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

Protocol ID: BGB-A317-LBL-007-201

NCT05609370

26 February 2025

CLINICAL STUDY PROTOCOL TITLE PAGE

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

Brief Title:

A Study to Investigate the Efficacy and Safety of LBL-007 Plus Tislelizumab in Combination With Bevacizumab Plus Fluoropyrimidine Versus Bevacizumab Plus Fluoropyrimidine as Maintenance Therapy in Patients With Unresectable or Metastatic Microsatellite Stable/Mismatch Repair Proficient Colorectal Cancer

Protocol Number:	BGB-A317-LBL-007-201
Amendment Number:	Protocol Amendment 4.0
Investigational Medicinal Products:	LBL-007 and Tislelizumab (BGB-A317)
Regulatory Agency Identification Number(s):	US IND 161962
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive, 3rd Floor San Mateo, California 94404 USA
Approval Date:	*See electronic signature*
Contact Information:	BeiGene Medical Officer Phone: 1.877.828.5568 Email: clinicaltrials@beigene.com

INVESTIGATOR SIGNATURE PAGE

I have read the protocol, appendices, and accessory materials related to study BGB-A317-LBL-007-201 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials.
- To protect the rights, safety, and welfare of the patients under my care.
- To provide oversight to all personnel to whom study activities have been delegated. This includes personnel at my site as well as personnel working in any facility where study activities are my responsibility.
- To control all investigational products provided by the sponsor and maintain records of the disposition of those products.
- To conduct the study in accordance with all applicable laws and regulations, the requirements of the ethics committee of record for my clinical site, and current GCP as outlined by ICH E6(R2).
- To obtain approval for the protocol and all written materials provided to patients before initiating the study at my site.
- To obtain informed consent – and updated consent in the event of new information or amendments – from all patients enrolled at my study site before initiating any study-specific procedures or administering investigational products to those patients.
- To maintain records of each patient's participation and all data required by the protocol in an accurate and timely manner.

Acceptance of this protocol constitutes my agreement that no confidential information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its affiliates, unless and only to the extent required by applicable laws and regulations.

Name: *Last name, First name*	**Title:** *Title at Institution*	**Institution:** *Address*
Signature:		**Date:** *DD Month YYYY*

DOCUMENT HISTORY

Amendment Version Number	Approval Date	Type of Protocol Amendment
BGB-A317-LBL-007-201 Amendment 3.0	26 September 2024	Substantial
BGB-A317-LBL-007-201 Amendment 2.0	30 June 2023	The assessment is not applicable for the United States; not assessed at time of amendment for submission in Australia; assessed as substantial per China local regulation
BGB-A317-LBL-007-201 Amendment 1.0	07 October 2022	The assessment is not applicable for the United States; not assessed at time of amendment for submission in Australia; assessed as substantial per China local regulation
Original protocol	05 July 2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

This Protocol Amendment 4.0 replaces Protocol Amendment 3.0. This amendment is considered substantial.

The primary purpose of Protocol Amendment 4.0 is to provide directives to close out the study and add description of continuous access to study treatment during the Extended IP Access Period.

The changes made in this amendment are described in the table below. Editorial and formatting changes are not included in this summary. Previous amendments are detailed in Appendix 1.

Protocol Amendment Summary of Changes Table

Section Number and Title	Summary of Change	Brief Rationale for Change
Section 1.3.1 Schedule of Activities; Section 6.7 Continued Access to Study Drug During the Extended IP Access Period; Section 8.8 Biomarkers; Section 8.12.3 Survival Follow-up; Section 10.6 Data Collection and Management Responsibilities; Section 10.8 Data Quality Assurance;	Added descriptions of continuous access of study drugs during the Extended IP Access Period, provided related instructions on safety monitoring, tumor response evaluation, PK/ADA and biomarker sample collection, SAE reporting, and data collection and management.	To update the approach for continued access to study drug, as well as to provide management guidance for patients entering the Extended IP Access Period.
Section 3.1 Objectives and Endpoints; Section 9.2 Analysis Sets; Section 9.3.4 Efficacy Analyses; Section 9.3.5 Safety Analyses; Previous Section 1.3.2 Pharmacokinetic and Immunogenicity Sampling Schedules (*deleted section*); Previous Section 1.3.3 Blood Biomarker Sampling Schedule (*deleted section*); Previous Section 8.8 Pharmacokinetics (*deleted section*); Previous Section 8.10	• Removed OS, PFS2, PK, and ADA from endpoints and objectives. • Removed PK Analysis Set and ADA Analysis Set. • Removed all exploratory endpoints and exploratory analysis. • Removed pharmacokinetic, immunogenicity, and biomarker sampling schedules. • Simplified the wording about statistical analyses of efficacy and safety.	To simplify the protocol due to study termination.

Section Number and Title	Summary of Change	Brief Rationale for Change
Pharmacodynamics (*deleted section*); Previous Section 8.11 Genetics (*deleted section*); Previous Section 8.12 Immunogenicity Analyses (*deleted section*); Previous Section 9.3.6 Pharmacokinetic Analyses (*deleted section*); Previous Section 9.3.7 Immunogenicity Analyses (*deleted section*); Previous Section 9.3.8 Other Exploratory Analysis (*deleted section*);		
Section 6.10.2.2 Safety Monitoring Plan; Section 8.6.4.1 Prompt Reporting of Serious Adverse Events;	• Clarified that during the Extended IP Access Period, safety assessments will be concordant with the protocol or per the investigator's discretion based on local or institutional guidelines. • Updated time frames and documentation methods for reporting serious adverse events.	To reflect the impact of continued access to study drug during the extended IP access period.
Section 4.1.1.3 Treatment Period	Clarified that all patients will receive study treatment up to 2 years until disease progression per RECIST v1.1, unacceptable toxicity, or withdrawal of informed consent.	To reflect the impact of continued access to study drug during the extended IP access period.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition/Explanation
5-FU	5-fluorouracil
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AxMP	auxiliary medicinal product
BGB-A317	tislelizumab
BOR	best overall response
BRAF	B-raf proto-oncogene, serine/threonine kinase
bTMB	blood tumor mutational burden
CK	creatine kinase
CK-MB	creatine-kinase cardiac muscle isoenzyme
CL	clearance
C_{max}	maximum concentration
CNS	central nervous system
CPS	Combined Positive Score
CR	complete response
CRC	colorectal cancer
CSR	clinical study report
CT	computed tomography
ctDNA	circulating tumor DNA
DCR	disease control rate
DLT	dose-limiting toxicity
dMMR	deficient mismatch repair
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture (system)

Abbreviation or Term	Definition/Explanation
EGFR	epidermal growth factor receptor
EOI	end of infusion
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-CR29	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Colorectal Cancer Module
EOT	End-of-Treatment (Visit)
FDA	Food and Drug Administration
FDG	fluorine-18 [F-18] fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GEP	gene expression profiling
GFR	glomerular filtration rate
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
iBOIN	Bayesian optimal interval design with informative prior
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
imAE	immune-mediated adverse event
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LAG-3	lymphocyte activation gene-3
LV	leucovorin or levoleucovorin
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Term	Definition/Explanation
MMR	mismatch repair
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
MSI-L	microsatellite instability-low
MSS	microsatellite stable
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NCI-PRO-CTCAE	National Cancer Institute Patient-Reported Outcomes Version of The Common Terminology Criteria For Adverse Evets
NK	natural killer
NMPA	National Medical Products Administration
NOAEL	no-observed-adverse-effect-level
NSAIDs	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung carcinoma
ORR	overall response rate
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein ligand-1
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
pMMR	proficient mismatch repair
PR	partial response
PT	Preferred Term
QoL	quality of life
QTcF	QT interval corrected by Fridericia’s formula
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SMC	Safety Monitoring Committee

Abbreviation or Term	Definition/Explanation
SoA	Schedule of Activities
SOC	System Organ Class
SOI	start of infusion
T3	triiodothyronine
T4	thyroxine
$t_{1/2}$	half-life
TAP	Tumor Area Positivity
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
TMB	tumor mutational burden
TMDD	target-mediated drug disposition
Treg	regulatory T (cells)
ULN	upper limit of normal
Vc	central volume of distribution
VEGF	vascular endothelial growth factor

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Synopsis	
Study Title	A Phase 1b/2, Randomized, Open-Label Study Investigating the Efficacy and Safety of LBL-007 Plus Tislelizumab in Combination With Bevacizumab Plus Fluoropyrimidine Versus Bevacizumab Plus Fluoropyrimidine as Maintenance Therapy in Patients With Unresectable or Metastatic Microsatellite Stable/Mismatch Repair Proficient Colorectal Cancer
Brief Study Title	A Study to Investigate the Efficacy and Safety of LBL-007 Plus Tislelizumab in Combination With Bevacizumab Plus Fluoropyrimidine Versus Bevacizumab Plus Fluoropyrimidine as Maintenance Therapy in Patients With Unresectable or Metastatic Microsatellite Stable/Mismatch Repair Proficient Colorectal Cancer
Brief Summary	This is a Phase 1b/2, randomized, multicenter, open-label study to investigate the efficacy and safety of LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine, and LBL-007 in combination with bevacizumab plus fluoropyrimidine versus bevacizumab plus fluoropyrimidine, in programmed cell death protein ligand-1 (PD-L1) positive and negative population groups, respectively, as maintenance therapy in patients with unresectable or metastatic microsatellite stable (MSS)/mismatch repair proficient (pMMR) colorectal cancer (CRC). The study consists of Phase 1b and Phase 2. Phase 1b as a safety run-in period will investigate the safety, tolerability, and pharmacokinetic (PK) of LBL-007 in combination with tislelizumab, bevacizumab, and fluoropyrimidine before expanding the enrollment to more patients in Phase 2. In Phase 2, patients will be randomized in the PD-L1 positive population group and the PD-L1 negative population group, respectively, for the investigation of efficacy and safety between LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine and LBL-007 in combination with bevacizumab plus fluoropyrimidine.
Sponsor	BeiGene, Ltd.
Amendment Version	Protocol Amendment 4.0
Regulatory Agency Identifier Number(s)	US IND 161962
Rationale	CRC is the third most common cancer and the second-highest cancer-related cause of death worldwide. The treatment for advanced MSS/pMMR CRC has had no significant improvement in decades. No solid clinical evidence to demonstrate the benefit of immune-oncology therapies. Lymphocyte activation gene 3 (LAG-3, CD223) is an inhibitory receptor on T cells and its expression is regulated by TCR activation. It is highly coexpressed with programmed cell death protein-1 (PD-1) and other inhibitory receptors. PD-1 and LAG-3 co-blockade enhances T-cell function and exhibits synergistic antitumor activity. Emerging data demonstrate promising anticancer activities of LAG-3 plus PD-L1 across tumor types with the potential to achieve greater benefit compared with standard of care. The current study targeting MSS/pMMR CRC is the first randomized Phase 2 study of LBL-007 in combination with tislelizumab. Overall, the safety profile supports further development of LBL-007 in combination with tislelizumab.
Objectives and Endpoints	
Objectives	**Endpoints**

