopapular rash; vitiligo
Skin (moderate)	follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet syndrome
Skin (severe-rare)	full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation
Endocrine	thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism, such as fatigue, weakness, and weight gain; insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	pneumonitis/diffuse alveolitis
Eye	episcleritis; conjunctivitis; iritis/uveitis
Musculoskeletal	arthritis; arthralgia; myalgia; myasthenic syndrome/myasthenia gravis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure
Neurologic	encephalitis; Guillain-Barre syndrome; meningitis; meningoradiculitis; meningoencephalitis; neuropathy

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed by the sponsor or designee after the data collection is completed and the database is locked and released. Data will be listed and summarized per sponsor agreed reporting standards, wherever applicable. Details of the statistical analyses will be included in a separate statistical analysis plan.

9.1. Statistical Analysis

9.1.1. Randomization Methods

Patients will be randomly assigned to treatment arms using the IRT system for this study by block randomization. The inclusion and exclusion criteria may not be identical for all open treatment arms, and the patient will only be randomized to the arms that he/she is eligible for. The initial randomization will use a 1:1 ratio between each of the experimental arms and the common reference arm and will be stratified by the PD-L1 expression (CPS = 1 to 19 versus ≥ 20). The randomization ratio may be modified to account for emerging safety data, efficacy data, and feasibility considerations.

9.1.2. Analysis Sets

The ITT Analysis Set is defined as all patients who undergo randomization in one of the treatment arms. Patients will be analyzed according to the treatment arm/group they are randomized. The ITT Analysis Set will be used as the primary analysis population for all efficacy and demographic analyses unless specified otherwise.

The Safety Analysis Set includes all patients who receive at least 1 dose of study drug(s). Patients will be analyzed according to the treatment they received. All safety and exposure analyses will be conducted using the Safety Analysis Set unless specified otherwise.

The Efficacy Evaluable Analysis Set includes all patients who receive at least 1 dose of study drug(s), have evaluable disease at baseline, and have at least 1 evaluable postbaseline tumor response assessment unless any clinical disease progression or death occurred before the first postbaseline tumor assessment. The Efficacy Evaluable Analysis Set will be used as the supportive analysis population for efficacy endpoints.

The PK Analysis Set includes all patients who receive at least 1 dose of study drug(s) and have ≥ 1 measurable post-dose concentration(s).

The Biomarker Analysis Set includes all patients who receive at least 1 dose of study drug(s) and have ≥ 1 evaluable biomarker measurement.

9.1.3. Patient Disposition

The number of patients enrolled, randomized, treated, and discontinued from any study treatment and/or from the study, and those with important protocol deviations will be counted. The primary reason for study treatment and/or study discontinuation 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 database cutoff date will be summarized using the data from the eCRF.

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

9.1.4. Demographic and Other Baseline Characteristics

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

9.1.5. Prior and Concomitant Medications

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

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

9.2. Efficacy Analysis

Primary and secondary efficacy endpoints will be based upon investigators' tumor assessments per RECIST v1.1 and will be summarized as follows to evaluate the anticancer activities of the study drug(s):

- ORR is defined as the proportion of patients who have a confirmed CR or a confirmed PR, as assessed by the investigators using RECIST v1.1.
- DOR is defined as the time from the first determination of a confirmed response per RECIST v1.1 until the first documentation of progression or death, whichever occurs first. DOR is only summarized for patients with a confirmed response.
- CBR is defined as the proportion of patients with a best overall response of a confirmed CR, a confirmed PR, or a durable stable disease (stable disease duration ≥ 24 weeks).
- DCR is defined as the proportion of patients with a best overall response of a confirmed CR, a confirmed PR, or stable disease.
- PFS is defined as the time from the date of randomization to the date of the first documentation of PD assessed by the investigators per RECIST v1.1 or death, whichever occurs first.
- OS is defined as the time from the date of randomization to the date of death due to any cause.

9.2.1. Primary Efficacy Analysis

Confirmed ORR assessed by the investigators will be reported. The corresponding 95% CIs will be reported using the Clopper-Pearson method (Clopper and Pearson 1934). The ORR difference between any experimental arm and the reference arm will be evaluated.

9.2.2. Secondary Efficacy Analysis

The PFS, DOR, CBR, DCR and OS will be summarized for each treatment arm. The difference between any experimental arm and the reference arm will be reported. The PFS, DOR and OS will be estimated using the Kaplan-Meier method.

The CBR and DCR will be analyzed similarly to ORR.

9.2.3. Exploratory Efficacy Analysis

Time to response is defined as the time from the date of randomization to the date of the first objective response. Time to response will be estimated using the Kaplan-Meier method.

The correlation of response and exploratory tumor-based and/or blood-based biomarkers may be evaluated.

9.3. Safety Analyses

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

9.3.1. Extent of Exposure

The extent of exposure to each study treatment will be summarized descriptively as the number of doses received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient, dose intensity, and relative dose intensity.

The number (percentage) of patients requiring dose interruption, dose delay, and drug discontinuation due to AEs will be summarized for each study drug.

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

9.3.2. Adverse Events

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

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) and up to 30 days after the last dose of study drug(s) or initiation of new anticancer therapy, whichever occurs first. Only those AEs that are treatment emergent will be included in summary tables of TEAE.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by System Organ Class and Preferred Term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 within a System Organ Class and Preferred Term, even if the patient experienced more than 1 TEAE within a specific System Organ Class and Preferred Term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug(s).

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

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

9.3.3. Laboratory Analyses

Clinical laboratory (eg, hematology, serum chemistry, urinalysis) values will be evaluated for each laboratory parameter. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be provided. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated.

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

9.3.4. Vital Signs

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

9.4. Pharmacokinetic Analysis

Serum or plasma concentrations (as appropriate) for tislelizumab and other investigational agents may be tabulated and summarized by visit/cycle at which these samples are collected. Descriptive statistics (eg, means, medians, ranges, and standard deviations, as appropriate) may be provided.

Additional PK analyses, including population PK analyses and exposure-response analyses (efficacy or safety endpoints), may be conducted as appropriate and the results of these analyses may be reported separately from the main study report.

9.5. Other Exploratory Analysis

Summary statistics may be provided for pharmacodynamic biomarkers including cytokines/chemokines and soluble proteins, 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 may be performed as appropriate.

Exploratory predictive biomarker analyses including PD-L1, investigational agent-specific protein and/or ligands expression, and HPV status in tumor tissue may be performed in an effort to understand the association of these markers with study drug(s) response, such as efficacy and treatment resistance.

Additionally, the following may be evaluated as appropriate: exploratory biomarkers from patient derived tumor tissue(s) and blood (or blood derivatives) samples obtained before, during and/or after treatments. Candidate biomarkers may include, but are not limited to, gene expression profiling and tumor mutation analysis in tumor tissue and ctDNA/bTMB/mutation profile in peripheral blood.

9.6. Sample Size Consideration

This study is designed to obtain efficacy, safety, PK, and immunogenicity data on tislelizumab in combination with novel agents compared to tislelizumab alone. No formal hypothesis testing will be performed in the efficacy evaluation as the study is not designed to make explicit power and Type I error considerations for a hypothesis test.

9.6.1. Randomization Phase

The initial randomization will use a 1:1 ratio between each of the experimental arms and the common reference arm and will be stratified by the PD-L1 expression (CPS = 1 to 19 versus ≥ 20), as described in Section 9.1.1. A total of up to 40 patients per experimental arm may be enrolled in this phase of the study. The total sample size of the reference arm depends on the number of experimental arms and the timing of their enrollment. Randomization ratios may be modified to account for emerging safety data, efficacy data, and feasibility considerations.

The study is an activity-estimating study and not designed to make explicit power and Type I error considerations. Bayesian posterior probability may be used to facilitate the evaluation of whether an experimental arm would have a relatively sufficient antitumor activity.

9.7. Interim Monitoring

This section provides the futility and safety monitoring process that will be performed during the course of the study to evaluate the clinical activity and safety of any treatment arm. This process will be conducted separately for each treatment arm.

9.7.1. Futility Interim Monitoring

A futility monitoring process will be conducted when any of the experimental arms has randomized approximately 20 patients, and when these patients have been followed up for at least 2 post-baseline tumor assessments. Bayesian posterior probability (to be calculated with a noninformative prior such as Beta [0.5, 0.5] for ORR) will be used to evaluate clinical antitumor activity, and the decision criteria may be based on the difference in ORR between an

experimental arm and the reference arm (ie, ΔORR). An experimental arm will be considered futile if the ORR in this group is unlikely to be better than the reference arm during the interim monitoring process (ie, Posterior Probability [ΔORR < 0] ≥ 90%). Enrollment in this experimental arm may be paused if the criterion for futility is met.

9.7.2. Safety Stopping Rules

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

The safety stopping boundaries for at least possibly treatment-related deaths is listed in Table 6, which is derived based on the 90% Bayesian posterior probability that the incidence rate of deaths at least possibly related to the study treatment is > 5%, calculated with a weak prior distribution Beta (0.005, 0.095).

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

Table 6: Safety Stopping Boundaries for Number of Patients With at Least Possibly Treatment-Related Deaths

Number of Patients in an Arm	Number of Patients With at Least Possibly Treatment-Related Deaths That Will Trigger Pause in Enrollment
1-2	≥ 1
3-11	≥ 2
12-23	≥ 3
24-36	≥ 4
37-40	≥ 5

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Safety Oversight Committee

The Safety Oversight Committee will enable efficient assessment of safety data and maintain oversight of benefit-risk profile for all investigational agents throughout the study. It will include relevant internal/sponsor members (including representatives of Pharmacovigilance/Drug Safety, Clinical Pharmacology, and Biostatistics with other members, as appropriate) that are otherwise not directly associated with the study.

The Safety Oversight Committee have responsibility for conducting prespecified and ad hoc assessments of safety to recommend actions including discontinuation or modification for a specific investigational agent due to safety concerns.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

11.1. Access to Information for Monitoring

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

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

11.2. Access to Information for Auditing or Inspections

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

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

12.2. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/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 acknowledging receipt of each shipment of study product (quantity and condition), patient drug dispensation records, and returned or destroyed study product. Dispensation records will document quantities received from the sponsor's designated depot or its designee and quantities dispensed to patients, including batch/lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

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

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

13. ETHICS/PROTECTION OF HUMAN PATIENTS

13.1. Ethical Standard

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

13.2. Institutional Review Board/Independent Ethics Committee

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

The investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments. In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and the IRB/IEC. Investigators may receive written investigational new drug 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. Protocol amendments must be submitted to health 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 health 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). The sponsor may utilize a protocol amendment to add new experimental arms to this study when new treatments become available, for discontinuing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modifying the patient population (eg, regarding biomarker status). Prior to implementing any new experimental arm, protocol amendment, and respective health authority and IRB/IEC approvals should be obtained.

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

13.3. Informed Consent

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

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

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

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

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

13.4. Patient and Data Confidentiality

The 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 GCP Guideline, as implemented locally. Such laws may be more stringent than the requirements in this protocol.

The 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 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 that 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 are 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 investigator and site may provide certain of this personal or medical information to the sponsor or its representatives. Such personal or medical information may not be provided as part of the protocol (eg, as part of the eCRF or on samples or reports submitted to the central laboratory, on safety reporting forms [except in China], or on product dispensing logs provided to the sponsor, etc).

The investigator and site must use only the specific forms and clinical study systems, (eg, the EDC system and any secure file transfer platforms) 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 investigator, site, and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable laws. If the sponsor identifies personal or medical information that was not properly de-identified, it may be required to report the disclosure under local applicable laws.

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

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

The investigator agrees that all information received from the sponsor, including but not limited to the Investigator's Brochure(s), 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.

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 European Medicines Agency 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. Literature revealed varying clinical outcomes and distribution of prognosis factors between different racial groups of patients with HNSCC. Specifically, a study of 304,138 patients reported that after adjusting multiple clinical and demographic predictors including age, sex, race, ethnicity, income, stage, surgical treatment, comorbidity score, metastatic disease, HPV status, and travel distance, Black race was associated with an inferior OS (HR: 1.09, 95% CI: 1.03 to 1.15, p = 0.002) compared to White race (Baliga et al 2023). In addition, studies reported diverse mutation spectrum (Chaudhary et al 2020), histology (Koyuncu et al 2022) as well as p16 positivity and HPV status across different racial groups (Weinberger et al 2010), which suggest identification of race-related determinants of disease prognosis may help with the understanding of racial disparities in head and neck cancer outcomes. Data insights obtained through collecting and analyzing of race data in correlation with factors stated above will assist to inform the entire immune-oncology community about personalized treatment strategies and future directions of clinical development.

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.

13.5. Financial Disclosure

Investigators (including any sub-investigators and coinvestigators) are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of the clinical investigators, and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure financial interests and arrangements of the clinical investigators with the sponsor that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Entry in the Electronic Case Report Form

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

14.1.2. Data Collection

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

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

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

14.1.3. Data Management/Coding

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

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

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

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

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

As a part of patient management, the investigator should collect and maintain patient clinical source documents per the requirements of local institutions during the Extended IP Access Period.

14.2. Data Integrity and In-House Blinding

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

14.3. Study Records Retention

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

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

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

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

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

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

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers away from the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage away from the site.