Protocol Synopsis	
Primary: **Phase 1b** • To assess the safety and tolerability of LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine. **Phase 2** • To evaluate the efficacy between LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine (Arm A) and bevacizumab plus fluoropyrimidine (Arm C) as maintenance therapy in the programmed cell death protein ligand-1 (PD-L1) positive population (defined as Tumor Area Positivity [TAP] score ≥ 1% by the Ventana PD-L1 [SP263] assay) through progression-free survival (PFS), as assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) in patients with unresectable or metastatic microsatellite stable (MSS)/mismatch repair proficient (pMMR) colorectal cancer (CRC).	**Primary:** **Phase 1b** • Adverse events (AE) and serious AEs (SAE) as characterized by type, frequency, severity (as graded by National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0 [NCI-CTCAE v5.0]), timing, seriousness, and relationship to study treatments; physical examinations, electrocardiograms (ECGs), and laboratory assessments as needed; and AEs meeting protocol-defined dose-limiting toxicity (DLT) criteria. **Phase 2** • PFS, as assessed by the investigator per RECIST v1.1, defined as the time from the date of randomization to the date of first documentation of disease progression or death, whichever occurs first, in the Intent-to-Treat (ITT) Analysis Set of Arms A and C for PD-L1 positive population.
Secondary: • To evaluate the efficacy of LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine (Arm A) and bevacizumab plus fluoropyrimidine (Arm C) as maintenance therapy in the PD-L1 positive population through overall response rate (ORR) and duration of response (DOR). • To assess the efficacy of LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine (Arm D) and bevacizumab plus fluoropyrimidine (Arm E) in PD-L1 negative population (TAP < 1%) through PFS, ORR, and DOR. • To assess the safety and tolerability of LBL-007 with or without tislelizumab, in combination with bevacizumab plus fluoropyrimidine.	**Secondary:** • ORR and DOR as assessed by the investigator, in the ITT Analysis Set of Arms A and C for PD-L1 positive population. o ORR, defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) from the time of randomization. o DOR, defined as the time from the first confirmed objective response after randomization until the first documentation of disease progression or death, whichever comes first. • PFS, ORR, and DOR as assessed by the investigator, in the ITT Analysis Set of Arms D and E for PD-L1 negative population. • The incidence and severity of AEs according to NCI-CTCAE v5.0.
Study Design:	This is a Phase 1b/2, randomized, multicenter, open-label study to investigate the efficacy and safety of LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine, and LBL-007 in combination with bevacizumab plus fluoropyrimidine versus bevacizumab plus fluoropyrimidine, in PD-L1 positive and negative population groups, respectively (Arm A versus Arm C in PD-L1 positive population group, and Arm D versus Arm E in PD-L1 negative population group), as maintenance therapy in patients with unresectable or metastatic MSS/pMMR CRC. The study consists of Phase 1b and Phase 2. The study will be carried out at approximately 80 centers in Australia, China, and the United States. **Phase 1b** as a safety run-in period will investigate the safety, tolerability, and PK of LBL-007 in combination with tislelizumab, bevacizumab, and fluoropyrimidine before

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	expanding the enrollment to more patients in Phase 2. A maximum number of 36 patients will be enrolled in Phase 1b. Bayesian optimal interval design with informative prior will be used for the evaluation of LBL-007 in different doses (Zhou et al 2020). The planned doses for LBL-007 in the safety run-in period is 150 mg, 300 mg, and 600 mg once every 3 weeks or 200 mg and 400 mg once every 2 weeks. However, lower and/or intermediate doses of LBL-007 may be evaluated based on emerging clinical data, as appropriate. The dose for LBL-007 in Phase 2 will based on the emerging clinical data from Phase 1b and the recommendation from the Safety Monitoring Committee (SMC). If a dose > 600 mg once every 3 weeks or > 400 mg once every 2 weeks is recommended by the SMC, a protocol modification will be submitted to health authorities. The maintenance backbone includes bevacizumab and fluoropyrimidine (capecitabine or 5-fluorouracil [5-FU]/leucovorin or levoleucovorin [LV]). Capecitabine and 5-FU/LV will be initially evaluated in separate cohorts (Cohorts -1, 1a, and 1b) in Phase 1b. The SMC will review the safety and tolerability of quadruplet regimen with different fluoropyrimidines and provide recommendations on the choice of fluoropyrimidine in Cohort 2 and Phase 2. If both capecitabine and 5-FU/LV were confirmed to be safe based on the SMC's review, the choice of fluoropyrimidine in future cohorts will be at the investigator's discretion. **Phase 2:** Approximately 130 patients will be randomized in the PD-L1 positive population group and approximately 60 patients in the PD-L1 negative population group. Patients with PD-L1 positive status will be randomized in a 2:1:2 ratio to 1 of 3 treatment arms: • Arm A: LBL-007 + tislelizumab in combination with maintenance backbone • Arm B: LBL-007 in combination with maintenance backbone • Arm C: Maintenance backbone, ie, bevacizumab plus fluoropyrimidine The randomization will be stratified according to the following factor: • Liver metastases (absent versus present) Patients with PD-L1 negative status will be randomized in a 1:1 ratio to 1 of 2 treatment arms: • Arm D: LBL-007 + tislelizumab in combination with maintenance backbone • Arm E: Maintenance backbone, ie, bevacizumab plus fluoropyrimidine The study schema is shown in Figure 1. The Extended IP Access Period is established to provide continued access to study treatment for ongoing patients after the sponsor's decision of enrollment termination. The Extended IP Access Period will begin when Protocol Amendment 4.0 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 any discontinuation criterion 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 resign 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.

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	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:	The patients enrolled in this study are at least 18 years of age, with unresectable or metastatic CRC, who have locally or centrally confirmed pMMR or MSS status and have no disease progression after induction treatment in first-line therapy. Patients should not have received prior systemic therapy for CRC in the metastatic setting except for the induction treatment of the first-line therapy. Patients should have measurable disease according to RECIST v1.1, an ECOG Performance Status score of 0 or 1, and adequate organ function.
Number of Patients	The study plans to enroll approximately 226 patients: • Phase 1b (safety run-in): a maximum number of 36 patients. • Phase 2 (Proof-of-Concept): Approximately 130 patients with PD-L1 positive status (TAP ≥ 1%) and 60 patients with PD-L1 negative status (TAP < 1%). For Phase 2, approximately 130 patients with PD-L1 positive status will be randomized in a 2:1:2 ratio into 3 arms. With 72 events observed in Arm A versus Arm C, there will be 70% power to detect PFS difference with a one-sided alpha level of 0.05 if the true PFS HR equals 0.60. The efficacy data collected from patients in Arm B will be used to describe the component contribution of LBL-007. In addition, approximately 60 patients with PD-L1 negative status will be randomized in a 1:1 ratio into 2 arms for Phase 2. With a sample size of 30 patients in each arm, the binomial probabilities of detecting ≥ 1 TEAEs with a frequency of 5% and 1% are approximately 79% and 26%, respectively.
Study Drug/Treatments	For all cohorts and arms containing 5-FU in combination with LV: • The dose of 5-FU should not exceed the lowest dose level in induction treatment. • The dose of leucovorin or levoleucovorin will follow the relevant local guidance and/or prescribing information, where applicable, and should be no less than the lowest dose level in induction treatment. **Phase 1b** **Cohort -1 (LBL-007 + tislelizumab + bevacizumab + capecitabine):** • LBL-007 will be administered at a dose of 150 mg intravenously once every 3 weeks. • Tislelizumab will be administered at a dose of 200 mg intravenously once every 3 weeks. • Bevacizumab or its biosimilar (POBEVCY®, Bio-Thera Solutions, Ltd.; or MVASI®, Amgen Inc.) will be administered at a dose of 7.5 mg/kg intravenously once every 3 weeks. • Capecitabine 850 mg/m^2 will be administered twice daily orally for 2 weeks, followed by a one-week treatment break every 3 weeks. **Cohort -1b (LBL-007 + tislelizumab + bevacizumab + 5-FU):** • LBL-007 will be administered at a dose of 100 mg intravenously once every 2 weeks.

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	• Tislelizumab will be administered at a dose of 300 mg intravenously once every 4 weeks. • Bevacizumab or its biosimilar will be administered at a dose of 5 mg/kg intravenously once every 2 weeks. • 5-FU 1600 to 2400 mg/m^2 (continuous infusion over 46 to 48 hours) in combination with LV will be administered intravenously once every 2 weeks. Note: Cohort -1b will be initiated only if Cohort -1 is not tolerable due to capecitabine, assessed by the SMC. In this case, only a regimen containing 5-FU will be implemented in the subsequent study treatment. **Cohort 1a (LBL-007 + tislelizumab + bevacizumab + capecitabine):** • LBL-007 will be administered at a dose of 300 mg intravenously once every 3 weeks. • Tislelizumab will be administered at a dose of 200 mg intravenously once every 3 weeks. • Bevacizumab or its biosimilar will be administered at a dose of 7.5 mg/kg intravenously once every 3 weeks. • Capecitabine 850 mg/m^2 will be administered twice daily orally for 2 weeks, followed by a one-week treatment break every 3 weeks. **Cohort 1b (LBL-007 + tislelizumab + bevacizumab + 5-FU):** • LBL-007 will be administered at a dose of 200 mg intravenously once every 2 weeks. • Tislelizumab will be administered at a dose of 300 mg intravenously once every 4 weeks. • Bevacizumab or its biosimilar will be administered at a dose of 5 mg/kg intravenously once every 2 weeks. • 5-FU 1600 to 2400 mg/m^2 (continuous infusion over 46 to 48 hours) in combination with LV will be administered intravenously once every 2 weeks. **Cohort 2 (LBL-007 + tislelizumab + bevacizumab + fluoropyrimidine):** • LBL-007 will be administered at a dose of 600 mg intravenously once every 3 weeks, or 400 mg intravenously once every 2 weeks. The doses between 300 mg and 600 mg once every 3 weeks, or 200 mg to 400 mg once every 2 weeks, may be assessed based on a review of tolerability and exposure data by the SMC. • Tislelizumab will be administered at a dose of 200 mg intravenously once every 3 weeks or 300 mg intravenously once every 4 weeks. • Bevacizumab or its biosimilar will be administered at a dose of 7.5 mg/kg intravenously once every 3 weeks or 5 mg/kg intravenously once every 2 weeks. • Capecitabine 850 mg/m^2 will be administered twice daily orally for 2 weeks, followed by a one-week treatment break every 3 weeks. Alternatively, 5-FU 1600 to 2400 mg/m^2 (continuous infusion over 46 to 48 hours) in combination with LV will be administered intravenously once every 2 weeks. **Phase 2** **Arm A and Arm D (LBL-007 + tislelizumab + bevacizumab + fluoropyrimidine):** • LBL-007 will be administered at a dose of 600 mg intravenously once every 3 weeks, or 400 mg intravenously once every 2 weeks. A lower dose than 600 mg once every 3 weeks or 400 mg once every 2 weeks may be