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

14.4. Protocol Deviations

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

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

14.5. Study Report and Publications

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

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

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor for review before submission or presentation in accordance with the clinical study agreement. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be presented in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the

publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

14.6. Study and Study Center Closure

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

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

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

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

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

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

14.7. Information Disclosure and Inventions

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

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

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

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

These restrictions do not apply to the following:

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

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

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APPENDIX 1. SCHEDULE OF ASSESSMENTS [a]

Assessment	Screening [b]	Treatment cycles				EOT Visit [c]	Safety Follow-up [d]	Survival Follow-up [e]
		Cycles 1 to 3 (every 3 weeks)			Cycle 4 and subsequent cycles (every 3 weeks)			
Days (window)	**-28 to ~ -1**	**1 (± 3) [f]**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**0 to 7 Days**	**30 (± 7) days of the last dose**	**Every 3 months (± 14 days)**
Informed consent [b]	x							
Inclusion/exclusion criteria	x							
Randomization/enrollment [g]	x							
Demographics/medical history/prior medications [h]	x							
Vital signs/ height and weight [a, i]	x	x			x	x	x	
Physical examination [a, j]	x	x			x	x	x	
ECOG Performance Status [a]	x	x			x	x	x	
12-lead ECG [a, k]	x	As clinically indicated				x	x	
Adverse events [a, l]	x	x	x [m]	x [m]	x	x	x	
Concomitant medications	x	x	x [m]	x [m]	x	x	x	
Hematology [a, n]	x	x	x	x	x	x	x	
Serum chemistry [a, n]	x	x	x	x	x	x	x	
Coagulation parameters [a, n]	x	x			x	x	x	
Urinalysis [a, n]	x	As clinically indicated						

Assessment	Screening [b]	Treatment cycles				EOT Visit [c]	Safety Follow-up [d]	Survival Follow-up [e]
		Cycles 1 to 3 (every 3 weeks)			Cycle 4 and subsequent cycles (every 3 weeks)			
Days (window)	**-28 to ~ -1**	**1 (± 3) [f]**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**0 to 7 Days**	**30 (± 7) days of the last dose**	**Every 3 months (± 14 days)**
CK and CK-MB [a, n, o]	x	x	x	x	x	x	x	
Pregnancy test [a, p]	x	x			x	x	x	
Thyroid function [a, q]	x	x (Cycle 3 only)			x (every 2 cycles starting from Cycle 5)	x	x	
HBV/HCV tests [a, r]	x	As clinically indicated						
Pulmonary function test [a, s]		As clinically indicated [s]						
Pharmacokinetics Tislelizumab [a, t] (Reference and Experimental Arms)		x			x		x	
Pharmacokinetics BGB-A425 [a, t] (Experimental Arm 1 and 3)		x			x		x	
Pharmacokinetics LBL-007 [a, t]		x			x		x	

Assessment	Screening [b]	Treatment cycles				EOT Visit [c]	Safety Follow-up [d]	Survival Follow-up [e]
		Cycles 1 to 3 (every 3 weeks)			Cycle 4 and subsequent cycles (every 3 weeks)			
Days (window)	**-28 to ~ -1**	**1 (± 3) [f]**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**0 to 7 Days**	**30 (± 7) days of the last dose**	**Every 3 months (± 14 days)**
(Experimental Arm 2 and 3)								
Anti-tislelizumab, anti-BGB-A425, and/or anti-LBL-007 antibodies [a, u]		x			x		x	
Tumor assessment [a, v]	x	Every 6 weeks (± 7 days) from randomization for the first 52 weeks, then every 12 weeks (± 7 days)						x
Archival or fresh tumor tissue [a, w]	x	x (~ Cycle 3)				x		
Blood collection for biomarker analysis (cytokine/chemokine or soluble proteins) [a, x]		x (predose of Cycle 1 and Cycle 2)	x (Cycle 1 only)					
Blood collection for biomarker analysis (Immunophenotyping) [a, y]		x (predose of Cycle 1 and Cycle 2)	x (Cycle 1 only)					

Assessment	Screening [b]	Treatment cycles				EOT Visit [c]	Safety Follow-up [d]	Survival Follow-up [e]
		Cycles 1 to 3 (every 3 weeks)			Cycle 4 and subsequent cycles (every 3 weeks)			
Days (window)	**-28 to ~ -1**	**1 (± 3) [f]**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**0 to 7 Days**	**30 (± 7) days of the last dose**	**Every 3 months (± 14 days)**
Blood collection for biomarker analysis (ctDNA/TMB/ mutation profiling) [a, z]		x (predose of Cycle 1 and Cycle 3)				x		
Tislelizumab administration [aa] (Reference and Experimental Arm[s])		x			x			
BGB-A425 administration [bb] (Experimental Arm 1 and Arm 3)		x			x			
LBL-007 administration [cc] (Experimental Arm 2 and Arm 3)		x			x			
Subsequence anti-cancer therapy [a]							x	x
Survival status [a]								x

Abbreviations: AE, adverse event; CK, creatine kinase; CKMB, creatine kinase cardiac muscle isoenzyme; CPS, combined positive score; CT, computed tomography; ctDNA, circulating tumor DNA; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End-of-Treatment; FFPE, formalin-fixed paraffin-embedded; FT3, free triiodothyronine; FT4, free thyroxine; HBV, hepatitis B virus; HCV, hepatitis C virus; IEC, Independent Ethics Committee; imAE, immune-mediated adverse event; IRB, Institutional Review Board; IRT, Interactive ; LAG-3, lymphocyte activation gene-3; MRI, magnetic resonance imaging; PK, pharmacokinetic; SAE, serious adverse event; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; TMB, tumor mutation burden; TSH, thyroid stimulating hormone.

[a] During the Extended IP Access Period (see Section 3.9.1), patient management and monitoring, including tumor and response evaluations, safety assessments, study drug modifications, and follow-up will be concordant with the protocol or per the investigator's discretion based on local or institutional guidelines. No further data will be collected by the sponsor in eCRFs. However, as a part of patient management, the investigator must collect and maintain patient clinical source documents per the requirements of local institutions. All SAEs should still be reported to the sponsor safety database through paper forms per requirements and timelines described in Section 8.6.2. Samples for PK, ADA, and biomarker assessments will not be collected during the Extended IP Access Period.

[b] Written informed consent is required before performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed before obtaining informed consent and ≤ 28 days before randomization/enrollment may be used for screening assessments rather than repeating such tests. Patients who enter the Extended IP Access Period will re-sign the informed consent form.

[c] The EOT Visit will be conducted within 7 days after the investigator decides to permanently discontinue study treatment or before the initiation of a new anticancer treatment, whichever occurs first. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT Visit, tests need not be repeated. Tumor assessment is not required at the EOT Visit provided that < 6 weeks have passed since the last assessment. Patients who discontinue study treatment before disease progression will need to undergo tumor assessments as outlined in Section 7.5.

[d] A Safety Follow-up Visit is required to occur 30 days (± 7 days) after the last dose of study drug(s) or before the initiation of a new anticancer treatment, whichever occurs first, unless the time window overlaps with the time window of the EOT Visit. Additional safety follow-up at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of study drug(s) will be made by telephone to assess imAEs and relevant concomitant medications. See Section 3.5. For women of childbearing potential, a pregnancy test should be conducted at qualified local laboratories following the longest contraception requirement (see Appendix 11) .

[e] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months after the EOT/Safety Follow-up Visit until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up.

[f] The visit window of ± 3 days is not applicable to Day 1 of Cycle 1.

[g] Patients enrolled will be randomized to a treatment arm via IRT. All patients are required to receive study treatment ≤ 2 business days after randomization/enrollment.

[h] Includes age or year of birth, gender, self-reported race/ethnicity and history of treatment for the primary diagnosis, including prior medication, locoregional treatment(s), histological subtype, metastatic site, and surgical treatment(s). Information on radiographic studies performed before study entry may be collected for review by the investigator. Preexisting AEs at baseline should be recorded as medical history.

[i] Vital signs include body temperature, pulse rate, and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be collected while the patient is in a seated position after resting for 10 minutes. The patient's vital signs must be recorded ≤ 60 minutes before, during, and approximately 30 minutes after the first infusion of study drug(s) on Day 1 of Cycle 1. For subsequent infusions, vital signs will be collected ≤ 60 minutes before infusion and, if clinically indicated, during and 30 minutes after the infusion of study drug(s). Weight will be recorded on Day 1 of each cycle, and at the EOT Visit. Height measurements are only required at screening.

[j] A complete physical examination is required (as detailed in Section 7.4) at screening visit. At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed.

[k] The ECG recordings will be obtained during screening, the EOT Visit, and as clinically indicated at other timepoints. Patients should be resting in a semirecumbent supine position for ≥ 10 minutes before each ECG recording.

[l] After informed consent has been signed but before the administration of the study treatment, only SAEs should be reported. After the initiation of study drug(s), all AEs and SAEs, except those AEs clearly due to disease progression (see Section 8.6.4), will be reported until 30 days after the last dose of study drug(s) or the initiation of a new anticancer therapy, whichever occurs first (see Section 8.6.1). All imAEs should be recorded until 90 days after the last dose of tislelizumab or investigational agent(s) (whichever occurs later), regardless of the initiation of new anticancer therapy. Telephone contacts with patients should be conducted at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of study drug(s) to assess imAEs and relevant concomitant medications (ie, those associated with an imAE or any new anticancer therapy). SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

[m] Review of AEs and concomitant medications may be conducted by telephone on Days 8 and 15.

[n] Local laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2. If laboratory tests at screening are not performed ≤ 7 days before Day 1 of Cycle 1, these tests should be repeated and reviewed before the first dose of study drug(s). Hematology, serum chemistry (including liver function tests) and coagulation will be performed weekly for the first 3 cycles, then on Day 1 of each subsequent cycle and EOT Visit (data collected as specified in Appendix 2). After Cycle 1, results are to be reviewed ≤ 48 hours before study drug administration. Urinalysis is 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.

[o] All patients will have CK and CK-MB testing at all scheduled visits during the first 3 treatment cycles, all predose assessments from Cycle 4 onward, and at the EOT and Safety Follow-up Visit. If CK-MB fractionation is not available, troponin I and/or troponin T may be tested instead. Refer to Section 7.4.4.1 for additional information.

[p] For women of childbearing potential, including women who have had a tubal ligation, urine pregnancy tests will be performed at each visit before study drug administration, at the EOT Visit and at each Safety Follow-up Visit, including the additional visit for pregnancy follow-up (see footnote c). A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

[q] Local laboratory assessments of thyroid function (FT3, FT4, and TSH) will be performed at screening, every 2 cycles starting on Day 1 of Cycle 3 (ie, Day 1 of Cycles 3, 5, 7, etc), and at the EOT Visit. Total T3 (TT3) is acceptable in case free triiodothyronine analysis is not available.

[r] Patients with detectable HBV DNA or HCV RNA at screening will have viral load reassessed every 4 cycles (ie, Day 1 of Cycles 5, 9, 13, etc).

[s] Consider pulmonary function test including carbon monoxide (DLCO) for patients presenting with new or worsening pulmonary symptoms or signs, such as shortness of breath or hypoxia.

[t] Predose serum or plasma samples for tislelizumab, BGB-A425 (anti-TIM-3 monoclonal antibody injection), and/or LBL-007 (anti-LAG-3 monoclonal antibody injection) (≤ 60 minutes before starting infusion) are required to be collected on Day 1 of Cycles 1, 2, 5, 9, 17, and at the Safety Follow-up Visit. Postdose serum or plasma samples (≤ approximately 30 minutes after completing study drug infusion) are required to be collected on Day 1 of Cycles 1 and 5. Should a patient present with any ≥ Grade 3 imAE, an additional blood PK sample may be taken. These tests are required when allowed by local regulations/IRBs/IECs.

[u] Blood used to test for anti-tislelizumab, anti-BGB-A425, and/or anti-LBL-007 antibodies should be collected ≤ 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 5, 9, and 17 and at the mandatory Safety Follow-up Visit. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required when allowed by local regulations/IRBs/IECs.

[v] All measurable and evaluable lesions are required to 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 imaging protocol for CT or MRI). During the study, tumor imaging will be performed every 6 weeks (± 7 days), from randomization for the first 52 weeks and then every 12 weeks (± 7 days) after 52 weeks. Refer to Section 7.5 for details.

[w] During the screening period, patients will undergo PD-L1 positivity confirmation determined by PD-L1 (CPS≥1) by a local laboratory (using PD-L1 IHC 22C3 pharmDx assay) or by 22C3 pharmDx assay in central testing. All patients must provide archival tumor tissues (FFPE blocks or approximately 15 freshly cut unstained slides) or fresh tumor tissues for prospective analysis of PD-L1 expression (if local PD-L1 data are not available) and for retrospective analysis of exploratory biomarkers. Archival tissue collected within 6 months from screening is strongly preferred. However, archival tissue collected within 2 years is acceptable. Tumor 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. Refer to Section 7.7.1 for details.

[x] Blood samples for cytokine/chemokine or soluble protein analysis will be collected on Cycle 1 Day 1 (predose), Cycle 1 Day 8, and Cycle 2 Day 1 (predose). Please refer to the laboratory manual for additional detailed information. (Note: For sites in mainland China, blood-based biomarkers, including cytokine/chemokine and soluble proteins, will be explored in the blood samples.)

[y] Blood samples for immunophenotyping analysis will be collected on Cycle 1 Day 1 (predose), Cycle 1 Day 8, and Cycle 2 Day 1 (predose). Please refer to the laboratory manual for additional detailed information. (Note: Blood samples for immunophenotyping assay will be collected only for patients in mainland China.)

[z] Blood samples for ctDNA/TMB/mutation profiling will be collected at Cycle 1 Day 1 (predose), Cycle 3 Day 1 (predose) and EOT visit for patients who have confirmed disease progression. Please refer to the laboratory manual for additional detailed information. (Note: For sites in mainland China, blood-based biomarkers, including ctDNA/TMB/mutation profiling will be explored in the blood samples.)

[aa] Tislelizumab will be administered intravenously on Day 1 of Cycle 1 and once every 3 weeks thereafter. For administration details for each arm, see below: for Reference Arm, refer to Appendix 14 Section 4; for Experimental Arm 1, refer to Appendix 15 Section 4; for Experimental Arm 2, refer to Appendix 16 Section 5; for Experimental Arm 3, refer to Appendix 17 Section 4.

[bb] BGB-A425 will be administered intravenously on Day 1 of Cycle 1 and once every 3 weeks thereafter. For Experimental Arm 1, refer to Appendix 15 Section 4 for details; for Experimental Arm 3, refer to Appendix 17 Section 4 for details.

[cc] LBL-007 will be administered intravenously on Day 1 of Cycle 1 and once every 3 weeks thereafter. For Experimental Arm 2, refer to Appendix 16 Section 5 for details; for Experimental Arm 3, refer to Appendix 17 Section 4 for details.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Serum chemistry	Hematology	Coagulation	Urinalysis	Thyroid function[d]
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Total bilirubin Direct bilirubin Blood urea nitrogen or urea Potassium Sodium Total calcium[a] Creatinine Glucose Total protein Creatine kinase[b] CK-MB[b]	Hematocrit Hemoglobin Platelet counts WBC count Lymphocyte count Neutrophil count	Prothrombin time Partial thromboplastin time or activated partial thromboplastin time International normalized ratio	Glucose Protein Blood Ketones 24-hour protein[c]	Free triiodothyronine Free thyroxine Thyroid stimulating hormone

Abbreviations: CK-MB, creatine kinase cardiac isoenzyme; WBC, white blood cell.

[a] Total calcium values will be corrected for patients with hypoproteinemia.

[b] All patients will have creatine kinase and CK-MB testing at screening, and at all scheduled visits during the first 3 treatment cycles, all predose assessments from Cycle 4 onwards, and at the End-of-Treatment/Safety Follow-up visit. If CK-MB fractionation is not available, assess troponin I and/or troponin T instead. Refer to Section 7.4.4.1 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[c] On routine urinalysis, if urine protein is ≥ 2+ by dipstick, then obtain a 24-hour urine sample for total protein.

[d] Local laboratory assessments of thyroid function (FT3, FT4, and TSH) will be performed at screening, every 2 cycles starting on Day 1 of Cycle 3 (ie, Day 1 of Cycles 3, 5, 7, etc), and at the EOT Visit. Total T3 (TT3) is acceptable in case free triiodothyronine analysis is not available.

APPENDIX 3. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

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

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

APPENDIX 4. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

Source: Eisenhauer et al 2009

Definitions

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

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

Measurable Disease

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

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

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

Nonmeasurable Disease

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

Bone lesions:

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

Cystic lesions:

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

Target Lesions

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

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

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

Nontarget Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal

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

Guidelines for Evaluation of Measurable Disease

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

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

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

pathological response when biopsies are obtained or to determine relapse in studies where recurrence after complete response (CR) or surgical resection is an endpoint.

- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.
- Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Response Criteria

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes 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 (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- Both PR and PD: If the change in sum of diameters is consistent with both PR and PD at a tumor assessment visit, PD should take precedence.
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report form may be designed to have target nodal lesions recorded in a separate section where, to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD 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 electronic case report form (eCRF). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially nonreproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that measurement should be recorded, even if it is below 5 mm.

- Lesions that split or coalesce on treatment: When 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 Nontarget Lesions

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

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

- When the patient has only nonmeasurable disease: This circumstance arises in some phase 3 studies when it is not a criterion of study entry to have measurable disease. The same general concept applies here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare 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 it may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the patient should be considered to have had overall 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 preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in 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 FDGPET at baseline, with a positive FDGPET at follow-up, is a sign of PD based on a new lesion.

- No FDGPET at baseline and a positive FDGPET at follow-up: If the positive FDGPET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDGPET 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 FDGPET scan). If the positive FDGPET 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
SD	Non-PD or not all evaluated	No	SD
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; SD, stable disease.

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

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

Best response determination in studies where confirmation of complete or partial response IS NOT required: Best response in these studies is defined as the best response across all timepoints (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response 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 studies where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent timepoint as specified in the protocol (generally 4 weeks later).

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order 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 studies where confirmation of response is required, repeated "NE" (not evaluable) timepoint assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be addressed in determination of response and progression. For example, in most studies it is reasonable to consider a patient with timepoint responses of PR-NE-PR as a confirmed response.

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

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

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

Confirmation of Measurement/Duration of Response

Confirmation

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

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

Duration of Overall Response

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

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

Duration of Stable Disease

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

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

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

APPENDIX 5. PREEXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

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

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

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

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

APPENDIX 6. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

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

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

APPENDIX 7. INFUSION-RELATED REACTIONS, HYPERSENSITIVITY REACTIONS AND IMMUNE-MEDIATED ADVERSE EVENTS: EVALUATION AND MANAGEMENT

Management of Infusion-Related Reactions and Hypersensitivity Reactions

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

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

Treatment Modifications for Symptoms of Infusion-Related or Hypersensitivity Reactions Associated with Study Drug(s) Administration

NCI-CTCAE Grade	Treatment Modification for Study Drug(s)
Grade 1 - mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Closely monitor for worsening signs or symptoms. Medical management as needed. Subsequent infusions should be given after appropriate premedication and at the reduced infusion rate.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, corticosteroids, and/or intravenous fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reaction has resolved or decreased to Grade 1 in severity. Closely monitor for worsening signs or symptoms. Appropriate 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 observation or clinical management.	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: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Event.

If the infusion rate of study drug(s) has been decreased by 50% or suspended due to an infusion-related reaction, this decreased rate must be maintained for all subsequent infusions and be administered 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 tislelizumab and/or investigational agent treatment.

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

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

NCI-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 antihistamines, antipyretics, glucocorticoids, epinephrine, bronchodilators, and oxygen.

In the event of a systemic anaphylactic/anaphylactoid reaction, the infusion must be stopped immediately, and the patient discontinued from study treatment. Systemic anaphylactic/anaphylactoid reactions typically manifest within minutes following administration of the drug/antigen and are 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 or without edema); and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea.

The patient will be administered epinephrine injection and dexamethasone infusion if severe hypersensitivity reaction is observed. The patient should be closely monitored, and an intensive care unit (ICU) should be alerted for possible transfer as indicated.

Evaluation of Immune-Mediated Adverse Events

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

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

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

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

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

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

Immune-mediated Toxicity	Diagnostic Evaluation Guideline
Thyroid disorders	Scheduled and repeated thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss, and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath, or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including DLCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.
Neurological toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.

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, and cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain, or distension, consider colonoscopy with biopsy and surgical intervention as appropriate.
Eye disorders	If a patient experiences acute, new onset, or worsening of eye inflammation; blurred vision; or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3 to 4; every 2 to 3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging (eg, ultrasound scan for metastases or thromboembolism). Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to a nephrologist for further management assistance.
Dermatology	Consider other causes by conducting a physical examination. Consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin, and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

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

Management of Immune-Mediated Adverse Events

Immune-mediated AEs can escalate quickly. Study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention as appropriate 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 study medical monitor.

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

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

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

Management of Immune-Mediated Adverse Events

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker, and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with comorbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Hypophysitis	**1-2** Mild-moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4.	Continue study treatment.
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse intravenous methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinologist's advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to ≤ Grade 2. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider *Pneumocystis* infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.

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

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

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

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Creatinine > 3 x baseline or > 3-6 x ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate intravenous (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6 x 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 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
Ocular toxicity	**1** Asymptomatic eye examination/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral corticosteroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Discontinue study treatment.
	4 Blindness (at least 20/200) in the affected eyes	Initiate intravenous (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
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 to worsen, hold study treatment until symptoms improve to baseline or Grade 0-1.
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ Stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improve to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider intravenous corticosteroids if not contraindicated by infection.	Discontinue study treatment.

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Life-threatening	cardiac failure according to local guidelines. If no immediate response, change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab, or anti-thymocyte globulin.	baseline and after discussion with the study medical monitor.
Other immune-mediated adverse events	**≤ 2**	Clinical management per local guideline based on adverse event type and severity.	Continue study treatment.
	3		Hold study treatment until improved to Grade 0-1. For recurrent Grade 3: Discontinue study treatment.
	4		Discontinue study treatment.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; ECG, electrocardiogram; INR, international normalized ratio; LFT, liver function test; MMF, mycophenolate mofetil; MUGA, multigated acquisition scan; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.
[a] If clinically significant cardiac enzyme abnormalities are detected during laboratory assessment and serial cardiac enzyme assessments pose logistical hardship for the patient, then patient hospitalization should strongly be considered until immune-mediated myocarditis has been ruled out.

APPENDIX 8. MANAGEMENT OF NON-IMMUNE-MEDIATED ADVERSE EVENTS

Guidance in this appendix should be followed if, in the opinion of the investigator, the non-immune-mediated toxicity is suspected of being related to tislelizumab or the investigational agent(s). In the event that the toxicity is considered related to all treatment component(s), the most conservative guidelines should be followed.

Refer to the dose modification guidance of each investigational agent in the appendices.

System	Adverse Event	Toxicity Management	Study Drug Management
Hematologic	**Anemia** Grade 3	Treat with appropriate supportive care as medically indicated.	Hold study treatment until resolved to Hgb ≥ 9 g/dL. If resolved ≤ 7 days, then maintain current dosage. If resolved > 7 days, decrease the dose of the investigational agent treatment as recommended in the dose modification guidance of the investigational agent. If blood transfusion is required, consider decreasing the dose of the investigational agent treatment as recommended in the dose modification guidance of the investigational agent. Follow the drug-specific guidance for toxicity management.
	Anemia Grade 4	Maximize supportive therapy until Hgb ≥ 9 g/dL.	Hold study treatment until resolved to Hgb ≥ 9 g/dL. After resolution, decrease the dose of the investigational agent as recommended in the dose modification guidance of the investigational agent. Follow the drug-specific guidance for toxicity management.
	Neutropenia (ANC decrease) Grade 3	Treat with appropriate supportive care as medically indicated until ANC ≥ 1000/mm^3.	Hold study treatment until resolved to ANC ≥ 1000/mm^3 or baseline. If resolved in ≤ 7 days, then maintain current dosage. If resolved in > 7 days, then decrease the dose of the investigational agent as recommended in the dose modification guidance of the investigational agent. Follow the drug-specific guidance for toxicity management.

System	Adverse Event	Toxicity Management	Study Drug Management
	Neutropenia (ANC decrease) Grade 4	Maximize appropriate supportive therapy until ANC ≥ 1000/mm^3.	Hold study treatment until resolved to ANC ≥ 1000/mm^3 or baseline. After resolution, decrease the dose of the investigational agent as recommended in the dose modification guidance of the investigational agent. Follow the drug-specific guidance for toxicity management.
	Febrile neutropenia ≥ Grade 3	Maximize appropriate supportive therapy. Rule out other etiologies of fever.	Hold study treatment until neutrophil count ≥ 1000/mm^3. After resolution, decrease the dose of the investigational agent as recommended in the dose modification guidance of the investigational agent. For Grade 4 event, discontinue treatment. Follow the drug-specific guidance for toxicity management.
	Thrombocytopenia (platelet count decrease) Grade 2	Monitor and treat with appropriate supportive care as medically indicated.	Maintain current dosage if no concerns of clinically significant risk of bleeding; continue to monitor using additional hematology assessments as required.
	Thrombocytopenia (platelet count decrease) Grade 3	Treat with appropriate supportive care as medically indicated.	Hold study treatment until resolved to ≤ Grade 1 or baseline. After resolution, decrease the dose of the investigational agent as recommended in the dose modification guidance of the investigational agent. Follow the drug-specific guidance for toxicity management.
	Thrombocytopenia (platelet count decrease) Grade 4	Treat with appropriate supportive care as medically indicated.	Hold study treatment until resolved to ≤ Grade 1 or baseline. After resolution, decrease the dose of the investigational agent as recommended in the dose modification guidance of the investigational agent. Follow the drug-specific guidance for toxicity management.