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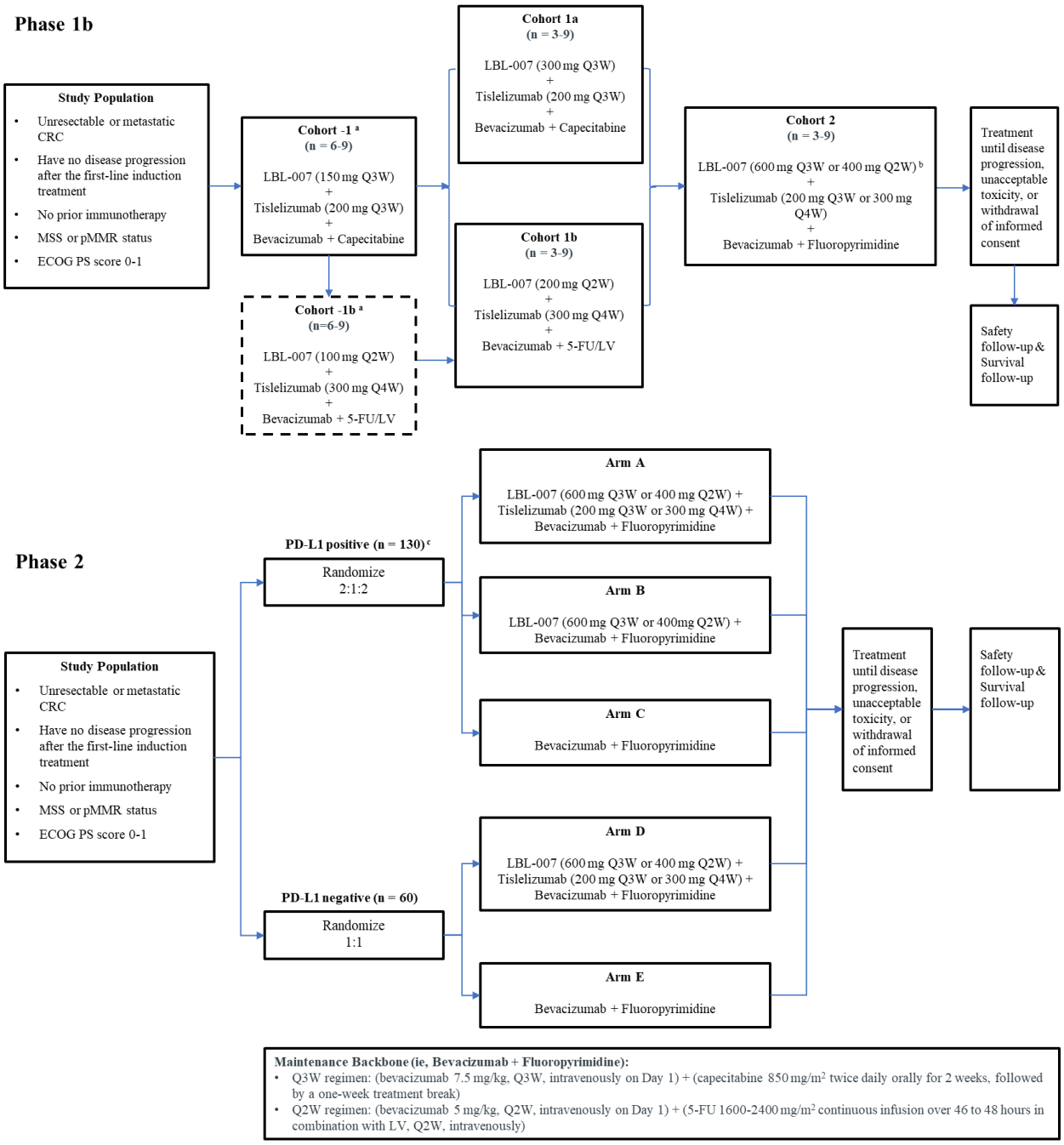
	determined as recommended dose for Phase 2 based on tolerability, safety, and PK data from Phase 1b and the SMC recommendation. • Tislelizumab will be administered at a dose of 200 mg intravenously once every 3 weeks or 300 mg intravenously once every 4 weeks. • Bevacizumab or its biosimilar will be administered at a dose of 7.5 mg/kg intravenously once every 3 weeks or 5 mg/kg intravenously once every 2 weeks. • Capecitabine 850 mg/m^2 will be administered twice daily orally for 2 weeks, followed by a one-week treatment break every 3 weeks. Alternatively, 5-FU 1600 to 2400 mg/m^2 (continuous infusion over 46 to 48 hours) in combination with LV will be administered intravenously once every 2 weeks. **Arm B (LBL-007 + bevacizumab + fluoropyrimidine):** • LBL-007 will be administered at a dose of 600 mg intravenously once every 3 weeks, or 400 mg intravenously once every 2 weeks. A lower dose than 600 mg once every 3 weeks or 400 mg once every 2 weeks may be determined as recommended dose for Phase 2 based on tolerability, safety, and PK data from Phase 1b and the SMC recommendation. • Bevacizumab or its biosimilar will be administered at a dose of 7.5 mg/kg intravenously once every 3 weeks or 5 mg/kg intravenously once every 2 weeks. • Capecitabine 850 mg/m^2 will be administered twice daily orally for 2 weeks, followed by a one-week treatment break every 3 weeks. Alternatively, 5-FU 1600 to 2400 mg/m^2 (continuous infusion over 46 to 48 hours) in combination with LV will be administered intravenously once every 2 weeks. **Arm C and Arm E (bevacizumab + fluoropyrimidine):** • Bevacizumab or its biosimilar will be administered at a dose of 7.5 mg/kg intravenously once every 3 weeks or 5 mg/kg intravenously once every 2 weeks. • Capecitabine 850 mg/m^2 will be administered twice daily orally for 2 weeks, followed by a one-week treatment break every 3 weeks. Alternatively, 5-FU 1600 to 2400 mg/m^2 (continuous infusion over 46 to 48 hours) in combination with LV will be administered intravenously once every 2 weeks.
Ethical Considerations	The effects of LBL-007 in combination with tislelizumab in metastatic CRC are not yet fully known. LBL-007 in combination with tislelizumab is expected to be effective in treating CRC because combination therapies involving other drugs that inhibit LAG-3 have provided clinical benefit to patients with solid tumors in clinical studies. As of 10 January 2024, LBL-007 has been given to a total of 458 patients as a single drug or in combination with other anticancer drug(s). The purpose of this study is to investigate the efficacy and safety of a combined treatment of LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine. LBL-007 in combination with tislelizumab have not yet been approved. Bevacizumab and capecitabine are approved for use in CRC, but their use in combination with LBL-007 alone or LBL-007 in combination with tislelizumab is not. The actual efficacy of the study treatments for patients with CRC is not known. The side effects and toxicity seen in treated patients in these studies are similar to those that are expected for other immune-oncology drugs in the same class. However, the actual side effects that each patient experiences may vary.

1.2. Study Schema

Figure 1: Study Schema



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

Notes:

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

[b] The doses of LBL-007 between 300 mg and 600 mg once every 3 weeks, or 200 mg to 400 mg once every 2 weeks, may be assessed based on a review of tolerability and exposure data by the SMC.
[c] The randomization of PD-L1 positive population in Phase 2 will be stratified according to the following factor: liver metastases (absent versus present).

1.3. Schedule(s) of Activities

1.3.1. Schedule of Activities

Table 1: Schedule of Activities [1]

Study Procedures	Protocol Section	Prescreening (for Phase 2) [2]	Screening [3]	Treatment Cycles								Follow-up				
				Cycle 1			Cycle 2			≥ Cycle 3	EOT Visit [4]	Safety Follow-up [5]			Efficacy Follow-up [6]	Survival Follow-up [7]
Visit Days		**-56 before randomization**	**-28 to -1**	**1**	**8**	**15 [8]**	**1**	**8**	**15 [8]**	**1**	**After Last Dose**	**+ 30 (visit)**	**+ 60 (phone call)**	**+ 90 (phone call)**	**—**	**Every 3 months**
Visit Window [9] (Days)				**—**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**	**0 to 7**	**± 7**	**± 14**	**± 14**	**—**	**± 14**
Administrative																
Prescreening informed consent	8.1.1, 10.3	X														
Informed consent [1]	8.1.2.1, 10.3		X													
Review inclusion/exclusion criteria	5.1, 5.2, 8.2.1	X	X													
Demographics/ medical history/ disease history [10]	8.1.2.3		X													
Administration of study drug(s)																
LBL-007 [11]	6.1			X			X			X						
Tislelizumab [12]	6.1			X			X			X						
Bevacizumab [13]	6.1			X			X			X						

Study Procedures	Protocol Section	Prescreening (for Phase 2) [2]	Screening [3]	Treatment Cycles								Follow-up				
				Cycle 1			Cycle 2			≥ Cycle 3	EOT Visit [4]	Safety Follow-up [5]			Efficacy Follow-up [6]	Survival Follow-up [7]
Visit Days		**-56 before randomization**	**-28 to -1**	**1**	**8**	**15 [8]**	**1**	**8**	**15 [8]**	**1**	**After Last Dose**	**+ 30 (visit)**	**+ 60 (phone call)**	**+ 90 (phone call)**	**—**	**Every 3 months**
Visit Window [9] (Days)				**—**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**	**0 to 7**	**± 7**	**± 14**	**± 14**	**—**	**± 14**
Capecitabine [14]	6.1			X			X			X						
5-FU/LV [15]	6.1			X			X			X						
Efficacy Assessments																
Tumor assessment [1, 4, 16]	8.4		X	Every 9 weeks (63 days ± 7 days) from Day 1 of Cycle 1							X [4]				X	
Survival status [1]	8.12.3															X
Safety Assessments																
Physical examination [1, 17]	8.5.1		X	X			X			X	X	X				
Vital signs/height and weight [1, 18]	8.5.2		X	X	X	X	X	X	X	X	X	X				
ECOG Performance Status [1]	8.5.3		X	X			X			X	X	X				
Triplicate 12-lead ECG (for Phase 1b) [1, 19]	8.5.4		X	Predose, approximately 30 min after the completion of the last study treatment infusion(s) on Cycle 1, and as clinically indicated							X	X				
Single 12-lead ECG (for Phase 2) [1, 19]	8.5.4		X	As clinically indicated							X	X				

Study Procedures	Protocol Section	Prescreening (for Phase 2) [2]	Screening [3]	Treatment Cycles								Follow-up				
				Cycle 1			Cycle 2			≥ Cycle 3	EOT Visit [4]	Safety Follow-up [5]			Efficacy Follow-up [6]	Survival Follow-up [7]
Visit Days		**-56 before randomization**	**-28 to -1**	**1**	**8**	**15 [8]**	**1**	**8**	**15 [8]**	**1**	**After Last Dose**	**+ 30 (visit)**	**+ 60 (phone call)**	**+ 90 (phone call)**	**—**	**Every 3 months**
Visit Window [9] (Days)				**—**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**	**0 to 7**	**± 7**	**± 14**	**± 14**	**—**	**± 14**
Ophthalmologic examination [1, 20]	8.5.1		X													
Hematology [1, 4, 21]	8.5.5		X	X	X	X	X	X	X	X	X [4]	X				
Clinical chemistry [1, 4, 21]	8.5.5		X	X	X	X	X	X	X	X	X [4]	X				
Coagulation [1, 4, 21]	8.5.5		X	X	As clinically indicated						X [4]	X				
Urinalysis [1, 21]	8.5.5		X	X			X			X	X	X				
Cardiac enzyme monitoring [1, 4, 22]	8.5.7		X	X	X	X	X	X	X	X	X [4]	X				
Pregnancy test [1, 23]	8.5.6		X	X			X			X	X	X				
Thyroid function [1, 24]	8.5.5		X				X			X		X				
HBV/HCV/HIV tests [1, 25]	8.5.8, 8.1.2.6		X	Every 4 cycles starting at Cycle 5 in patients with detectable HBV DNA at screening or as clinically indicated in all patients												
Pulmonary function tests [1, 26]	8.1.2.5		X	As clinically indicated												
AEs and SAEs [1, 27, 28]	8.5.9		X	X	X [28]	X [28]	X	X [28]	X [28]	X	X	X	X	X		

Study Procedures	Protocol Section	Prescreening (for Phase 2) [2]	Screening [3]	Treatment Cycles								Follow-up				
				Cycle 1			Cycle 2			≥ Cycle 3	EOT Visit [4]	Safety Follow-up [5]			Efficacy Follow-up [6]	Survival Follow-up [7]
Visit Days		**-56 before randomization**	**-28 to -1**	**1**	**8**	**15 [8]**	**1**	**8**	**15 [8]**	**1**	**After Last Dose**	**+ 30 (visit)**	**+ 60 (phone call)**	**+ 90 (phone call)**	—	**Every 3 months**
Visit Window [9] (Days)				—	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**	**0 to 7**	**± 7**	**± 14**	**± 14**	—	**± 14**
Prior and concomitant medications [28]	6.9		X	X	X	X [28]	X	X [28]	X [28]	X	X	X	X	X		
Prior and concomitant procedures [28]	6.9		X	X	X	X [28]	X	X [28]	X [28]	X	X	X	X	X		
Patient-Reported Outcomes																
EORTC QLQ-C30 [29]	8.7			X			X			X [29]	X					
EORTC QLQ-CR29 [29]	8.7			X			X			X [29]	X					
NCI-PRO-CTCAE [30]	8.7						X			X	X					