System	Adverse Event	Toxicity Management	Study Drug Management
	Other hematologic event Grade 3	Treat with appropriate supportive care as medically indicated.	Hold study treatment. If improved to ≤ Grade 1 or baseline, decrease the dose of the investigational agent as recommended in the dose modification guidance of the investigational agent. If event recurs at the reduced dose after receiving optimal supportive care, permanently discontinue study treatment. Follow the drug-specific guidance for toxicity management.
	First occurrence of other hematologic Grade 4 event	Treat with appropriate supportive care as medically indicated.	Hold study treatment until improved to ≤ Grade 1 or baseline. After resolution, decrease the dose of the investigational agent as recommended in the dose modification guidance of the investigational agent, or permanently discontinue study treatment. Follow the drug-specific guidance for toxicity management.
	Other recurrent hematologic Grade 4 event	Treat with appropriate supportive care as medically indicated.	Permanently discontinue study treatment.
Nonhematologic	**Non-hematologic event** Grade 3	Treat with appropriate supportive care as medically indicated.	Hold study treatment. If improved to ≤ Grade 1 or baseline, decrease the dose of the investigational as recommended in the dose modification guidance of the investigational agent. If event recurs at the reduced dose after receiving optimal supportive care, permanently discontinue study treatment. Follow the drug-specific guidance for toxicity management.
	Non-hematologic Grade 4 event	Treat with appropriate supportive care as medically indicated.	Permanently discontinue study treatment. Follow the drug-specific guidance for toxicity management.

Abbreviations: ANC, absolute neutrophil count; Hgb, hemoglobin.

APPENDIX 9. FORMULA FOR ESTIMATING RENAL FUNCTION

The Cockcroft-Gault Formula:

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

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

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

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

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

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

a Age in years and weight in kilograms.

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

Abbreviation: Clcr/CLcr, creatinine clearance.

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

The Chronic Kidney Disease Epidemiology Collaboration 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.

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [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 m^2 body surface area (BSA), which is an accepted average adult surface area.

Note: For patients with large BSA (tall or obese; indexed GFR < non-indexed GFR) and small BSA (short or very thin; indexed GFR > non-indexed GFR), the indexed GFR may be converted to non-indexed GFR by the formula:

Non-indexed GFR = Indexed GFR x BSA (m^2)/1.73 m^2.

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

Adopted from: Levey et al 2009.

APPENDIX 10. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

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

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

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

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

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

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

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

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

Adapted from Clinical Trials Facilitation Group (CTFG) 2020.

APPENDIX 11. PREGNANCY REPORTING PERIOD

If a female patient or the female partner of a male patient becomes pregnant during the following period for any arm, the pregnancy must be reported as specified in Section 8.6.6.

Arm	Treatment	Pregnancy Reporting Period
Reference Arm	Tislelizumab	On treatment or ≤ 120 days after the last dose of tislelizumab
Experimental Arm 1	Tislelizumab + BGB-A425	On treatment or ≤ 180 days after the last dose of study drug(s)
Experimental Arm 2	Tislelizumab + LBL-007	On treatment or ≤ 120 days after the last dose of tislelizumab or ≤ 60 days after the last dose of LBL-007, whichever occurs later
Experimental Arm 3	Tislelizumab + BGB-A425+ LBL-007	On treatment or ≤ 180 days after the last dose of BGB-A425, ≤ 120 days after the last dose of tislelizumab, or ≤ 60 days after the last dose of LBL-007, whichever occurs later

APPENDIX 12. LIST OF PROHIBITED CHINESE HERBAL AND PATENT MEDICINES

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

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

Drug Name (Chinese)	Drug Name (English)
康莱特软胶囊	Kanglaite soft capsules
慈丹胶囊	Cidan capsule
槐耳颗粒	Huaier Keli
海生素注射液	Haishengsu injection
消癌平丸/片/胶囊/颗粒	Xiaoaiping Wan/Pian/Jiao Nang/Ke Li
消癌平注射液	Xiaoaiping Zhusheye
牛黄醒消丸	Niuhuang Xingxiao pill
猪苓多糖注射液	Polyporus polysaccharide injection
白花蛇舌草注射液	Hedyotis Diffusa wild injection
紫龙金片	Zi Long Jin Pian
肝复乐片/胶囊	Ganfule tablet/Jiaonang
肿节风片	Zhongjiefeng tablet
胃复春片	Weifuchun Pian
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	Jinfukang Koufuye
金蒲胶囊	Jinpu capsule
金龙胶囊	Jinlong capsule
香菇多糖	Lentinan
鸦胆子油乳注射液	Yadanzi/Brucea javanica Youru Zhusheye
鸦胆子油软胶囊/口服乳液	Yadanziyou Ruan Jiao Nang/Kou Fu Ru Ye

Terminology list: Jiao Nang/Jiaonang, capsule; Ke Li/Keli, granule; Kou Fu Ye/koufuye, oral liquid; Pian, tablet; Wan, pill/bolus; Zhu She Ye/Zhusheye, injection.

APPENDIX 13. LIST OF POTENTIAL HEPATOTOXIC DRUGS

The drugs listed in the table below have been associated with the potential to cause drug-induced liver injury. Liver function tests should be carefully monitored in patients taking these medications as concomitant medications.

For a full list of potential hepatotoxic drugs, please refer to the United States Food and Drug Administration Drug Induced Liver Injury Rank (DILIrank) Dataset:

https://www.fda.gov/science-research/liver-toxicity-knowledge-base-ltkb/drug-induced-liver-injury-rank-dilirank-dataset

amiodarone	abacavir	acetazolamide
dantrolene	allopurinol	febuxostat
flutamide	bicalutamide	griseofulvin
ketoconazole	chlorzoxazone	methimazole
leflunomide	dactinomycin	terbinafine
nefazodone	diclofenac	etravirine
propylthiouracil	diflunisal	tolvaptan
stavudine	fenoprofen	acarbose
tolcapone	hydroxyurea	bexarotene
valproic acid	imatinib	voriconazole
zidovudine	labetalol	atomoxetine
nevirapine	mefenamic acid	erlotinib
isoniazid	methyldopa	sorafenib
gemtuzumab ozogamicin	nitrofurantoin	darunavir
danazol	sulindac	didanosine
sunitinib	tamoxifen	interferon alfa-2b
pazopanib	tizanidine	interferon alfa-2a, recombinant
divalproex sodium	fluconazole	ethambutol
oxandrolone	itraconazole	infliximab
tipranavir	clomipramine	fosphenytoin
lapatinib	clarithromycin	gemcitabine
mercaptopurine	testosterone	levofloxacin
indomethacin	etodolac	nilutamide
phenytoin	busulfan	nortriptyline
rifampin	disulfiram	riluzole

orlistat	minocycline	ritonavir
zafirlukast	telithromycin	duloxetine

Source: Chen et al 2016.

APPENDIX 14. REFERENCE ARM: TISLELIZUMAB

1. Introduction of Tislelizumab

Refer to protocol Section 1 for details.

2. Medicinal Product Approval Status

The regulatory approval status of tislelizumab is provided in Table 1. No auxiliary medicinal products, defined by Article 2(8) of Regulation (EU) 536/2014, will be used in this study.

Table 1: Regulatory Approval Status of Tislelizumab in Study BGB-HNSCC-201

Country/Region	Approved for Treatment of First-Line HNSCC (Yes/No)
	Tislelizumab
China	No
USA	No
Korea	No
Australia	No
European Union	No

Abbreviations: HNSCC, head and neck squamous cell carcinoma; USA, United States of America.

3. Formulation, Packaging, Labeling, and Handling

Tislelizumab is a monoclonal antibody formulated for intravenous infusion in a single-use vial (20R glass, United States Pharmacopeia [USP] type I), containing a total of 100 mg of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in a single-use glass vial with a rubber stopper and capped by an aluminum flip-off seal 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 temperature and light conditions as specified on the label and in the pharmacy manual. Refer to the pharmacy manual for details regarding reconstitution, intravenous administration, accountability, and disposal. Refer to the Tislelizumab Investigator's Brochure for other details regarding tislelizumab.

4. Dosage, Administration, and Compliance

The first dose of study drug(s) is to be administered ≤ 2 business days after randomization/enrollment. All patients will be monitored continuously for adverse events (AEs). Treatment modification (ie, dose delay, reduction, or interruption) or discontinuation will be based on specific laboratory and AE criteria, as described in Appendix 4.

In special situations (eg, when administration is delayed due to management of AEs or in the case of an infusion-related reaction), administration of the subsequent study drugs may be delayed to the second day of each cycle.

The dosing schedule for tislelizumab treatment in the reference arm is provided in Table 2. Tislelizumab 200 mg will be administered on Day 1 of each 21-day cycle (once every 3 weeks).

Table 2: Selection and Timing of Dose for Each Patient (Reference Arm)

Study Drug	Dose	Frequency of Administration	Route of Administration	Duration of Treatment
Tislelizumab	200 mg	Cycle 1 Day 1, then once every 3 weeks	Intravenous infusion	See Protocol Section 3.3

Tislelizumab will be administered by intravenous infusion. Specific instructions for product preparation, storage, and administration are provided in the Pharmacy Manual.

The delivery period of the initial infusion (Day 1 of Cycle 1) will be ≥ 60 minutes; if this is well tolerated, then the delivery period of subsequent infusions may be shortened to ≥ 30 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (refer to protocol Section 6).

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1, patients must be monitored for ≥ 60 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 2 onward, a monitoring period of ≥ 30 minutes is required.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Appendix 7.

4.1. Overdose or Incorrect Administration

Any overdose of tislelizumab (defined as ≥ 600 mg of tislelizumab in a 24-hour period) or incorrect administration of study drug(s) should be noted in the patient's chart and on the appropriate electronic case report form (eCRF).

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

5. Investigational Medicinal Product Accountability

The investigational medicinal product(s) (IMP[s]) required for completion of this study (tislelizumab and investigational agents) will be provided by the sponsor, as required by local or country-specific guidance. The investigational site will acknowledge receipt of the IMP(s). Any damaged shipments will be replaced, as appropriate.

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

6. Dose Modification

Dose modification is defined as any of the following: dose reduction, dose delay, missed doses, and dose interruption. A dose delay is a deviation from the prescribed dosing schedule (ie, the drug is withheld beyond the visit window). A dose interruption is an interruption of an infusion.

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 below. Reasons for dose reductions or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

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

6.1. Dose Delay or Interruption for Tislelizumab

There will be no dose reduction for tislelizumab in this study.

Tislelizumab treatment may be temporarily suspended if the patient experiences a toxicity that is suspected to be related to tislelizumab and requires a dose to be withheld. Tislelizumab treatment should resume as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) and ≤ 12 weeks after the last dose of tislelizumab.

If the patient is unable to resume tislelizumab ≤ 12 weeks after the last dose of tislelizumab, then the patient should be discontinued from treatment. If the patient is not able to resume tislelizumab ≤ 12 weeks after the last dose for unforeseen non-drug-related reasons, continued treatment may be allowed if approved by the medical monitor. For patients in study arms receiving tislelizumab in combination with the investigational drug(s), tislelizumab administration may continue if the investigational drug is delayed or discontinued after consultation and agreement with the medical monitor. Additional dose modification details for tislelizumab when given in combination with an investigational agent in experimental arms are provided in the investigational agent-specific appendix.

Specific treatment modifications to manage tislelizumab-related toxicities, such as imAEs and infusion-related reactions, are described in protocol Section 8.7 and Appendix 7.

7. Concomitant Therapy

Refer to protocol Section 6.2 for concomitant therapies.

8. Risks Associated With Tislelizumab

Tislelizumab is an investigational agent that is currently in clinical development. The following recommendation is based on results from nonclinical and clinical studies with tislelizumab and published data on other molecules within the same biologic class.

The programmed cell death protein ligand-1 (PD-L1)/ programmed cell death protein-1 (PD-1) pathway is involved in peripheral immune tolerance; therefore, this type of therapy may increase the risk of imAEs, specifically the induction or exacerbation of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in protocol Section 8.7.2.

An imAE may occur at any time during or after treatment. Often, the etiology of imAEs is not clear, and other causes should be ruled out. This may require diagnostic testing and consultation with a specialist. Suggested evaluation and management guidelines for suspected imAEs are provided in Appendix 7. Refer to the Tislelizumab Investigator's Brochure for additional details.

APPENDIX 15. EXPERIMENTAL ARM 1: TISLELIZUMAB+BGB-A425

1. Introduction of BGB-A425

BGB-A425 is a humanized immunoglobulin G1 (IgG1) variant monoclonal antibody against T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) under clinical development for the treatment of human malignancies.

TIM-3 is an immune-checkpoint receptor primarily expressed on immune cells, such as T cells, natural killer (NK) cells, dendritic cells (DCs), and monocytes/macrophages (Anderson et al 2016). A large body of literature suggests that TIM-3 plays a key role in promoting T-cell exhaustion and maintaining immune tolerance, both in chronic viral infections and in the tumor microenvironment (Du et al 2017; Das et al 2017; Thommen et al 2015). When expressed on effector T cells, engagement of TIM-3 with one of its ligands (such as phosphatidylserine [PtdSer] and galectin-9 [Gal-9]) reduces cytokine production, T-cell proliferation, and cytotoxicity (Fourcade et al 2010; Sakuishi et al 2010). A similar phenomenon was also observed for the NK cells of cancer patients. In addition, T-regulatory (Treg) cells expressing TIM-3 demonstrated greater immunosuppressive functions compared to TIM-3-negative Tregs (Sakuishi et al 2013).

Some studies have also shown that activation of TIM-3 suppresses immune responses mediated by certain myeloid cells (eg, DCs, monocytes, and macrophages), especially in the inhibition of type I interferon and interleukin-12 (IL-12) production. Upregulation of TIM-3 expression on tumor-infiltrating lymphocytes, macrophages, and tumor cells has been reported in many types of cancers such as lung (Zhuang et al 2012), liver (Li et al 2012), stomach (Jiang et al 2013), kidney (Komohara et al 2015), breast (Heon et al 2015), head and neck (Liu et al 2017), colon (Xu et al 2015), and cervical cancer (Cao et al 2013). The increased expression of TIM-3 in these cancers is associated with a poor prognosis and/or patient survival.

Refer to the BGB-A425 Investigator's Brochure for additional information.

1.2. Background Information on BGB-A425

1.2.1. Pharmacology

BGB-A425 binds to the extracellular domain (ECD) of human TIM-3 with high specificity and affinity (Kd = 0.22 nM) as demonstrated by target-binding assays and surface plasmon resonance (SPR) characterization. BGB-A425 competitively blocks the binding of PtdSer 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). Furthermore, 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 Fc□RIIIA, in in vitro binding assays. BGB-A425 does not induce

antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) in the cell-based assays.

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 due to the significant sequence divergence between human and mouse TIM-3.

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

1.2.2. Toxicology

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 repeated dose ranging from 20 to 200 mg/kg once every 2 weeks for 13 weeks. The toxicokinetic (TK) profile was characterized in monkey studies and the systemic exposure appeared to be dose proportional with no gender difference or accumulation over the dosing period. No apparent immunotoxicity was observed as no changes in clinical pathology or histopathology were observed in these studies.

No apparent increase in cytokine release was observed from an in vitro cytokine release assay following treatment of nonactivated 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 TK profile was well characterized with dose-proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The no-observed-adverse-effect level 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 the treatment of patients with advanced cancer.

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

1.2.3. Clinical Pharmacology

As of the data cutoff date of 15 February 2022, serial pharmacokinetic (PK) data were collected from 25 patients from across the first 7 dose cohorts (receiving 6, 20, 60, 200, 400, 800, and 1600 mg) in dose escalation of 1 ongoing clinical study. BGB-A425 exhibited rapid clearance (CL) and short half-life ($t_{1/2}$) at doses of 6 mg and below which is consistent with target-mediated drug disposition for monoclonal antibodies (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 detailed information regarding clinical pharmacology studies.

1.2.4. Prior Clinical Experience With BGB-A425

As of 09 July 2024, there are 2 ongoing clinical studies investigating BGB-A425: BGB-900-102 and BGB-HNSCC-201. The safety and efficacy assessments are summarized below.

1.2.4.1. Safety Assessment of BGB-A425

As of the data cutoff date of 09 July 2024, safety data from 210 patients treated with surzebiclimab in combination with tislelizumab with and without LBL-007 showed the majority of AEs to be Grade 1 or 2. Dose escalation did not identify a maximum tolerated dose.

Overall, current data suggest that the combination of BGB-A425 and tislelizumab has a manageable safety profile.

Please refer to the most recent edition of the BGB-A425 Investigator's Brochure for detailed safety information.

1.2.4.2. Efficacy Assessment of BGB-A425

Refer to the most recent edition of BGB-A425 Investigator's Brochure for detailed efficacy information.

1.3. BGB-A425 Rationales

1.3.1. Rationale for BGB-A425 Recommended Phase 2 Dose

The combination recommended Phase 2 dose (RP2D) was determined primarily from the Phase 1 safety, tolerability, preliminary antitumor activity, pharmacodynamic biomarker and PK data.

Based on the saturation assessment of TIM-3 receptor occupancy in PBMCs, plateauing of soluble TIM-3 release and comparable PK profiles to competitors' RP2D, the RP2D is determined as BGB-A425 600 mg in combination with tislelizumab 200 mg administered once every 3 weeks, which will be evaluated in the Phase 2 dose expansion phase.

1.3.2. Rationale for Combination of BGB-A425 and Tislelizumab in the Treatment of Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

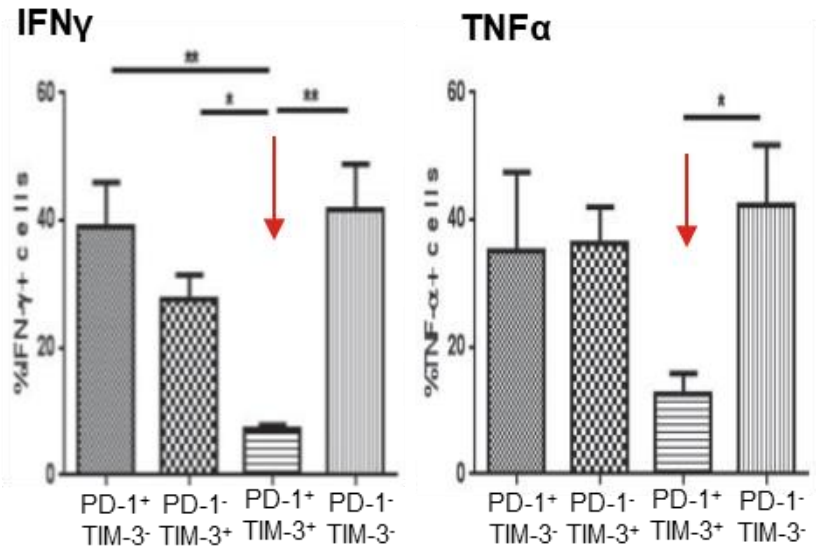
Blocking antibodies targeting PD-1 have achieved remarkable results in the treatment of recurrent or metastatic (R/M) HNSCC. However, it is also worth noting that this therapeutic strategy typically achieves a < 30% ORR as a monotherapy in patients whose tumors exhibit PD-L1 Combined Positive Score (CPS) ≥ 1 expression and/or are microsatellite stable (Chen and Han 2015).

TIM-3 was shown to be co-expressed with PD-1 on the surface of tumor-infiltrating lymphocytes (TILs). A preclinical study by Shayan et al observed compensatory upregulation of TIM-3 expression in a murine HNSCC model treated with anti-PD-1 (Shayan et al 2016). Moreover, Jie et al reported that the frequency of TIM-3^+ $CD8^+$ and PD-1^+ $CD8^+$ TILs was significantly increased among non-responders to cetuximab neoadjuvant therapy compared with responders, indicating that simultaneous blockade of TIM-3 and PD-1 may improve the clinical outcome for HNSCC patients (Jie et al 2017). A Phase Ia/Ib study presented at the 2019 ASCO-SITC Clinical Immuno-Oncology Symposium reported good tolerability of anti-TIM-3 antibody (LY3321367) monotherapy or in combination with anti-PD-1 antibody (LY3300054) in advanced solid tumors,

including HNSCC (Harding et al 2019). A Phase I dose-escalation study (NCT03708328) is ongoing to evaluate the safety and preliminary antitumor activity of a PD-1/TIM-3 bispecific antibody (RO7121661) in patients with advanced or metastatic solid tumors, including HNSCC.

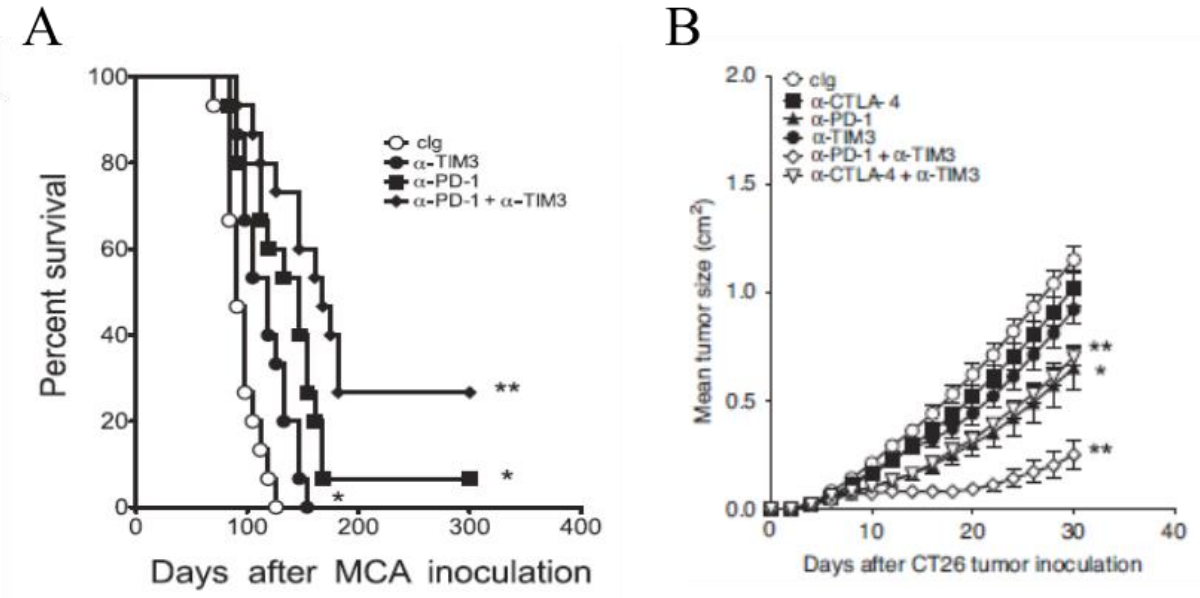
TIM-3 and PD-1 function as immune checkpoint receptors in the overlapping regulation of immune tolerance. As noted above, TIM-3 and PD-1 have been shown to be overexpressed on the TILs from patient samples of various solid tumors including HNSCC, Subsequently, the activation of TIM-3 and PD-1 represent TILs from both patients or animals across solid tumor types with the most exhausted immunophenotype (ie, cytokine expression, proliferation etc.), compared with TIM-3$^+$ or PD-1$^+$ exhausted T cells (Figure 1), which can be reversed with combined blockade of TIM-3 and PD-1 (Shayan et al 2016). 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.

Figure 1: Impaired T Cell Function Was Observed in TIM-3$^+$/PD-1$^+$ CD8$^+$ TILs From HNSCC Patients



Abbreviations: IFN γ: interferon γ; PD-1: programmed cell death protein-1; TIM-3: T cell immunoglobulin and mucin-domain containing-3; TNF α: tumor necrosis factor α.

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

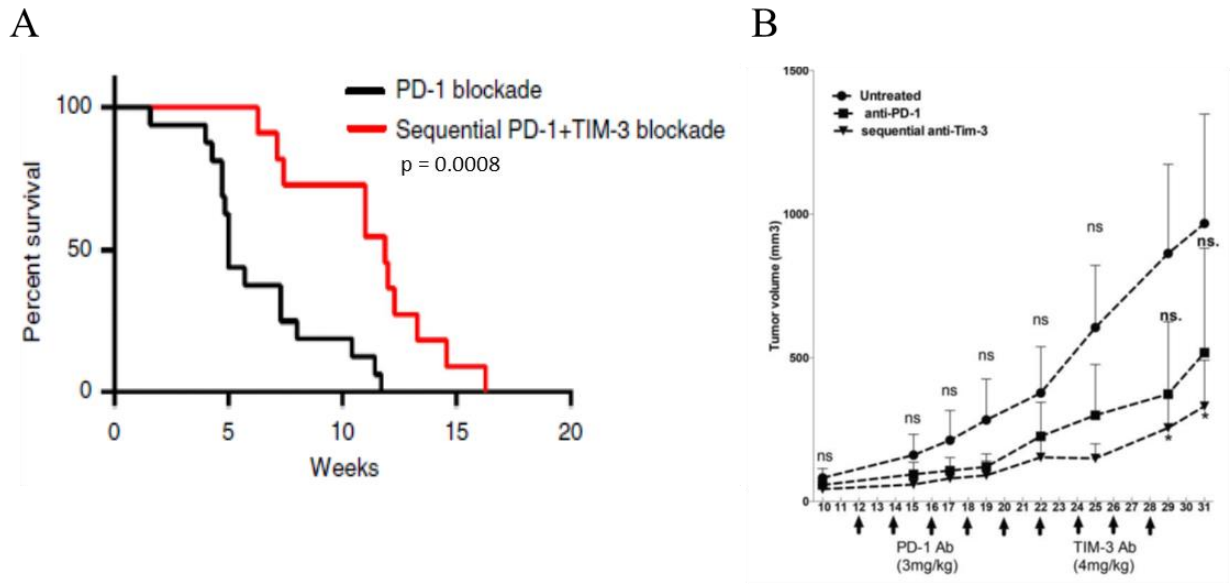


Abbreviations: cIg, control immunoglobulin; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; MCA, methylcholanthrene; PD-1, programmed cell death protein-1; TIM-3, T-cell immunoglobulin and mucin-domain containing-3

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).

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).

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 including HNSCC.