1.3.1.1. Footnotes for Table 1: Schedule of Activities

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

1. During the Extended IP Access Period (see Section 6.7), 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 8.6.4. Samples for PK, ADA, and biomarker assessments will not be collected during the Extended IP Access Period. Patients who enter the Extended IP Access Period will resign the informed consent form.
2. Prescreening period is optional at the investigator's discretion and will start during the induction treatment before the screening if the patient is considered eligible for the clinical study. The overall duration for Pre-Screening is 56 days before the randomization. A separate prescreening informed consent must be obtained. During the Prescreening Period of Phase 2, patients will undergo PD-L1 and MSI-H/dMMR status confirmation. The Prescreening Period allows early exclusion for the patients who experienced disease progression during induction treatment.
3. Screening evaluations will be performed ≤ 28 days before starting the study treatment (for Phase 1b) or randomization (for Phase 2). Written informed consent is required before performing any study-specific procedure. Results of standard-of-care tests or examinations performed before informed consent has been obtained and within 28 days before starting the study treatment (for Phase 1b) or randomization (for Phase 2) may be used for screening assessments rather than repeating the standard-of-care tests unless otherwise indicated. The ICF signature alone does not define the start of the screening period, but the first study-related assessment date is to be used for the date of the Screening Visit.
4. The EOT Visit is conducted within 7 days after the investigator determines to discontinue the study treatment (including all drugs) regardless of any reasons. If routine laboratory tests (eg, hematology, clinical chemistry) were completed within 7 days before the EOT Visit, these tests do not need to be repeated. Tumor assessment is not required at the visit provided that ≤ 9 weeks have passed since the last assessment.
5. Patients will be asked to return to the clinic for a Safety Follow-up Visit to occur 30 days (± 7 days) after the last dose of study drug, or before the initiation of a new anticancer treatment, whichever occurs first. Patients who discontinue LBL-007 and tislelizumab in Phase 1b and Arm A and Arm D of Phase 2, or LBL-007 in Arm B of Phase 2 will be asked to return to the clinic or will be contacted via telephone to assess imAEs and concomitant medications (if appropriate, ie, associated with an

imAE) at 60 and 90 (± 14) days after the last dose of LBL-007 or tislelizumab, whichever is later, regardless of whether they start a subsequent anticancer therapy. If patients report a suspected imAE at a follow-up visit or a telephone contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

6. Efficacy Follow-Up Period: Patients who discontinue study treatment(s) for reasons other than progressive disease (eg, toxicity) will continue to undergo tumor assessments following the original schedule until the patient experiences progressive disease, death, loss to follow-up, withdrawal of consent, start a new anticancer therapy, or study termination, whichever occurs first.
7. Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months after the Safety Follow-up Visit, until death, withdrawal of consent, loss to follow up, 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.
8. The Day 15 visits apply only to the 3-week regimens in this study.
9. A minor change in visit scheduling due to operational feasibility is permitted (eg, visit window falls on a nonworking day such as a weekend or public holiday), and this will not be considered a protocol deviation.
10. Cancer history will include an assessment of prior anticancer surgery, prior locoregional therapy to liver, prior radiotherapy, and prior drug therapy including start and stop dates, best response, and reason for discontinuation. Radiographic studies performed before study entry may be collected for review by the investigator. Preexisting AEs at baseline should be recorded as medical history.
11. LBL-007 will be given intravenously on Day 1 of each cycle (see Section 6.1 for details). The delivery period of the LBL-007 infusion will be over 60 (± 5) minutes for all cycles. Note: Tislelizumab infusion must always occur after infusion of LBL-007 has completed.
12. Tislelizumab will be administered by intravenous infusion beginning with the first dose on Day 1 of Cycle 1 (see Section 6.1 for details). The delivery period of the initial infusion (Day 1 of Cycle 1) will be over 60 (± 5) minutes. If well tolerated, the delivery period of subsequent infusions can be shortened to over 30 (± 5) minutes.
13. Bevacizumab will be administered by intravenous infusion beginning with the first dose on Day 1 of Cycle 1 (see Section 6.1 for details). The delivery period of the infusion (Day 1 of each Cycle) will be over 30 (± 5) minutes. The delivery period for the bevacizumab infusion on Day 1 of Cycle 1 may follow local guidelines, if applicable.
14. Capecitabine will be administered twice daily orally, from the morning of Day 1 to the evening of Day 14 or from the evening of Day 1 to the morning of Day 15 of each 21-day cycle.

15. 5-FU 1600 to 2400 mg/m^2 (continuous infusion over 46 to 48 hours) in combination with LV will be administered intravenously, once every 2 weeks on Day 1 of each 14-day cycle for all enrolled patients. The dose of 5-FU should not exceed the lowest dose level in induction treatment. The dose of leucovorin or levoleucovorin will follow the relevant local guidance and/or prescribing information, where applicable, and should be no less than the lowest dose level in induction treatment.
16. Tumor imaging will be performed ≤ 28 days before the first dose date (Phase 1b) or randomization (Phase 2). Results of standard-of-care tests or examinations performed before obtaining informed consent and ≤ 28 days before starting the study treatment may be used for the purposes of screening rather than repeating the standard of care tests. During the study, tumor response will be evaluated by the investigator every 9 weeks (63 days ± 7 days) from Day 1 of Cycle 1, in accordance with RECIST v1.1. Tumor assessments must be performed on schedule regardless of whether the study treatment(s) have been administered or withheld, ie, they should not be adjusted for delays in cycles. See Section 8.4 for more information.
17. Refer to Section 8.5.1 for details regarding physical examination assessment requirements for screening and subsequent timepoints. In addition, investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during study treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.
18. Height assessment is required only at screening. Weight will be measured before study treatment administration in every cycle. Vital signs will include measurements of body temperature (˚C), pulse rate, and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be measured while the patient is in a seated position after resting for 10 minutes. If coinciding with study treatment infusions, the patient's vital signs must be recorded within 60 minutes before the study treatment administration.
19. For patients in Phase 1b, the triplicate 12-lead ECG recordings will be obtained during screening, predose, and approximately 30 minutes after the completion of the last study treatment infusion(s) on Cycle 1, the EOT Visit, the Safety Follow-up Visit, and as clinically indicated at other timepoints. For patients in Phase 2, the single 12-lead ECG recordings will be obtained during screening, the EOT/Safety Follow-up Visit, and as clinically indicated at other timepoints. The patient should rest in semirecumbent supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (eg, television, radio, conversation, etc) before each ECG collection.
20. 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.

21. Local laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Table 11. If laboratory tests at screening are not performed ≤ 7 days before Day 1 of Cycle 1, these tests should be repeated and reviewed before starting the study treatment. After Cycle 1, tests are to be conducted and results are to be reviewed within 48 hours before study treatment administration. Hematology and clinical chemistry will be performed weekly for the first 2 cycles and then at the beginning of each subsequent cycle. Coagulation test will be conducted ≤ 7 days before Day 1 of Cycle 1, at the EOT Visit, at the Safety Follow-up Visit, and as clinically indicated at other timepoints. Urinalysis will be conducted at Screening, on Day 1 of each cycle (≤ 7 days before Day 1 of Cycle 1, ≤ 2 days before Day 1 of Cycle 2, and ≤ 3 days before Day 1 of Cycle 3 and subsequent cycles), Safety Follow-up Visits, and as clinically indicated. Refer to Appendix 3 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.
22. CK and CK-MB testing will be implemented for all patients at screening, repeated at all scheduled visits during the first 3 treatment cycles, all predose assessments from Cycle 4 onwards, the EOT Visit, and the Safety Follow-up Visit (30 days [± 7 days] after the last dose). If CK-MB fractionation is not available, serum troponins (troponin I and/or T) may be tested instead.
23. Urine or serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented with a negative result within 7 days before Day 1 of Cycle 1. Urine pregnancy tests will be performed at each visit before dosing, and at the EOT/Safety Follow-up Visits. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.
24. Analysis of free T3, free T4, and thyroid stimulating hormone will be performed by the local study site laboratory or a central laboratory. Thyroid function tests will be performed at screening, on Day 1 of each cycle starting at Cycle 2 (≤ 2 days before Day 1 of Cycle 2, ≤ 3 days before Day 1 of Cycle 3 and subsequent cycles), and at 30-day Safety Follow-up Visit. Results are to be reviewed within 48 hours before study treatment administration where applicable.
25. Viral hepatitis B and C serologic markers and viral load (if applicable) will be tested by a central laboratory or the local laboratory. Testing at screening will consist of HBsAg, HBsAb, HBcAb, HCV antibody. HBV DNA or HCV RNA will be assessed in patients positive for HBsAg or HCV antibody, respectively. Patients with detectable HBV DNA at screening will have viral load reassessed every 4 cycles (ie, Day 1 of Cycle 5, 9, 13, etc) starting from Cycle 5.
26. Patients who are suspected of having or known to have serious and/or severe respiratory conditions, or who exhibit significant respiratory symptoms unrelated to the underlying cancer, or who have a history of thoracic radiotherapy will undergo pulmonary function testing that may include, but is not limited to, spirometry and assessment of diffusion capacity done during the screening period to assist the determination of suitability for the study.

27. The AEs and laboratory abnormalities will be graded per the NCI-CTCAE v5.0. All AEs will also be evaluated for seriousness. After the ICF has been signed but before the administration of study treatment(s), only SAEs associated with protocol-defined procedures should be reported to the sponsor. After initiation of study treatment(s), all AEs and SAEs, regardless of relationship to study treatment(s), will be reported until either 30 days after the last dose of study treatment(s) or initiation of subsequent anticancer therapy, whichever occurs first. ImAEs (serious and nonserious) should be reported until 90 days after the last dose of study treatments regardless of whether the patient starts a subsequent anticancer therapy. All SAEs considered related to the study treatment(s) that are brought to the attention of the investigator should be reported, regardless of time since the last dose of treatment.
28. Review of AEs and concomitant medications and procedures may be conducted by telephone on Cycle 1 Days 8 and 15 and Cycle 2 Days 8 and 15 if the patient is unable to make it to the clinic.
29. Both questionnaires will be completed at predose on Day 1 of every cycle from Cycle 1 (baseline) throughout to Cycle 4, and then to coincide with scheduled tumor assessments (every 9 weeks [± 7 days]) until the EOT Visit.
30. The questionnaire will be completed at predose on Day 1 of every cycle from Cycle 2 until the EOT Visit.

2. INTRODUCTION

2.1. Study Rationale

2.1.1. Background Information on Colorectal Cancer

2.1.1.1. Epidemiology

CRC is the third most common cancer and the second-highest cancer-related cause of death worldwide (Sung et al 2021). In 2020, approximately 147,950 individuals were estimated to be diagnosed with CRC and 53,200 would die from the disease (Siegel et al 2020). In the recent years, the estimated global burden of CRC increased by 60% to an estimated over 2.2 million new cases and 1.1 million deaths by 2030 (Sawicki et al 2021).

According to the GLOBOCAN 2020 data, there is a broad geographic variation in CRC incidence and mortality among various countries of the world. The disease is widely recognized as a marker of the country's socioeconomic development. The highest colon cancer incidence rates are found in European regions, Australia/New Zealand, and Northern America (Arnold M et al 2017; Bray et al 2018; World Cancer Research Fund/American Institute for Cancer Research 2018). CRC patient population is rapidly shifting towards a younger age. Incidence has increased among those younger than 65 years, with a 1% annual increase in those aged 50 to 64 years and 2% annual increase in those younger than 50 years. CRC death rates also showed age-dependent trends, declining by 3% annually for those 65 years and older, compared to a 0.6% annual decline for individuals aged 50 to 64 years and a 1.3% annual increase for individuals younger than 50 years (Siegel et al 2020). A worrying rise in patients younger than 50 years presenting with colorectal cancer has been observed, especially rectal cancer and left-sided colon cancer (Bailey et al 2015; Kasi et al 2019; Wolf et al 2018).