1.4. Benefit-Risk Assessment of BGB-A425

While anti-PD-1/PD-L1 monotherapy has demonstrated benefit in response rate and overall survival in patients with untreated HNSCC and PD-L1 expression CPS ≥ 1, it is evident that not

all patients treated with anti-PD-1/PD-L1 agents experience durable response or prolonged survival. Therefore, identifying novel targeted agents that can synergize with and improve the efficacy of the current available treatment would be of immense value for this patient population. There is limited human experience with BGB-A425; 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 in promoting tumor immune escape, the combination of anti-TIM-3 with anti-PD-1 could further improve the anti-tumor response. Combined with the clinical efficacy that has been demonstrated for PD-1 blockade via tislelizumab, the data strongly suggest that BGB-A425 has the potential to significantly improve and/or extend the therapeutic benefits of tislelizumab. 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 of the cutoff date of 20 July 2022, tislelizumab has been evaluated in 3220 patients (Tislelizumab Investigator's Brochure) with a safety and efficacy profile similar to what has been reported for other anti-PD-1 therapies. However, based upon their mechanism(s) of action, and preclinical as well as clinical data, treatment with BGB-A425 and tislelizumab is expected to increase the rate of immune-mediated toxicities compared with treatment with tislelizumab monotherapy. A comprehensive algorithm and practice guidelines have been established to monitor, diagnose, and manage such immune-mediated toxicities (Appendix 8). This monitoring plan will be utilized to evaluate patient safety during the course of the study. An independent Safety Oversight Committee and safety stopping rule has been created by the sponsor to continuously analyze the safety data and make appropriate changes in the protocol to minimize patient toxicities.

In summary, there is strong scientific rationale that the combined blockade of the TIM-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 HNSCC.

2. 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 1. No auxiliary medicinal products, defined by Article 2(8) of Regulation (EU) 536/2014, will be used in this study.

Table 1: Investigational Medicinal Products Used in Study BGB-HNSCC-201 and Their Regulatory Approval Status

Country/Region	Approved for Treatment of First-Line HNSCC (Yes/No)	
	BGB-A425	Tislelizumab
China	No	No
USA	No	No
Korea	No	No
Australia	No	No
European Union	No	No

Abbreviations: HNSCC, head and neck squamous cell carcinoma; USA, United States of America.

3. Formulation, Packaging, and Handling

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; United States Pharmacopeia [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.

4. Dosage and Administration

The dosing schedule for BGB-A425 in combination with tislelizumab in the experimental arm for BGB-A425 (Experimental Arm 1) is provided in Table 2.

Table 2: Selection and Timing of Dose for Each Patient (Experimental Arm 1)

Study Drug	Dose	Frequency and sequence of Administration	Route of Administration	Duration of Treatment
Tislelizumab	200 mg	Day 1 of each cycle (3 weeks)	Intravenous infusion	See Protocol Section 3.3
BGB-A425	600 mg	Day 1 of each cycle (3 weeks) Administer after tislelizumab		

Tislelizumab and BGB-A425 will be administered separately by intravenous infusion. Tislelizumab and BGB-A425 must be prepared and administered as separate infusions and may not be administered with any other drug. Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

Dosing administration and monitoring times are provided in Table 2. Monitoring must occur in an area where emergency medical equipment and appropriately trained staff are available. Duration of infusion and post infusion monitoring can be decreased if study drug infusion(s) is well tolerated. The infusion and post infusion rules are outlined in Table 3.

Table 3: Administration of BGB-A425 and Tislelizumab and Monitoring Time

Cycle	BGB-A425 and Tislelizumab Combination
Cycle 1 Day 1 (or first 2 administrations in case of dose delays)	Tislelizumab infusion ≥ 60 minutes followed by BGB-A425 infusion ≥ 60 minutes Patient monitoring for ≥ 60 minutes post completion of last infusion
Cycle 2 Day 1 onwards	Tislelizumab infusion ≥ 30 minutes followed by BGB-A425 infusion ≥ 30minutes Patient monitoring for ≥ 30 minutes post completion of last infusion

Notes: The infusion rate of tislelizumab or BGB-A425 may be decreased or the infusion may be stopped in the event of an infusion-related reaction.
Local laboratory assessments of thyroid function (FT3, FT4, and TSH) will be performed at screening, every 2 cycles starting on Day 1 of Cycle 3 (ie, Day 1 of Cycles 3, 5, 7, etc), and at the EOT Visit. Total T3 (TT3) is acceptable in case free triiodothyronine analysis is not available.

The treatment for the overdose or incorrect administration of BGB-A425 is the same as that for tislelizumab as described in Appendix 14 Section 4.1.

5. Dose Modification

Refer to Appendix 14 Section 6 for dose modification of tislelizumab.

No dose reductions will be allowed for BGB-A425.

If a dose delay for any study drug is required, both BGB-A425 and tislelizumab must be delayed and, if applicable, restarted at the same time. Exceptions may be considered following consultation between the investigator and the medical monitor.

Guidance for dose delay and interruption for BGB-A425 is the same as tislelizumab (Appendix 14 Section 6).

Treatment modifications to manage BGB-A425-related toxicities, such as immune-mediated adverse events (imAEs) and infusion-related reactions, are described in Appendix 7.

Every effort should be made to administer the study treatment as described; however, in the event of significant non-immune-mediated toxicity, dosing may be interrupted in accordance with Appendix 8. There will be no dose reduction of BGB-A425 or tislelizumab. When treatment can be resumed following resolution of toxicities as listed in Appendix 8, BGB-A425 and tislelizumab will be given at its initial dose, respectively.

6. Concomitant Therapy

Refer to protocol Section 6.2 for concomitant therapies.

6.1. Potential Interactions Between BGB-A425 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. Because BGB-A425 is 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. Risks Associated With BGB-A425 and Tislelizumab

BGB-A425, and tislelizumab are investigational agents that are currently in clinical development. Limited clinical information is available for BGB-A425 (Section 1.2). Safety data are available from 33 patients treated with BGB-A425, and 3220 patients treated with tislelizumab (BGB-A425 Investigator's Brochure; 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 ongoing BGB-900-102 study, and nonclinical and clinical studies with tislelizumab, as well as published data on other anti-TIM-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 7. BGB-A425 mediated TIM-3 inhibition may increase the risk of imAEs, though no apparent immunotoxicity, or toxicity in general, have been observed in animal models treated with BGB-A425 (Section 1.2 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.

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.

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APPENDIX 16. EXPERIMENTAL ARM 2: TISLELIZUMAB+ LBL-007

1. Introduction of LBL-007

LBL-007 is a fully human anti-lymphocyte activation gene-3 (LAG-3) monoclonal immunoglobulin (Ig) G4/κ isotype antibody codeveloped by Nanjing Leads Biolabs Co., Ltd. and BeiGene, Ltd. for the treatment of advanced solid tumors. Refer to the LBL-007 Investigator's Brochure for additional information.

1.1. Lymphocyte Activation Gene-3

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 has also been reported in B cells (Kisielow et al 2005) and plasmacytoid dendritic cells (pDCs) (Workman et al 2009). The main ligand for LAG-3 is the major histocompatibility complex (MHC) Class II protein (Huard et al 1995), and engagement of LAG-3 by MHC II ligand leads to a state of T cell exhaustion, characterized by the attenuation of T-cell activation, inability to proliferate in response to antigen and reduced cytokine production (Huang et al 2004; Workman and Vignali 2003; Workman et al 2004). Liver sinusoidal endothelial cell lectin (LSECtin) (Xu et al 2014), galectin 3 (Kouo et al 2015), and fibrinogen-like protein 1 (FGL1) (Wang J 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 their LAG-3^- counterparts (Camisaschi et al 2010; Huang et al 2004). A LAG-3 blockade has been shown to promote T cell proliferation and enhance cytotoxic T cells functions (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 programmed cell death protein-1 (PD-1) on tumor-infiltrating T cells, LAG-3 and PD-1 double positive T cells are in a more severe dysfunctional state than T cells expressing either 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 upregulated in several solid tumors that are inherently resistant or that become refractory to PD-1 blockade including, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), melanoma, and bladder cancer (Datar et al 2019, Gettinger et al 2017, Hanna et al 2018, Johnson et al 2018, Kates et al 2021). Preclinical studies in mouse models have shown that a co-blockade of PD-1 and LAG-3 restores the function of exhausted T cells and synergizes to inhibit tumor growth by enhancing antitumor immunity (Mimura et al 2021; Yang et al 2017; Ghosh et al 2019). These 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 to anti-PD-1 therapy. Indeed, the combination has been proven to be effective in clinic, in patients with previously untreated metastatic or unresectable melanoma in whom a combination of LAG-3 and PD-1 inhibition provided greater benefit than PD-1 blockade alone (Tawbi et al 2022).

1.2. Background Information on LBL-007

1.2.1. Pharmacology

LBL-007 binds to the human LAG-3 extracellular domain with high specificity and affinity ($K_D = 4.39 \times 10^{-10}$ M). LBL-007 effectively blocks the binding of LAG-3 to MHC II molecules, and thereby activates the immune system. An in vitro binding assay showed that LBL-007 also blocks the binding of LAG-3 with other ligands, including FGL-1, LSECtin, and galectin-3. In addition, in vivo studies in human LAG-3 knock-in mice showed LBL-007 significantly inhibiting the tumor growth 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.

1.2.2. Toxicology

The nonclinical toxicity and toxicokinetic profile of LBL-007 was characterized in a single dose study in cynomolgus monkeys and in repeated-dose studies in rats and cynomolgus monkeys dosed weekly. 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 maximum tolerated dose (MTD) was 300 mg/kg; no mortality or moribundity was observed in cynomolgus monkeys.

In the 3-week repeated dose study in rats, no LBL-007-related abnormal changes were observed in body weight, food consumption, ophthalmological examination, urinalysis, lymphocyte subsets, complement counts, or 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 likely off-target toxicities. Given that in vitro data indicated that cellular and tissue binding with LBL-007 was highly specific to monkey and human, and the absence of LBL-007 pharmacological activity in the rats, the findings in the 3-week repeat-dose study are of uncertain clinical relevance.

The 4-week repeated 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 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 levels 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 the increase of the infusion dose. No sex 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.

1.2.3. Clinical Pharmacology

Study WLZB-LBL-007-AST-001:

LBL-007 exhibited dose-dependent increase in exposure over the dose range of 3.0 mg/kg to 10 mg/kg after single intravenous infusion. The time to peak concentration ranged from 1 to 9 hours, and the mean elimination half-life ranged from 182 to 196 hours in the dose range of 3 mg/kg to 10 mg/kg. LBL-007 exhibited non-linear pharmacokinetics (PK) between the 0.05 mg/kg and 1 mg/kg dose levels and linear PK between 3 mg/kg and 10 mg/kg.

The PK characteristics of LBL-007 after multiple dose administration once every 2 weeks were similar to those of a single dose. There was no significant accumulation in exposure of LBL-007 in the lower dose groups (0.05 to 3 mg/kg once every 2 weeks). Little accumulation was observed in higher doses groups (6 and 10 mg/kg once every 2 weeks).

Study LBL-007-CN-002:

After a single intravenous infusion of 0.25 mg/kg, 1 mg/kg, 3 mg/kg, or 6 mg/kg LBL-007 in combination with anti PD-1 antibody toripalimab (3 mg/kg), the mean time to maximum LBL-007 concentration ranged from 1.0 to 2.0 hours; $t_{1/2}$ was 43.6, 108, 166, and 192 hours, respectively, with a dose-dependent trend; the mean C_{max} values were 3.35, 9.93, 36.7, and 73.0 μg/mL, respectively; the mean AUC_{0-336} values were 266.3, 1486, 5012, and 11175 h•μg/mL, respectively. The exposure parameter C_{max} increased dose proportionally, while AUC_{0-336} increased slightly more compared with the increase of dosage. Mean changes in V_{ss} ranged from 4.78 to 6.83 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 1.02 to 1.55 and 1.02 to 1.54, respectively, suggesting a slight accumulation of LBL-007 in vivo.

1.2.4. Prior Clinical Experience With LBL-007

As of 12 August 2024, LBL-007 has been investigated in 10 clinical studies with a total of 746 patients who received LBL-007.

1.2.4.1. Safety Assessment of LBL-007

The data available to date suggest that the safety profile of LBL-007 in combination with tislelizumab with/without surzebiclimab are consistent with the safety profile of LBL-007 monotherapy, tislelizumab monotherapy, or surzebiclimab monotherapy.

Refer to the most recent edition of LBL-007 Investigator's Brochure for detailed safety information.

1.2.4.2. Efficacy Assessment of LBL-007

Refer to the most recent edition of LBL-007 Investigator's Brochure for detailed efficacy information.

1.3. LBL-007 Rationale

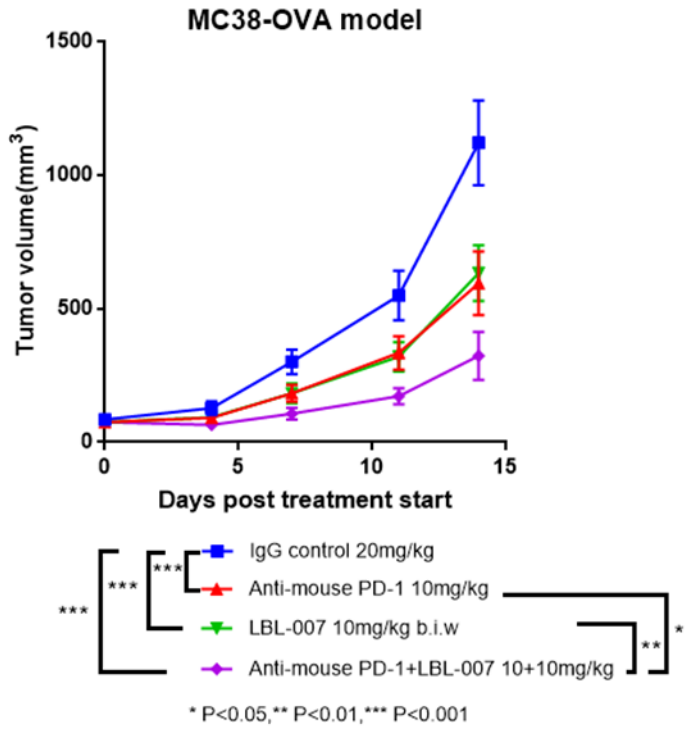
1.3.1. Rationale for LBL-007 in Combination With Tislelizumab as First-Line Treatment In Patients With R/M HNSCC

Based on multiple preclinical and clinical studies, anti-LAG-3 and anti-PD-1 molecules have synergistic effects across several malignant tumors. Coordinated inhibition of LAG-3 and PD-1 can further enhance the immune response and exert the best antitumor effect of the combination drugs.

In a preclinical mouse study (Study R-LBL-007-008-2), 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 1). There were no significant differences in body weight between groups.

Refer to the LBL-007 Investigator's Brochure for additional details.

Figure 1: Tumor Growth Curve After Treatment With LBL-007, Anti-Mouse PD-1 and the Combination in MC38-OVA Model



Abbreviations: MC38-OVA, mouse colorectal cancer cell line stably expressing OVA protein; PD-1, programmed cell death protein-1.

The synergic antitumor efficacy for anti-LAG-3 antibody in combination with anti-PD-1 antibody has been preliminarily validated in a clinical study.

The first anti-LAG-3 antibody (relatlimab, Bristol Myer Squibb, Princeton, NJ) was recently approved by the United States (US) Food and Drug Administration (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). In the study of LBL-007 in combination with anti-PD-1 antibody toripalimab in melanoma (LBL-007-CN-002), a total of 32 efficacy-evaluable patients had an ORR of 12.5% and a DCR of 53.1% (4 PRs and 13 stable diseases). Of the 11 evaluable patients with cutaneous acral melanoma who had not received anti-PD-(L)-1 antibody treatment, the ORR was 27.3% and the DCR was 81.8%. In the study of LBL-007 in combination with toripalimab in the treatment of advanced malignancies (Study LBL-007-CN-003), efficacy was assessed in 4 patients, all of whom had stable disease.

LAG-3 is highly expressed on Tregs of HNSCC patients (Jie et al 2013) and 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-(L)1 therapy, showed that LAG-3^{+}/PD-1^{+} co-expressed $CD8^{+}$T cells was increased among non-responders, compared with anti-PD-(L)1 responders (23.1% versus 1.2%,

p = 0.02); whereas the expression of CTLA4 was not significantly changed, which could be a driven mechanism of anti-PD-(L)1 resistance (Hanna et al 2018). Recent evidence suggests that LAG-3 exhibits significant upregulation in HPV-positive HNSCC compared to HPV-negative HNSCC, suggesting that HPV-positive HNSCC may benefit significantly from LAG-3 blockade (Panda et al 2020).

In conclusion, as indicated by both nonclinical research and clinical studies as well as the high expression level of LAG-3 in HNSCC tumors along with supporting pharmacological toxicology and clinical PK data of LBL-007, the synergistic blockade effect of LAG-3 and PD-(L)1 pathways provided a strong scientific rationale to expand the investigation of tislelizumab in combination with LBL-007 as 1L treatment in patients with R/M HNSCC.

1.3.2. Rationale for Selection of LBL-007 Dose in Combination With Tislelizumab

In the single-agent dose escalation trial of WLZB-LBL-007-AST-001, the highest dose of 10 mg/kg (once every 2 weeks) was tested in 7 patients with no DLT and was generally well tolerated. Limited drug accumulation was observed at steady-state due to its short half-life. The dose of 10 mg/kg (once every 2 weeks) provides exposure coverage up to 600 mg (for an average body weight of 60 kg) LBL-007 dosed once every 3 weeks, and 600 mg LBL-007 (once every 3 weeks) could be chosen as the highest dose as in the range of the LBL-007 starting dose in combination with 200 mg tislelizumab administered every 3 weeks.

In LBL-007-CN-003 study, doses up to 400 mg of LBL-007 (once every 3 weeks) were evaluated with toripalimab with no DLT (n = 6) observed. Similarly, in LBL-007-CN-002, the combination of LBL-007 (doses ranging up through 6 mg/kg; once every 2 weeks) with toripalimab was well tolerated with no DLT observed in 14 patients at this dose. Additionally, in the ongoing LBL-007-CN-004 study, doses of 300 mg and 600 mg LBL-007 (once every 3 weeks) were evaluated with tislelizumab with no DLT observed in either dose.

Considering the safety and tolerability of this combination, the starting dose of LBL-007 will be 600 mg, for combining with 200 mg tislelizumab.

1.4. Benefit-Risk Assessment

As described previously, both preclinical and clinical studies of LBL-007 or other anti-LAG-3 antibodies combined with PD-1 inhibitors have shown the synergistic effect and improved antitumor activity along with a favorable safety profile.

As of the cutoff date of 20 July 2022, tislelizumab has been evaluated in 3220 patients (Tislelizumab Investigator's Brochure) with a safety and efficacy profile similar to what has been reported for other anti-PD-1 therapies. However, based upon their mechanism(s) of action, and preclinical as well as clinical data, treatment with LBL-007 and tislelizumab is expected to increase the rate of immune-mediated toxicities compared with treatment with tislelizumab monotherapy. A comprehensive algorithm and practice guidelines have been established to monitor, diagnose, and manage such immune-mediated toxicities (Appendix 8). This monitoring plan will be utilized to evaluate patient safety during the course of the study.

It is therefore expected that tislelizumab + LBL-007 will potentially have a favorable benefit-risk ratio and clinical efficacy in patients with HNSCC.

2. 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 1. No auxiliary medicinal products, defined by Article 2(8) of Regulation (EU) 536/2014, will be used in this study.

Table 1: Investigational Medicinal Products Used in Study BGB-HNSCC-201 and Their Regulatory Approval Status

Country/Region	Approved for Treatment of First-Line HNSCC (Yes/No)	
	Tislelizumab	LBL-007
China	No	No
USA	No	No
Korea	No	No
Australia	No	No
European Union	No	No

Abbreviations: HNSCC, head and neck squamous cell carcinoma; USA, United States of America.

3. Formulation, Packaging, Labeling, and Handling

LBL-007 is a recombinant 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, United States Pharmacopeia [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 stored as specified on the label. Do not freeze. Shaking should be avoided.

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

4. Dosage and Administration

The dosing schedule for LBL-007 in combination with tislelizumab in the experimental arm for LBL-007 (Experimental Arm 2) is provided in Table 2.

Table 2: Selection and Timing of Dose for Each Patient (Experimental Arm 2)

Study Drug	Dose	Frequency and sequence of Administration	Route of Administration	Duration of Treatment
LBL-007	600 mg	Day 1 of each cycle (3 weeks) Administer first	Intravenous infusion	See Protocol Section 3.3
Tislelizumab	200 mg	Day 1 of each cycle (3 weeks) Administer after LBL-007		

Abbreviation: RP2D, recommended Phase 2 dose.

Tislelizumab and LBL-007 will be administered separately by intravenous infusion. Tislelizumab and LBL-007 must be prepared and administered as separate infusions and may not be administered with any other drug. Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

Dosing administration and monitoring times are provided in Table 3. Monitoring must occur in an area where emergency medical equipment and appropriately trained staff are available. If infusions of study drugs are well tolerated in the first cycle, duration of infusion and monitoring time can be decreased in subsequent cycles, as outlined in Table 3.

Table 3: Administration of LBL-007 and Tislelizumab and Monitoring Time

Cycle	LBL-007 and Tislelizumab Combination
Cycle 1 Day 1 (or first 2 administrations in case of dose delays)	LBL-007 infusion ≥ 60 minutes followed by tislelizumab infusion ≥ 60 minutes Patient monitoring for ≥ 60 minutes post completion of last infusion
Cycle 2 Day 1 onwards	LBL-007 infusion ≥ 30 minutes followed by tislelizumab infusion ≥ 30 minutes Patient monitoring for ≥ 30 minutes post completion of last infusion

Note: The infusion rate of tislelizumab or LBL-007 may be decreased or the infusion may be stopped in the event of an infusion-related reaction.

The treatment for the overdose or incorrect administration of LBL-007 is the same as that for tislelizumab as described in Appendix 14 Section 4.1.

5. Dose Modification

Refer to Appendix 14 Section 6 for dose modification of tislelizumab.

No dose reductions will be allowed for LBL-007.

If a dose delay for any study drug is required, both LBL-007 and tislelizumab must be delayed and, if applicable, restarted at the same time. Exceptions may be considered following consultation between the investigator and the medical monitor.

Guidance for dose delay and interruption for LBL-007 is the same as tislelizumab (Appendix 14 Section 6).

Treatment modifications to manage LBL-007-related toxicities, such as immune-mediated adverse events (imAEs) and infusion-related reactions, are described in Appendix 7.

Every effort should be made to administer the study treatment as described; however, in the event of significant non-immune-mediated toxicity, dosing may be interrupted in accordance with Appendix 8. There will be no dose reduction of LBL-007 or tislelizumab. When treatment can be resumed following resolution of toxicities as listed in Appendix 8, LBL-007 and tislelizumab will be given at its initial dose, respectively.

6. Concomitant Therapy

Refer to protocol Section 6.2 for concomitant therapies.

6.1. Potential Interactions Between LBL-007 and Concomitant Medications

A PK drug-drug interaction of 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. LBL-007 is not expected to induce or inhibit the major drug metabolizing cytochrome P450 pathways. Because LBL-007 is 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. Based on the mechanism of action, any therapeutic protein drug-drug interaction is not expected between the investigational agents.

7. Risks Associated With LBL-007 and Tislelizumab

LBL-007 and tislelizumab are investigational products that are currently in clinical development. Limited clinical information is available for LBL-007 (see Section 1.2). Safety data are available from 69 patients treated with LBL-007 and 3220 patients treated with tislelizumab (LBL-007 Investigator's Brochure; Tislelizumab Investigator's Brochure). The following recommendation is based on results from nonclinical and clinical studies with LBL-007 and tislelizumab and published data on other molecules within the same biologic class (see Appendix 14 Section 8 for risks associated with tislelizumab).

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. Based on available data for relatlimab in combination with nivolumab in unresectable metastatic melanoma (Tawbi et al 2022), LAG-3/PD-1 combinational therapy can potentially increase the risk of imAEs compared with anti-PD-1 alone.

According to LBL-007 clinical studies for which safety results are currently available, the possible toxicities of LBL-007 include fatigue, allergic reactions, infusion-related reactions, gastrointestinal 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, management guidelines for suspected imAEs are provided in Appendix 7.

Refer to the LBL-007 Investigator's Brochure for additional details.

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APPENDIX 17. EXPERIMENTAL ARM 3: TISLELIZUMAB+BGB-A425+LBL-007

1. Introduction of LBL-007 and BGB-A425

Refer to Appendix 15 Section 1 and Appendix 16 Section 1.

1.2. Background Information on LBL-007 and BGB-A425

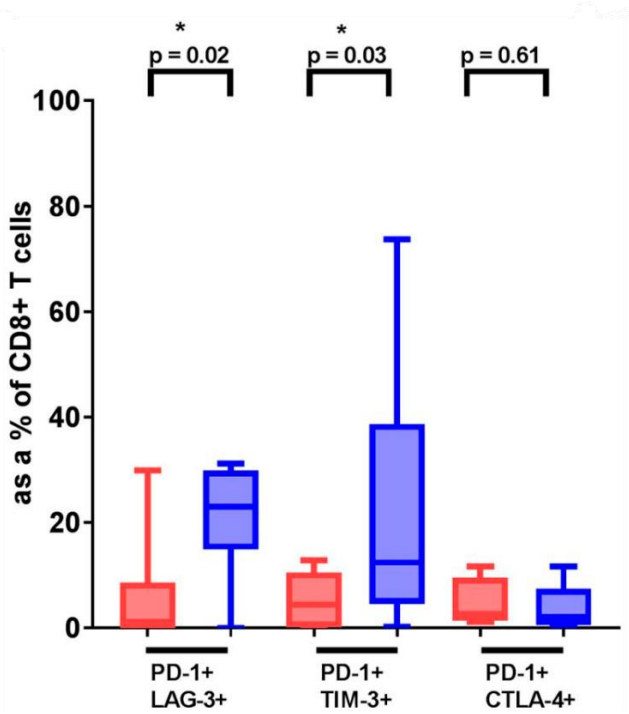
Refer to Appendix 15 Section 1.2 and Appendix 16 Section 1.2.