2.1.1.2. Background Information on MSS/pMMR CRC

CRC is classified into two categories: 1) The MSI-H group, which is caused by defects in the DNA MMR system and accounts for approximately 15% of tumors; and 2) the MSS group, which exhibits chromosomal instability and accounts for the remaining 85% of tumors (Brenner et al 2014; Cancer Genome Atlas Network 2012; Kloor and von Knebel Doeberitz 2016). At the protein level, MSI-H is similar to dMMR status, while MSI-L/MSS are similar to pMMR status (Koopman et al 2009). MSS mCRC is usually considered to be a typical "cold" cancer that presents a poor response to immunotherapy. Indeed, MSS mCRC accounts for approximately 95% of all mCRC cases (Overman et al 2018b). It is important to explore how these patients can benefit from adaptive immunotherapy.

Immune checkpoint therapy, pembrolizumab (KEYTRUDA®, Merck & Co., Inc.) and nivolumab (OPDIVO®, Bristol-Myers Squibb Company), received regulatory approval in 2017 for the treatment of heavily mutated tumors that are dMMR or have high levels of MSI-H. By contrast, current immune checkpoint inhibitors are ineffective in tumors that are pMMR and are MSS or have low levels of MSI-L (termed pMMR-MSI-L tumors).

2.1.2. Current Treatment of Colorectal Cancer

The 5-year relative survival rate for CRC ranges from 90% for patients diagnosed with localized disease to 14% for those diagnosed with metastasized disease (Siegel et al 2020).

Approximately 50% to 60% of patients diagnosed with CRC develop colorectal metastases (Van Cutsem et al 2019), and 80% to 90% of these patients have unresectable metastatic liver disease (Kemeny 2006; Muratore et al 2007). Patients with a resectable primary colon tumor and resectable synchronous metastases can be treated with a staged or simultaneous resection. Systematic treatment is still the main treatment option for most of patients who have an unresectable metastatic disease.

2.1.2.1. Current Systemic Treatment for Unresectable or Metastatic MSS/pMMR CRC

For the majority of patients with unresectable or metastatic MSS/pMMR CRC, systemic therapy is tailored with patient-specific and disease-specific predictive markers. Paralleled with the advances in surgical and allied specialties, the increasing number of effective drugs for CRC has led to substantial improvement of OS. Deciding whether the therapy is going to be curative or palliative is crucial and depends primarily on the tumor burden. Patients might have few (or oligo) metastases that can be resected and rendered cured. Moreover, patients with widely metastatic disease might become suitable candidates for local treatment pending a great response to systemic therapy. Downsizing these tumors with conversion therapies is increasingly being used (Falcone et al 2007). Systemic therapy for mCRC typically includes a chemotherapy backbone paired with a biologic. Fluoropyrimidines, oxaliplatin, and irinotecan chemotherapies form the chemotherapy backbone in various iterations of two-drug regimens (FOLFOX/ FOLFIRI/CapeOx) or three-drug regimen (FOLFIRINOX).

2.1.2.2. Maintenance Therapy in mCRC Treatment

In mCRC, induction combination chemotherapy with a targeted agent is considered the mainstay of treatment. In terms of toxicities, cumulative peripheral sensory neuropathy associated with oxaliplatin is a major safety concern and a cause for pause in many therapeutic settings. Irinotecan is typically associated with digestive toxicity (eg, nausea, vomiting, abdominal pain) which can have a severe impact on QoL. Principal toxicities associated with EGFR inhibitors are paronychia, skin fissures and acneiform rash, while hypertension, proteinuria and an increased risk of bleeding are related to bevacizumab, representing significant but generally more manageable AEs for our patients compared with cytotoxic agents. Considering that the objective of the treatment is to achieve optimal OS preserving QoL, reducing both the toxicity of any treatments administered and tumor-related symptoms weigh in heavily on the balance. Approaches to overcome cumulative toxicities include suspending chemotherapeutics such oxaliplatin or irinotecan while maintaining fluoropyrimidines, with or without targeted agents, until tumor progression (as an example, maintenance with 5-FU plus bevacizumab biweekly in case of peripheral sensory neuropathy with oxaliplatin); stopping all treatments and restarting them upon progression (stop-and-go strategy, the drugs are still effective when they are suspended); or using predefined treatment intervals in an attempt to avoid toxicity (for example, 12 weeks of treatment, programmed stop, and future restart).

2.2. Background

2.2.1. Background Information on LBL-007

LBL-007 is a fully human anti-LAG-3 monoclonal IgG4 antibody developed for the treatment of advanced solid tumors.

LAG-3 is a cell-surface molecule that is expressed on immune cells, including T cells, and negatively regulates T-cell proliferation and effector T-cell function.

LAG-3 is a transmembrane protein consisting of four Ig-like extracellular domains (D1–D4) and a cytoplasmic domain. One of the most principal ligands of LAG-3 was major histocompatibility complex class II (MHC class II) (Lythgoe et al 2021), a proline-enriched loop in D1 mediates their interactions. Multiple studies have demonstrated that the interactions between LAG-3 and MHC class II modulate the proliferation, activation, apoptosis, and cytokine secretion of multiple immune cells (Andreae et al 2002; Avice et al 1999; He et al 2016).

LAG-3 can be constitutively expressed or induced on multiple immune cells, including CD4/CD8+ T cells, NK cells, invariant NK T cells, plasmacytoid DCs, and B cells (Solinas et al 2019). Overexpression of LAG-3 has been detected in various cancers, where it participates in immune regulation and resistance to treatment, thus affecting patient survival (Long et al 2018; Westergaard et al 2020).

In addition, LAG-3 is also expressed on Treg cells and LAG-3+Treg cells are highly suppressive compared to LAG-3 - Treg cells (Huang et al 2004; Camisaschi et al 2010). LAG-3 blockade is shown to promote T-cell proliferation and enhance the function of cytotoxic T cells (Lichtenegger et al 2018). LAG-3 inhibition can also reduce the immunosuppressive activity of LAG-3+ Treg cells, resulting in enhanced activation of effector T cells (Huang et al 2004).

LAG-3 is frequently coexpressed with PD-1 on tumor-infiltrating T cells, while LAG-3 and PD-1 double positive T cells are in a more severe dysfunction state than T cells expressing PD-1 or LAG-3 alone. Moreover, LAG-3 expression is upregulated following anti-PD-1 treatment, and the frequency of LAG-3+ T cells is significantly higher in anti-PD-L1 resistant or nonresponsive patients with solid tumors, including NSCLC, head and neck squamous cell carcinoma, melanoma, and bladder cancer (Gettinger et al 2017; Datar et al 2019; Hanna et al 2018; Johnson et al 2018; Kates et al 2021). Co-blockade of PD-1 and LAG-3 synergize to restore the function of exhausted T cells and inhibit tumor growth by enhancing antitumor immunity in mouse models (Woo et al 2012; Yang et al 2017; Ghosh et al 2019; Mimura et al 2021). Those results suggest that the combination of anti-LAG-3 and anti-PD-1 could further improve the clinical outcome of anti-PD-1, and the combination therapy may provide clinical benefit for those patients who are resistant or do not response to anti-PD-1 therapy. Indeed, the combination has been proven to be effective in patients with previously untreated metastatic or unresectable melanoma, where co-blockade of LAG-3 and PD-1 provided a greater benefit with regard to progression-free survival than inhibition of PD-1 alone (Tawbi et al 2022).

2.2.1.1. Pharmacology

LBL-007 binds to the human LAG-3 extracellular domain with high specificity and affinity (K_d = 0.439 x 10^{-10} M). In vitro studies demonstrated that LBL-007 effectively blocks the

binding of LAG-3 to MHC II molecules, and thereby significantly promote T-cell activation. LBL-007 also blocks the binding of LAG-3 with other ligands, including FGL-1, LSECtin and Gal-3. In vivo pharmacological studies in human LAG-3 transgenic mice demonstrated significant inhibition of tumor growth by either the treatment of LBL-007 monotherapy, or in combination with an anti-PD-1 monoclonal antibody and an anti-TIM-3 antibody.

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

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

2.2.1.2. Toxicology

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

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

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

In the 3-week 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, immunoglobulin counts (IgA, IgG, IgM, and IgE) following intravenous infusion of LBL-007 at 20 mg/kg, 60 mg/kg, and 150 mg/kg once a week for 3 consecutive weeks (4 doses). Other abnormalities in hematology and blood chemistry recovered after 4 weeks of dose interruption. The weight coefficient of the liver was increased in female rats in the 150 mg/kg group, and slight to mild hepatocellular necrosis or inflammatory cell infiltration was observed in the histopathological examination. Considering the lack of binding activity of LBL-007 to the LAG 3 in rats, the effects of LBL-007 on the liver were considered to be mostly off-target toxicities. Given that in vitro data indicated cellular and tissue binding with LBL-007 were highly specific to monkey and human, and the absence of LBL-007 pharmacological activity in the rat, the findings in the 3-week repeated-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 NOAEL was 100 mg/kg. LAG-3 receptor occupancy was increased in female and male cynomolgus monkeys at 1 to 2, 24 to 25, 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 receptor occupancy was observed at all dose levels. At the dose level of 10, 30, and 100 mg/kg, after the first dose, the increased exposure of LBL-007 in the serum of monkeys in each LBL-007 group was correlated with increase of the infusion dose. No gender differences in exposure were observed. After 5 consecutive doses, the accumulation factors of LBL-007 ranged from 2.02 to 0.61, indicating a slight accumulation.

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

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

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

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

2.2.1.3. Clinical Pharmacology

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

In patients with advanced solid tumors, the mean $t_{1/2}$ of LBL-007 at a single dose of 0.25, 1, 3, 6, and 10 mg/kg was 49.5, 105, 196, 184, and 182 hours, respectively, based on PK collection up to 3 weeks. When the dosage was increased from 0.25 mg/kg to 6 mg/kg, the $t_{1/2}$ of LBL-007 tended to increase with increasing dose, and the CL rate tended to decrease with the increase of dosage, but when the dosage reached 3 mg/kg, they did not change with increasing dose, suggesting of saturation of TMDD pathway. No obvious accumulation was observed after multiple consecutive doses of 0.05 to 3 mg/kg, but the serum level increased slightly at doses between 6 to 10 mg/kg dose groups, suggesting that there may be small accumulation.

In patients with unresectable or metastatic melanoma, the $t_{1/2}$ of LBL-007 after a single intravenous infusion of 0.25, 1, 3, and 6 mg/kg LBL-007 in combination with toripalimab (3 mg/kg) was 43.63, 108.40, 165.89, and 192.30 hours, respectively, showing an upward trend as dose increases. The accumulation ratios for C_{max} and AUC after multiple doses of LBL-007 ranged from 1.018 to 1.553 and 1.019 to 1.543, respectively, suggesting a small accumulation of LBL-007 in vivo.

2.2.1.4. Prior Clinical Experience With LBL-007

LBL-007, as an IgG4 antibody targeting LAG-3 pathway, has similar mechanism of action compared with other LAG-3 antibody in the same class. The preliminary safety profile and anticancer activity for LBL-007 monotherapy and in combination with an anti-PD-1 antibody (toripalimab) are presented as below.

As of the data cutoff date of 10 January 2024, LBL-007 has been investigated in 10 clinical studies with a total of 458 patients who have received LBL-007. This includes 1 completed monotherapy study (Study WLZB-LBL-007-AST-001) and 9 ongoing combination therapy studies with available data.

2.2.1.4.1. Study WLZB-LBL-007-AST-001

As of 15 January 2022, a total of 22 patients were enrolled and received LBL-007 at 0.05 mg/kg (n = 2), 0.25 mg/kg (n = 4), 1 mg/kg (n = 3), 3 mg/kg (n = 3), 6 mg/kg (n = 3), or 10 mg/kg (n = 7), 20 of whom completed the tolerability evaluation. Preliminary safety results showed that the doses were well tolerated with no DLTs in any dose group. MTD was not reached with the maximum-administered dose of 10 mg/kg in this study.

Of the 22 patients, 21 (95.5%) experienced a total of 224 TEAEs, and TEAEs occurred in ≥ 10% of the patients were anemia (59.1%); hyperglycemia (27.3%); neutrophil count increased, hypocalcemia, upper respiratory tract infection, hyponatremia, and pyrexia (22.7% each); gamma-glutamyltransferase increased (18.2%); white blood cell count increased (18.2%); and weight decreased, platelet count decreased, hypoalbuminemia, hypercalcemia, decreased appetite, asthenia, and sinus tachycardia (13.6% each), as detailed in Table 2.

Table 2: Summary of Treatment-Emergent Adverse Events Coded by MedDRA SOC and PT (in ≥ 10% of Patients)

System Organ Class Preferred Term	Total (N = 22)	
	Number of events	Number of patients (%)
Treatment-Emergent Adverse Events	224	21(95.5)
Investigations	78	14(63.6)
Neutrophil count increased	5	5 (22.7)
Gamma-glutamyltransferase increased	7	4 (18.2)
White blood cell count increased	4	4 (18.2)
Weight decreased	5	3 (13.6)
Platelet count decreased	9	3 (13.6)
Blood and lymphatic system disorders	29	13 (59.1)
Anaemia	29	13 (59.1)
Metabolism and nutrition disorders	47	11 (50.0)
Hyperglycaemia	9	6 (27.3)
Hypocalcaemia	8	5 (22.7)
Hyponatraemia	8	5 (22.7)
Hypoalbuminaemia	7	3 (13.6)
Hypercalcaemia	6	3 (13.6)

System Organ Class Preferred Term	Total (N = 22)	
	Number of events	Number of patients (%)
Decreased appetite	4	3 (13.6)
General disorders and administration site conditions	13	10 (45.5)
Pyrexia	7	5 (22.7)
Asthenia	3	3 (13.6)
Infections and infestations	7	5 (22.7)
Upper respiratory tract infection	6	5 (22.7)
Cardiac disorders	8	4 (18.2)
Sinus tachycardia	3	3 (13.6)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SOC, System Organ Class.

During treatment, 9 patients (40.9%) experienced ≥ Grade 3 TEAEs. No patients experienced events of Grade 5. The most commonly reported TEAE of ≥ Grade 3 was anaemia (2 patients, 9.1%). All other TEAEs of ≥ Grade 3 were reported in 4.5% of patients (1 patient), as detailed in Table 3.

Table 3: Summary of Treatment-Emergent Adverse Events (≥ Grade 3) Coded by MedDRA SOC and PT

System Organ Class Preferred Term	Total (N = 22)
	≥ Grade 3
Treatment-Emergent Adverse Events	9 (40.9)
Investigations	2 (9.1)
Lymphocyte count decreased	1 (4.5)
Lipase increased	1 (4.5)
Blood and lymphatic system disorders	2 (9.1)
Anaemia	2 (9.1)
Metabolism and nutrition disorders	2 (9.1)
Hypocalcaemia	1 (4.5)
Hyponatraemia	1 (4.5)
Hypercalcemia	1 (4.5)
General disorders and administration site conditions	1 (4.5)
Asthenia	1 (4.5)
Gastrointestinal disorders	2 (9.1)

System Organ Class Preferred Term	Total (N = 22)
	≥ Grade 3
Abdominal pain upper	1 (4.5)
Gastrointestinal haemorrhage	1 (4.5)
Infections and infestations	2 (9.1)
Upper respiratory tract infection	1 (4.5)
Bronchitis	1 (4.5)
Respiratory, thoracic and mediastinal disorders	1 (4.5)
Bronchiectasis	1 (4.5)
Cardiac disorders	1 (4.5)
Supraventricular tachycardia	1 (4.5)
Vascular disorders	2 (9.1)
Hypertension	1 (4.5)
Deep vein thrombosis	1 (4.5)
Eye disorders	1 (4.5)
Blindness unilateral	1 (4.5)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SOC, System Organ Class.

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

During the treatment period, 8 patients (36.4%) experienced 13 SAEs. Of them, 9 SAEs occurred in 5 patients (22.7%) were considered to be related to the study treatment. Refer to the LBL-007 Investigator's Brochure for more detailed information on SAEs.

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

2.2.1.4.2. Study LBL-007-CN-002

As of 10 January 2024, in Part A (LBL-007+ toripalimab), 68 patients have been enrolled and treated with LBL-007 at 0.25 mg/kg (n = 4), 1.0 mg/kg (n = 3), 3.0 mg/kg (n = 16), 6.0 mg/kg (n = 42), and 10 mg/kg (n = 3) in combination with toripalimab (3 mg/kg, once every 2 weeks). In Part B, 11 patients were enrolled and treated with LBL-007 at 2 doses (3.0 mg/kg [n = 4] and

6.0 mg/kg [n = 7]) in combination with toripalimab (3 mg/kg, once every 2 weeks) plus axitinib (5 mg, twice per day).

Part A (LBL-007 + toripalimab)

As of 10 January 2024, of the 68 patients in Part A, approximately all patients (98.5%) experienced ≥ 1 TEAE, 23.5% of the patients experienced an SAE, and 38.2% of the patients experienced a ≥ Grade 3 TEAE.

The most frequently reported TEAEs by PT of any grade were COVID-19 (33.8%), AST increased (32.4%), ALT increased (30.9%), anaemia (29.4%), and blood lactate dehydrogenase increased and hypothyroidism (27.9% each). Most of the ALT increased and AST increased events were Grade 1 or 2.

Most SAEs were reported in a single patient each, except pneumonia and hypopituitarism, which were reported in 2 patients (2.9%) each. Eight patients (11.8%) experienced an SAE assessed to be related to LBL-007 or toripalimab by the investigator; most were reported in single patient each, except hypopituitarism, which was reported in 2 patients (2.9%). Both events were recovering to Grade 2.

Anaemia (10.3%), ALT increased, and malignant neoplasm progression (4.4% each) were the ≥ Grade 3 TEAEs by PT reported in ≥ 3 patients.

Part B (LBL-007 + toripalimab + axitinib)

Of the 11 patients in Part B, 90.9% of the patients experienced ≥ 1 TEAE, 27.3% of the patients experienced ≥ 1 SAE, and 54.5% of the patients experienced a ≥ Grade 3 TEAE.

The most frequently reported TEAEs by PT of any grade were ALT increased (72.7%), bilirubin conjugated increased (63.6%), AST increased, hypothyroidism, hypokalaemia, and COVID-19 (54.5% each).

Weight decreased, transaminases increased, neutrophil count decreased, and blood pressure increased (18.2% each) were the ≥ Grade 3 TEAEs by PT reported in 2 patients, while all other events were reported in 1 patient each.

Transaminases increased (18.2%) was the only event by PT reported in 2 patients. The SAEs considered to be related to LBL-007 or toripalimab by the investigator were a Grade 2 Wolff-Parkinson-White syndrome and a Grade 2 immune-mediated myocarditis reported in the same patient.

2.2.1.4.3. Study LBL-007-CN-003

As of 10 January 2024, 80 patients had been enrolled and received LBL-007 in combination with toripalimab, including 4 patients in the LBL-007 dose group of 200 mg (once every 3 weeks) and 76 patients in the 400 mg dose group (once every 3 weeks). Of the 80 patients, 73 patients (91.3%) experienced ≥ 1 TEAE, 16 patients (20.0%) experienced ≥ 1 SAE, and 19 patients (23.8%) experienced a ≥ Grade 3 TEAE. Four patients (5.0%) experienced TEAE leading to death. None of them were related to LBL-007. The incidence of a TEAE leading to dose modification of LBL-007 or toripalimab was 18.8%. TEAEs leading to discontinuation of LBL-007 or toripalimab occurred in 6 patients (7.5%). The imAEs were reported in 20 patients (25.0%). None of the patients experienced infusion-related reactions.

The most frequently reported TEAEs by PT of any grade were anaemia (40%), weight decreased, hypoalbuminaemia, and proteinuria (18.8% each), and AST increased and hyponatraemia (17.5% each).

Anaemia (6.3%), hyponatraemia, lymphocyte count decreased, ALT increased, and pneumonia (2.5% each) were the ≥ Grade 3 TEAEs by PT reported in ≥ 2 patients.

Four patients experienced fatal TEAEs; they were pneumonia and paracancerous pneumonia (reported in the same patient), malignant neoplasm progression, hypopharyngeal cancer, and disease progression. All fatal events were considered related to underlying disease and not to LBL-007 or toripalimab.

Pneumonia (2.5%) was the only SAE by PT reported in 2 patients. All other events were reported in 1 patient each.

2.2.1.4.4. Study LBL-007-CN-004

As of 10 January 2024, A total of 98 patients had been enrolled and treated with LBL-007. In Phase 1b, 21 patients received LBL-007 in combination with tislelizumab (BGB-A317), including 10 patients in the LBL-007 300 mg dose group (once every 3 weeks) and 11 patients in the 600 mg dose group (once every 3 weeks). In Phase 2 Part D1, 35 patients received LBL-007 in combination with chemotherapy. In Phase 2 Part D2, 42 patients received LBL-007 combined with tislelizumab, gemcitabine, and cisplatin.

Of the 98 patients overall, most patients (94.9%) experienced a TEAE, more than half (58.2%) of the patients experienced a ≥ Grade 3 TEAE, and a total of 38.8% of the patients experienced an SAE.

The 5 most frequently reported TEAEs by PT of any grade were anaemia (68.4%), white blood cell count decreased (62.2%), neutrophil count decreased (57.1%), AST increased (30.6%), and ALT increased (30.6%).

The most frequently reported ≥ Grade 3 TEAEs by PT were white blood cell count decreased (32.7%), neutrophil count decreased (29.6%), anaemia (20.4%), platelet count decreased (12.2%), lymphocyte count decreased and pneumonia (5.1% each).

Pneumonia and platelet count decreased (6.1% each), neutrophil count decreased and anaemia (5.1% each), white blood cell count decreased (4.1%), and myelosuppression (3.1%) were the SAEs by PT reported in ≥ 3 patients. Platelet count decreased (5.1%) and anaemia (3.1%) were the SAEs by PT reported in ≥ 3 patients and assessed to be related to LBL-007 or tislelizumab by the investigator.

2.2.1.4.5. Study BGB-900-102

As of 10 January 2024, in the safety lead-in phase, 71 patients have been enrolled and treated with LBL-007 at different doses (300 mg, 600 mg, 900 mg, or 1200 mg) combined with tislelizumab or tislelizumab + surzebiclimab; in the dose expansion phase, Cohorts 4 and 5 were initiated first. Twenty patients each in Cohort 4 (head and neck squamous cell carcinoma) and Cohort 5 (NSCLC) were treated with LBL-007 at 600 mg combined with surzebiclimab and tislelizumab.

Of the 71 patients, most patients (95.8%) experienced a TEAE, 42.3% of the patients experienced a ≥ Grade 3 TEAE, and 35.2% of the patients experienced an SAE.

The most frequently reported TEAEs by PT of any grade were anaemia (23.9%), nausea and fatigue (21.1% each), decreased appetite (19.7%), and dyspnoea and headache (12.7% each).

Anaemia (7.0%) and lymphocyte count decreased, disease progression, and dyspnoea (2.8% each) were the ≥ Grade 3 TEAE by PT reported in ≥ 2 patients.

All SAEs by PT were reported in 1 patient each, except dyspnoea and disease progression (2.8% each), which were reported in 2 patients. Immunotherapy-related SAEs were reported in 4 patients (5.6%); they were adrenal insufficiency, hypothyroidism, troponin T increased, immune-mediated arthritis, and capillary leak syndrome, reported in 1 patient each.

Refer to the LBL-007 Investigator's Brochure for more detailed information on LBL-007 safety and efficacy data.