1.3. LBL-007 Plus BGB-A425 Rationale

1.3.1. Rationale for Combination of BGB-A425, LBL-007, and Tislelizumab in the Treatment of R/M HNSCC

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 anti-tumor immunity (Gettinger et al 2017, Hanna et al 2018, Johnson et al 2018, Kates et al 2021). The 3-year observational study followed with HNSCC patients who treated with anti-PD-(L)1 therapy, showed that LAG-3^{+}/PD-1^{+} and TIM-3^{+}/PD-1^{+} co-expressed $CD8^{+}$T cells were both increased among non-responders, compared with anti-PD-(L)1 responders (23.1% versus 1.2%, p = 0.02; 12.4% versus 4.4%, p = 0.03, respectively); whereas the expression of CTLA4 was not significantly changed, which could be a driven mechanism of anti-PD-(L)1 resistance (Figure 1) (Hanna et al 2018).

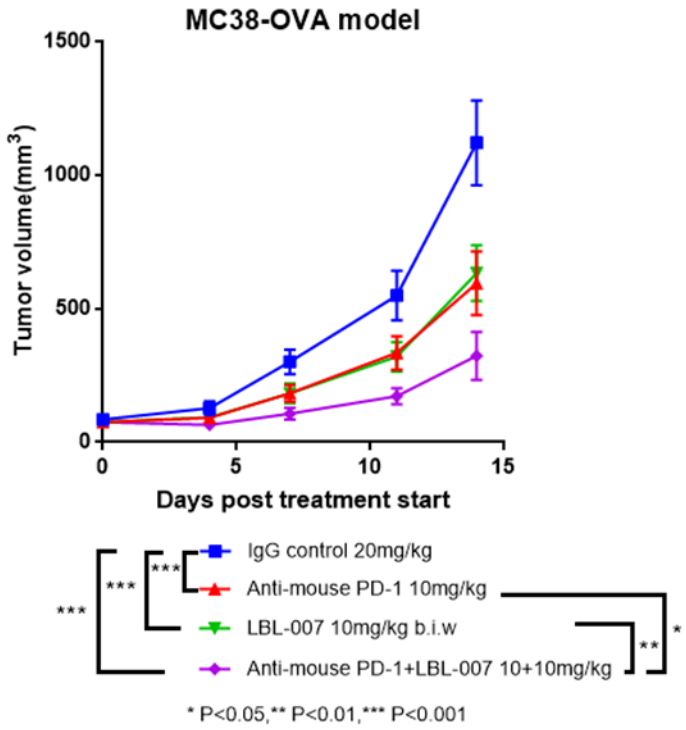
Figure 1: Correlating Immunophenotype With Response Among Anti–PD-1/L1 Treated Patients With HNSCC



Abbreviations: CD8: cluster of differentiation 8 ; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; LAG-3: lymphocyte activation gene-3; PD-1/L1: programmed cell death protein-1/ligand-1; TIM-3: T-cell immunoglobulin and mucin-domain containing-3.
Immune checkpoint co-expression appears increased among anti–PD-1/L1 non-responders (blue column, n = 34), compared with anti–PD-1/L1 responders (red column). Horizontal bars reflect median and 95% confidence intervals.
*P < 0.05 determined by Mann-Whitney test, Spearman's ρ (Hanna et al 2018).

In preclinical mouse study, LBL-007 in combination with anti-PD-1 significantly improved anti-tumor 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 2). There were no significant differences in body weight between groups.

Figure 2: Tumor Growth Curve After Treatment With LBL-007, Anti-Mouse PD-1 and the Combination in MC38-OVA Model



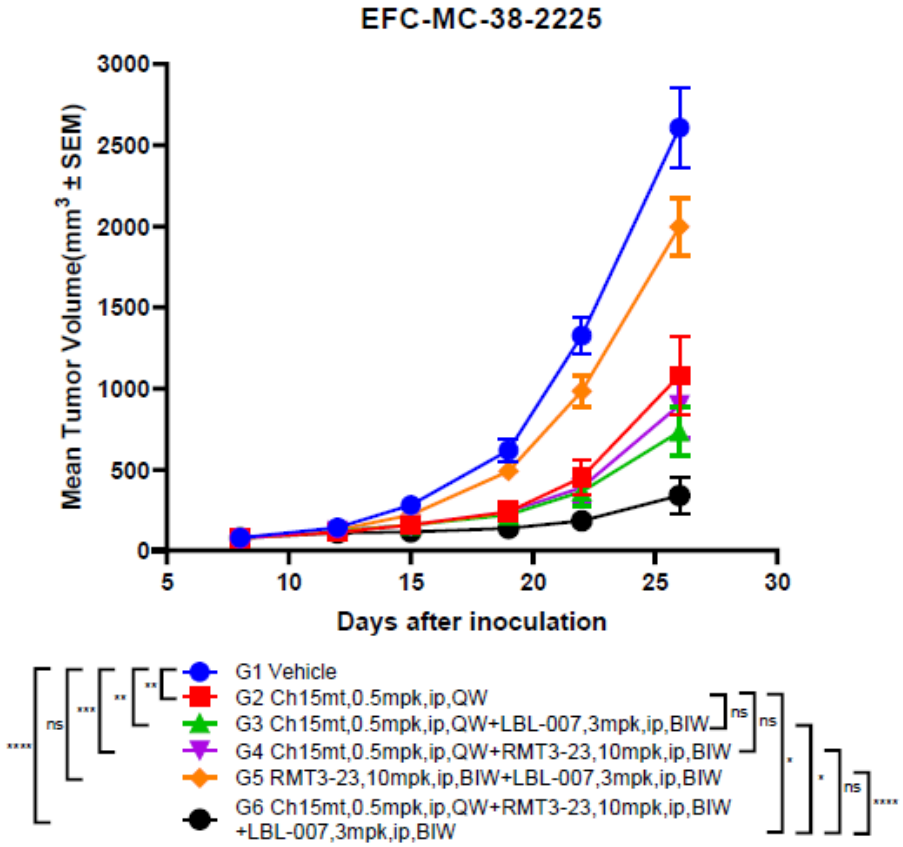
Abbreviations: IgG: immunoglobulin G; PD-1: programmed cell death protein-1.

The synergic antitumor efficacy for anti-LAG-3 antibody in combination with anti-PD-1 antibody has been preliminarily validated in clinical studies. 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 objective response rate (ORR) of 12.5% (4 patients experiencing PR) and a DCR of 53.1% (4 patients experiencing PR 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 3).

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 3: 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, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

1.3.2. Rationale for Selection of LBL-007 Dose in Combination With BGB-A425 and Tislelizumab in the Treatment of R/M HNSCC

Based on the single-agent dose escalation trial of WLZB-LBL-007-AST-001, 600 mg LBL-007 (once every 3 weeks) was chosen as the highest dose as in the range of the LBL-007 starting dose in combination with 200 mg tislelizumab administered every 3 weeks.

In LBL-007-CN-003 study, doses up to 400 mg of LBL-007 (once every 3 weeks) were evaluated with toripalimab (anti-PD-1 antibody) with no DLT (n = 6) observed. Similarly, in LBL-007-CN-002, the combination of LBL-007 (doses ranging up through 6 mg/kg; once every

2 weeks) with toripalimab was well tolerated with no DLT observed in 14 patients at this dose. Additionally, in the ongoing LBL-007-CN-004 study, doses of 300 mg and 600 mg LBL-007 (once every 3 weeks) were evaluated with tislelizumab with no DLT observed in either dose.

In BGB-900-102 study, as of 21 February 2023, a total of 3 patients received LBL-007 300 mg in combination with BGB-A425 600 mg and tislelizumab 200 mg once every 3 weeks, and a total of 4 patients received LBL-007 600 mg in combination with BGB-A425 600 mg and tislelizumab 200 mg once every 3 weeks. No DLT was reported in patients receiving 300 mg or 600 mg LBL-007 in combination with BGB-A425 and tislelizumab.

Considering the current safety and tolerability of this combination, the starting dose of LBL-007 will be 600 mg in combination with BGB-A425 600 mg and tislelizumab 200 mg, administered every 3 weeks.

2. 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 1. No auxiliary medicinal products, defined by Article 2(8) of Regulation (EU) 536/2014, will be used in this study.

Table 1: Investigational Medicinal Products Used in Study BGB-HNSCC-201 and Their Regulatory Approval Status

Country/Region	Approved for Treatment of First-line HNSCC (Yes/No)		
	BGB-A425	Tislelizumab	LBL-007
China	No	No	No
USA	No	No	No
Korea	No	No	No
Australia	No	No	No
European Union	No	No	No

Abbreviations: HNSCC, head and neck squamous cell carcinoma; USA, United States of America.

3. Formulation, Packaging, and Handling

Refer to Appendix 15 and Appendix 16.

4. Dosage and Administration

Randomization Phase

The dosing schedule for BGB-A425, LBL-007 in combination with tislelizumab in the experimental arm for BGB-A425 (Experimental Arm 3) is provided in Table 2.

Table 2: Selection and Timing of Dose for Each Patient (Experimental Arm 3)

Study Drug	Dose	Frequency and sequence of Administration	Route of Administration	Duration of Treatment
LBL-007	600 mg	Day 1 of each cycle (3 weeks) Administer first	Intravenous infusion	See Protocol Section 3.3

Study Drug	Dose	Frequency and sequence of Administration	Route of Administration	Duration of Treatment
Tislelizumab	200 mg	Day 1 of each cycle (3 weeks)		
BGB-A425	600 mg	Day 1 of each cycle (3 weeks) Administer after tislelizumab		

Tislelizumab, BGB-A425, and LBL-007 will be administered separately by intravenous infusion. Tislelizumab, BGB-A425, and LBL-007 must be prepared and administered as separate infusions and may not be administered with any other drug. Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

Dosing administration and monitoring times are provided in Table 3. Monitoring must occur in an area where emergency medical equipment and appropriately trained staff are available. Duration of infusion and postinfusion monitoring can be decreased if study drug infusion(s) is well tolerated. The infusion and postinfusion rules are outlined in Table 3.

Table 3: Administration of BGB-A425, LBL-007, and Tislelizumab and Monitoring Time

Cycle	BGB-A425 & LBL-007 & Tislelizumab Combination
Cycle 1 Day 1 (or first 2 administrations in case of dose delays)	LBL-007 infusion ≥ 60 minutes, followed by patient monitoring for ≥ 60 minutes, followed by tislelizumab infusion ≥ 60 minutes, followed by BGB-A425 infusion ≥ 60 minutes Patient monitoring for ≥ 120 minutes post completion of last infusion
Cycle 2 Day 1 onwards	LBL-007 infusion ≥ 30 minutes, followed by patient monitoring for ≥ 60 minutes, followed by tislelizumab infusion ≥ 30 minutes, followed by BGB-A425 infusion ≥ 30 minutes Patient monitoring for ≥ 60 minutes post completion of last infusion

Note: The infusion rate of tislelizumab or BGB-A425 may be decreased or the infusion may be stopped in the event of an infusion-related reaction.

The treatment for the overdose or incorrect administration of BGB-A425 and LBL-007 is the same as that for tislelizumab as described in Appendix 14 Section 4.1.

5. Dose Delay and Modification

Refer to Appendix 14 Section 6 for dose modification of tislelizumab.

No dose reductions will be allowed for LBL-007 and BGB-A425.

If a dose delay for any study drug is required, all doses LBL-007, BGB-A425 and tislelizumab must be delayed and, if applicable, restarted at the same time. Exceptions may be considered following consultation between the investigator and the medical monitor.

Guidance for dose delay and interruption for LBL-007 and BGB-A425 is the same as tislelizumab (Appendix 14 Section 6).

Treatment modifications to manage LBL-007 and BGB-A425-related toxicities, such as immune-mediated adverse events (imAEs) and infusion-related reactions, are described in Appendix 7.

Every effort should be made to administer the study treatment as described; however, in the event of significant non-immune-mediated toxicity, dosing may be interrupted in accordance with Appendix 8. There will be no dose reduction of LBL-007, BGB-A425 or tislelizumab. When treatment can be resumed following resolution of toxicities as listed in Appendix 8, LBL-007 and tislelizumab will be given at its initial dose, respectively.

6. Concomitant Therapy

Refer to Protocol Section 6.2 for concomitant therapies.

7. Risks Associated With BGB-A425, LBL-007 and Tislelizumab

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 (Appendix 15 Section 1,Appendix 16 Section 1).

Combined with the clinical efficacy that has been demonstrated for PD-1 blockade via tislelizumab (Protocol Section 1.2.4.2), the data strongly suggest that combination of BGB-A425 and LBL-007 has the potential to significantly improve and/or extend the therapeutic benefits of tislelizumab. As discussed in Protocol Section 1.2.4, PD-1 blockade by tislelizumab has been evaluated in more than 3220 patients with a safety and efficacy profile similar to what has been reported for other anti-PD-1 therapies. As discussed earlier in protocol Section 1.2 to Section 1.4, based upon the mechanism(s) of action, nonclinical as well as clinical data, the 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 an increase in immune-mediated toxicities compared with what has been observed with tislelizumab alone.

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.

In summary, there is strong scientific rationale that the combined blockade of the of TIM-3, 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.

7.1. Potential Interactions Between BGB-A425, LBL-007, Tislelizumab, 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.

8. Reference

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