2.2.2. Background Information on Tislelizumab

Tislelizumab is a humanized IgG4-variant monoclonal antibody against human PD-1 that is being developed for treatment of human malignancies in multiple organs and tissues. PD-1 is mainly expressed in activated T cells, including CD8+ cytotoxic T lymphocytes and CD4+ T-helper lymphocytes (McDermott and Atkins 2013). The PD-1 signaling cascade negatively regulates T cells and attenuates T-cell proliferation and functional activities, leading to T-cell exhaustion. PD-1 expression is markedly upregulated on tumor-infiltrating lymphocytes, while the expression of PD-L1 is significantly increased on tumor cells and tumor-associated immune cells in the presence of stimulating cytokines such as IFN-γ and interferon alpha in the tumor microenvironment (Riley 2009), which is observed in many types of human solid tumors.

2.2.2.1. 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 programmed cell death protein ligand-2, thus inhibiting PD-1-mediated negative signaling in T cells. In in vitro cell-based assays, tislelizumab was observed to consistently, and in a dose-dependent manner, enhance the functional activity of human T cells and preactivated, primary PBMC. Tislelizumab has demonstrated in-vivo antitumor activity in several allogeneic xenograft models, in which PBMC 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 FcγR such as FcγRI and FcγRIIIA, and it has very low binding affinity to C1q, a subunit of complement 1. In vitro assays with tislelizumab suggest either low or no antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, or complement-dependent cytotoxicity effects in humans (Labrijn et al 2009). Tislelizumab was specifically engineered to abrogate these potential mechanisms of T-cell clearance and potential resistance to anti-PD-1 therapy.

Please refer to the Tislelizumab Investigator's Brochure for additional details regarding nonclinical studies of tislelizumab.

2.2.2.2. Toxicology

The toxicity and safety profile of tislelizumab was characterized in single-dose toxicology studies in mice and cynomolgus monkeys and in a 13-week, repeated-dose toxicology study in cynomolgus monkeys.

Overall, no apparent toxicity was noted in mouse 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 the 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 NOAEL of tislelizumab in the 13-week monkey toxicity study was considered to be 30 mg/kg.

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

2.2.2.3. Clinical Pharmacology

A population PK analysis was performed based on the pooled data (PK, dosing information, demographics, and patient or disease characteristics) from 2596 patients across 12 clinical studies. The PK of tislelizumab was best characterized using a 3-compartmental model with linear clearance mechanism. No time-varying clearance was observed in tislelizumab PK. The typical estimates of CL, Vc, and peripheral volumes 2 and 3 (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%), Vc (16.7%), V_2 (74.7%), and V_3 (99.9%). The terminal $t_{1/2}$ was estimated to be approximately 23.8 days. The accumulation ratios were estimated to be 2.14 and 2.49 for AUC at steady state (AUC_{ss}) and minimum serum concentration at steady state ($C_{min,ss}$), respectively. Steady state is expected to be reached in approximately 12 weeks.

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

2.2.2.4. Prior Clinical Experience of Tislelizumab

The overall safety experience with tislelizumab, as a monotherapy or in combination with chemotherapy, is based on experience in 4588 patients (2569 patients treated with tislelizumab monotherapy and 2019 patients treated with tislelizumab in combination with chemotherapy) in clinical studies as of the cutoff date 27 October 2023. The safety profile of tislelizumab is consistent with that observed with other PD-1 inhibitors when given as a single agent or in combination with chemotherapy.

Tislelizumab has received market authorizations for various indications, including solid tumor and hematologic malignancies, in several countries. Refer to the Tislelizumab Investigator's Brochure for more detailed information.

As of the 27 October 2023 data cutoff date, 26 studies with tislelizumab are included in the Investigator's Brochure, 15 studies are ongoing and 11 studies have been completed. Of the 15 ongoing studies, 11 have data available for presentation in the Tislelizumab Investigator's Brochure, including 5 monotherapy studies, and 6 chemotherapy combination therapy studies.

For tislelizumab monotherapy, the safety profile is well tolerated in solid tumors and hematological malignancies. Most AEs were Grade 1 or 2 in the pooled solid tumor studies, and most ≥ Grade 3 TEAEs were assessed as unrelated to tislelizumab. AEs were generally reversible and manageable. The percentage of patients with tislelizumab-related TEAEs leading to tislelizumab discontinuation was small. In the hematological malignancies studies, most AEs were Grade 1 or 2, and most ≥ Grade 3 TEAEs were assessed as unrelated to tislelizumab. As with the solid tumor studies, AEs were generally reversible and manageable, and the percentage of patients with tislelizumab-related TEAEs leading to tislelizumab discontinuation was small. The safety profile for single-agent tislelizumab is similar to that observed with other PD-1 inhibitors in solid tumors and hematological malignancies.

Tislelizumab given in combination with chemotherapy is well tolerated. Most ≥ Grade 3 TEAEs were assessed as unrelated to tislelizumab in the pooled solid tumor studies using tislelizumab plus chemotherapy. The percentage of patients with tislelizumab-related TEAEs leading to tislelizumab discontinuation was small. The safety profile is consistent with that of other PD-1 inhibitors given in combination with chemotherapy.

The data collected in Phase 1 and Phase 2 studies show that tislelizumab monotherapy can result in antitumor activity across a variety of tumor types. Antitumor activity has been observed across the dose ranges evaluated in patients. Efficacy and safety data were also evaluated in pivotal Phase 2 and Phase 3 studies using tislelizumab as a monotherapy or in combination with chemotherapy in various tumor types.

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

2.2.3. Regulatory Status

A list of all IMPs and AxMPs that will be used in this study and their global regulatory approval status are provided in Table 4 and Table 5. Further details are included in Section 6.

Table 4: Investigational Medicinal Products Used in Study BGB-A317-LBL-007-201 and Their Regulatory Approval Status

Country/ Region	Approved for Treatment of Colorectal Cancer (Yes/No)	
	LBL-007	Tislelizumab
United States	No	No
Australia	No	No
China	No	Yes (microsatellite instability-high/deficient mismatch repair colorectal cancer in the late-line setting)

Table 5: Auxiliary Medicinal Product Used in Study BGB-A317-LBL-007-201 and Their Regulatory Approval Status

Country/ Region	Approved for Treatment of Colorectal Cancer (Yes/No)			
	Bevacizumab or its biosimilar	Capecitabine	5-Fluorouracil	Leucovorin or Levoleucovorin
United States	Yes	Yes	Yes	Yes
Australia	Yes	Yes	Yes	Yes
China	Yes	Yes	Yes	Yes

A detailed description of the chemistry, pharmacology, efficacy, and safety of LBL-007 and tislelizumab is provided in the Investigator's Brochure and Prescribing Information, respectively. Refer to the prescribing information for details on bevacizumab, capecitabine, 5-fluorouracil, leucovorin, and levoleucovorin.

2.3. Benefit/Risk Assessment

The safety profile of both tislelizumab monotherapy and LBL-007 monotherapy are considered as acceptable based on previous nonclinical and clinical data assessed in patients with advanced solid tumors. As discussed in Section 2.2.2, PD-1 blockade by tislelizumab has been evaluated in more than 4588 patients with a safety and efficacy profile similar to what has been reported for other anti-PD-L1 therapies.

The emerging safety data of LBL-007 in combination with anti-PD-1 therapies, including tislelizumab and toripalimab, presented a well-tolerated safety profile with no new safety signals identified, which also enables the combination of LBL-007 with the current standard-of-care treatment.

Together with the promising efficacy outcome from the Phase 1 study of MK-4280 (favezelimab) in combination with pembrolizumab, a promising anticancer activity has been observed in previously treated patients with advanced MSS-CRC, especially in those with PD-L1 CPS ≥ 1 status. The toxicity of favezelimab in combination with pembrolizumab was similar with that in favezelimab monotherapy. Any grade of TRAE was observed in 65.2% with the combination treatment arm and 65% in the monotherapy arm. The incidence of ≥ Grade 3 TRAE was 20% and 15% in the combination treatment arm and monotherapy arm, respectively. No grade 5 TRAEs were reported. Common TRAEs (≥ 15%) included fatigue (20.0%) and nausea

(15%) with favezelimab monotherapy, and fatigue (16.9%) with favezelimab plus pembrolizumab. Besides, the safety profile was comparable with the reported safety result in another Phase 1 study. In the study of BI 754111 as an anti-LAG-3 antibody in combination with an anti-PD-1 antibody BI 754091, the most commonly reported treatment-related AE was fatigue (any grade 60%, Grade ≥ 3 12.5%), and no Grade 5 AE was reported (Garralda et al 2021). The clinical study results of anti-LAG-3 in combination with anti-PD-1 monoclonal antibody showed favorable benefit risk profile in mCRC.

Bevacizumab plus fluoropyrimidine as recommended maintenance therapy has been well accepted in the first-line treatment with tolerable safety profile. Different safety profiles of bevacizumab, fluoropyrimidine, and checkpoint inhibitors are unlikely to augment the toxicities of the combination. Referring to the safety outcome from the MODUL study, implementing PD-L1 antibody in combination with maintenance backbone for the patients with MSS mCRC, the rate of Grade 3 TEAEs was slightly higher in the experimental arm. The most common Grade 3 TEAEs in the experimental versus control arms were hypertension (6.1% versus 4.2%), diarrhea (3.1% versus 2.1%), and palmar-plantar erythrodysesthesia syndrome (1.0% versus 3.5%) (Tabernero et al 2022).

Therefore, LBL-007 plus tislelizumab in combination with bevacizumab and fluoropyrimidine is not expected to exacerbate the known AEs related to immune checkpoint inhibitors.

Given the unmet medical need that there has been no therapeutic improvement in the maintenance therapy of MSS/pMMR CRC, the benefit-risk assessment, based on the available safety and efficacy data of anti-LAG-3 monoclonal antibodies with or without anti-PD-1 antibodies and the available efficacy data from the maintenance backbone in this indication, the benefit-risk of the combination of LBL-007 plus tislelizumab and bevacizumab and fluoropyrimidine is considered favorable to benefit.

As shown in Section 1.3, this study includes a comprehensive plan to monitor patient safety. The subsequent safety data will be continuously analyzed by the sponsor's study team and in consultation with investigator(s) as needed. An SMC will also be established to monitor the safety of the 4-agent combination with LBL-007 from the lowest dose to the expected dose in Phase 2, and recommend changes to the study enrollment based on safety data. The Phase 2 study will be conducted to evaluate the potential benefit and safety of LBL-007 with tislelizumab plus the current standard maintenance in patients with unresectable and metastatic MSS/pMMR CRC.

Taking into account the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with LBL-007 and tislelizumab are justified by the anticipated benefits that may be afforded to patients with unresectable and metastatic MSS/pMMR CRC.

More detailed information about the known and expected benefits and risks of LBL-007 and tislelizumab is provided in their respective Investigator's Brochure.

2.4. Study Conduct

This study will be conducted in compliance with the protocol approved by the IRB or IEC and in accordance with GCP standards.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1. Objectives and Endpoints

Table 6: Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1b • To assess the safety and tolerability of LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine.	**Phase 1b** • Adverse events (AE) and serious AEs (SAE) as characterized by type, frequency, severity (as graded by National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0 [NCI-CTCAE v5.0]), timing, seriousness, and relationship to study treatments; physical examinations, electrocardiograms (ECGs), and laboratory assessments as needed; and AEs meeting protocol-defined dose-limiting toxicity (DLT) criteria.
Phase 2 • To evaluate the efficacy between LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine (Arm A) and bevacizumab plus fluoropyrimidine (Arm C) as maintenance therapy in the programmed cell death protein ligand-1 (PD-L1) positive population (defined as Tumor Area Positivity [TAP] score ≥ 1% by the Ventana PD-L1 [SP263] assay) through progression-free survival (PFS), as assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) in patients with unresectable or metastatic microsatellite stable (MSS)/mismatch repair proficient (pMMR) colorectal cancer (CRC).	**Phase 2** • PFS, as assessed by the investigator per RECIST v1.1, defined as the time from the date of randomization to the date of first documentation of disease progression or death, whichever occurs first, in the Intent-to-Treat (ITT) Analysis Set of Arms A and C for PD-L1 positive population.
Secondary	
• To evaluate the efficacy of LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine (Arm A) and	• ORR and DOR as assessed by the investigator, in the ITT Analysis Set of Arms A and C for PD-L1 positive population.

Objectives	Endpoints
bevacizumab plus fluoropyrimidine (Arm C) as maintenance therapy in the PD-L1 positive population through overall response rate (ORR) and duration of response (DOR).	○ ORR, defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) from the time of randomization. ○ DOR, defined as the time from the first confirmed objective response after randomization until the first documentation of disease progression or death, whichever comes first.
• To assess the efficacy of LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine (Arm D) and bevacizumab plus fluoropyrimidine (Arm E) in PD-L1 negative population (TAP < 1%) through PFS, ORR, and DOR.	• PFS, ORR, and DOR as assessed by the investigator, in the ITT Analysis Set of Arms D and E for PD-L1 negative population.
• To assess the safety and tolerability of LBL-007 with or without tislelizumab, in combination with bevacizumab plus fluoropyrimidine.	• The incidence and severity of AEs according to NCI-CTCAE v5.0.

3.2. Estimands

Estimands are not included in this study.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1b/2, randomized, multicenter, open-label study to investigate the efficacy and safety of LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine, and LBL-007 in combination with bevacizumab plus fluoropyrimidine versus bevacizumab plus fluoropyrimidine, in PD-L1 positive and negative population groups, respectively (Arm A versus Arm C in PD-L1 positive population group, and Arm D versus Arm E in PD-L1 negative population group), as maintenance therapy in patients with unresectable or metastatic MSS/pMMR colorectal cancer.

The study will be carried out at approximately 80 centers in Australia, China, and the United States.

The study consists of Phase 1b and Phase 2.

Phase 1b, as a safety run-in period, will investigate the safety, tolerability, and PK of LBL-007 in combination with tislelizumab, bevacizumab, and fluoropyrimidine before expanding the enrollment to more patients in Phase 2. A maximum number of 36 patients will be enrolled in Phase 1b. Bayesian optimal interval design with informative prior (iBOIN) will be used for the evaluation of LBL-007 in different doses (Zhou et al 2020). The planned doses for LBL-007 in the safety run-in period is 150 mg, 300 mg, and 600 mg once every 3 weeks or 200 mg and 400 mg once every 2 weeks. However, lower and/or intermediate doses of LBL-007 may be evaluated based on emerging clinical data, as appropriate. The dose for LBL-007 in Phase 2 will based on the emerging clinical data from Phase 1b and the recommendation from the SMC. If a dose > 600 mg once every 3 weeks or > 400 mg once every 2 weeks is recommended by the SMC, a protocol modification will be submitted to health authorities.

The maintenance backbone includes bevacizumab and fluoropyrimidine (capecitabine or 5-FU/LV). Capecitabine and 5-FU/LV will be initially evaluated in separate cohorts (Cohorts -1, 1a, and 1b) in Phase 1b. The SMC will review the safety and tolerability of quadruplet regimen with different fluoropyrimidines and provide recommendations on the choice of fluoropyrimidine in Cohort 2 and Phase 2. If both capecitabine and 5-FU/LV were confirmed to be safe based on the SMC's review, the choice of fluoropyrimidine in future cohorts will be at the investigator's discretion.

In Phase 2, approximately 130 patients will be randomized in the PD-L1 positive population group and approximately 60 patients in the PD-L1 negative population group. Per updated nomenclature for vCPS by Ventana, TAP is defined as the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining at any intensity and tumor-associated immune cells with PD-L1 staining at any intensity. PD-L1 positive is defined as TAP score ≥ 1% by the Ventana PD-L1 (SP263) assay.

Crossover between 2-week regimen and 3-week regimen during the study treatment period is not allowed during the maintenance treatment.

Patients with PD-L1 positive status will be randomized in a 2:1:2 ratio to 1 of 3 treatment arms:

- Arm A (n = 52): LBL-007 + tislelizumab in combination with maintenance backbone

- Arm B (n = 26): LBL-007 in combination with maintenance backbone
- Arm C (n = 52): Maintenance backbone, ie, bevacizumab plus fluoropyrimidine

The randomization will be stratified according to the following factor:

- Liver metastases (absent versus present)

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

- Arm D (n = 30): LBL-007 + tislelizumab in combination with maintenance backbone
- Arm E (n = 30): Maintenance backbone, ie, bevacizumab plus fluoropyrimidine

The study schema is shown in Figure 1.

Every effort should be made to ensure that each drug is administered as originally scheduled. Patients who temporarily withhold or permanently discontinue a study treatment due to related AEs may continue on the other study treatment(s) as long as the patients are experiencing clinical benefit in the opinion of the investigator and after discussion with the medical monitor. However, for patients in Phase 1b, Arm A and Arm D, both LBL-007 and tislelizumab should be withheld or permanently discontinued simultaneously, if necessary.

4.1.1. Study Description

4.1.1.1. Prescreening Period

Prescreening period as described in Section 8.1.1 may start during the induction treatment before the screening if the patient is considered eligible for the clinical study. For the Phase 2 study, the PD-L1 levels and MSI-H/dMMR status could be determined in this period.

4.1.1.2. Screening Period

Screening evaluations will be performed ≤ 28 days before starting the study treatment (for Phase 1b) or randomization (for Phase 2).

Patients who agree to participate in this study will sign the ICF before undergoing any screening procedure. The screening period may begin before completion of the last cycle of induction treatment.

4.1.1.3. Treatment Period

The treatment period will start on the first day of study treatment administration and end when the patient is discontinued from all study treatments for any reason.

During the study treatment period, the investigator will evaluate the tumor response every 9 weeks (63 days ± 7 days) from Day 1 of Cycle 1, by RECIST v1.1.

All patients will receive study treatment up to 2 years until 1) disease progression per RECIST v1.1, 2) unacceptable toxicity, or 3) withdrawal of informed consent. Refer to Section 7 for more details.

If a patient discontinues study treatment(s) due to any reason other than progressive disease (eg, toxicity), tumor assessments will be performed according to the original schedule until disease

progression, death, start of new anticancer therapy, loss to follow-up, withdrawal of consent, or until the study terminates, whichever occurs first.

Patients will report any AEs and SAEs, regardless of causality to study treatments, occurring within either 30 days after the last dose of study treatment (all severity grades, per NCI-CTCAE v5.0) or initiation of new anticancer therapy, whichever occurs first. Patients must also report all imAEs occurring up to 90 days after the last dose of LBL-007 or tislelizumab, whichever occurs later, regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study treatment(s) that are brought to the attention of the investigator should be reported, regardless of time since the last dose of study treatment.

Vital signs, physical examinations, ECOG PS change, ECG results, and other examinations will also be used for safety assessment.

Refer to Section 6.7 regarding continued access to study drug during the extended IP access period.

Details of the study procedures and assessments and their timings are presented in Section 8 and the SoA (Section 1.3).

4.1.1.3.1. Rules for Dose Escalation and De-Escalation

All relevant data (safety data, available PK analyses, etc) will be reviewed by the medical monitor and the study team members from Global Patient Safety, Clinical Pharmacology, and Biostatistics with input from other study team members if appropriate. The dose-escalation decisions and/or safety management will be made based on the review of these data and in consultation with the SMC. As such, clinically important or persistent AEs that are not part of the DLT criteria may also be considered a DLT and should be reviewed by the SMC.

Dose levels from the initial dose of 150 mg once every 3 weeks to the maximum prespecified dose of LBL-007 will be evaluated sequentially. The SMC will recommend whether a dose modification is needed, or whether the current dosing regimen is tolerable, and the dosing level of LBL-007 can escalate to the planned next dose level. The final decision of dose escalation and study proceeding will be made by the sponsor.

The iBOIN design is employed to find the dose for the Phase 2 component of the study. This design is implemented similar to the traditional 3+3 design but is more flexible and possesses superior operating characteristics. The target DLT rate was assumed as $\phi = 0.33$, and the prior DLT rate for Cohort -1, Cohort 1a and Cohort 2 are (0.17, 0.33, 0.33) based on historical data with the prior effective sample size are (2, 2, 2). The iBOIN design uses the following rule, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation:

- if the observed DLT rate at the current dose is $\leq \lambda_e$, escalate the dose to the next higher dose level;
- if the observed DLT rate at the current dose is $> \lambda_d$, de-escalate the dose to the next lower dose level;
- otherwise, stay at the current dose.

The values for λ_e and λ_d vary with dose level and the number of patients treated on a dose. Table 7 provides equivalent decision boundaries, which will be used in the trial for dose escalation and de-escalation. The trial will be stopped if the number of patients treated at the current dose reaches 9 and the decision according to Table 7 is to stay at the current dose. The decision for Cohort 1b will follow the rule used for Cohort 1a.

Table 7: Dose Escalation/De-Escalation Rule for the iBOIN Design

Number of evaluable patients	3	4	5	6	7	8	9
Cohort -1 [a]							
Escalate if # of DLT ≤	N/A	N/A	N/A	1	2	2	2
De-escalate if # of DLT ≥	2	2	3	3	4	4	4
Cohort 1a/Cohort 1b							
Escalate if # of DLT ≤	0	1	1	1	1	2	2
De-escalate if # of DLT ≥	2	2	2	3	3	4	4
Cohort 2							
Escalate if # of DLT ≤	0	1	1	1	1	2	2
De-escalate if # of DLT ≥	2	2	2	3	3	4	4

Abbreviations: DLT, dose-limiting toxicity; iBOIN, Bayesian Optimal Interval Design with Informative Prior; N/A, not applicable.
Notes: # of DLT is the number of patients with at least 1 DLT. When none of the actions (ie, escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of patients. "N/A" means that the number of evaluable patients treated at the current dose is too small to consider the action corresponds to that row.
[a] The modified decision rule for Cohort -1 ensures that at least 6 patients have been evaluated.

4.1.1.3.2. Dose-Limiting Toxicities

The occurrence of any of the following toxicities during the first 21 days of study will be considered a DLT, if assessed by the investigator as possibly, probably, or definitely related to the study treatment administration:

Hematologic:

- Grade 4 neutropenia lasting > 7 days
- Febrile neutropenia (defined as ANC < 1 x 10^9/L with a single temperature of ≥ 38.3°C or a sustained temperature of ≥ 38°C for > 1 hour)
- Grade 3 neutropenia with infection
- Grade 3 thrombocytopenia with bleeding indicated for clinical intervention
- Grade 4 thrombocytopenia
- Grade 4 anemia

Nonhematologic:

- Grade 4 or higher toxicity
- Confirmed drug induced liver injury meeting Hy's Law
- Grade 3 toxicity that is clinically significant and does not resolve to baseline or ≤ Grade 1 within 3 days after initiating supportive care (unless excluded in the listed criteria)

Note: The following AEs will not be considered DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 rash lasting ≤ 7 days
- Grade 3 tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumors)
- Grade 3 fatigue lasting ≤ 7 days
- Grade 3 nausea, vomiting, or diarrhea lasting < 72 hours with or without supportive care
- ≥ Grade 3 electrolyte abnormality that lasts < 24 to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
- ≥ Grade 3 elevation of amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis
- Isolated Grade 3 elevation of ALT and/or AST that resolves to Grade 1 or lower or baseline within 7 days

4.1.2. Duration of the Study

The study is expected to remain open until approximately 12 months after the last patient has been enrolled. The study is estimated to take approximately 36 months from study initiation to complete.

The approximate duration of participation for each patient, from signing of the ICF up to the last study visit/last study assessment will be 12 months.

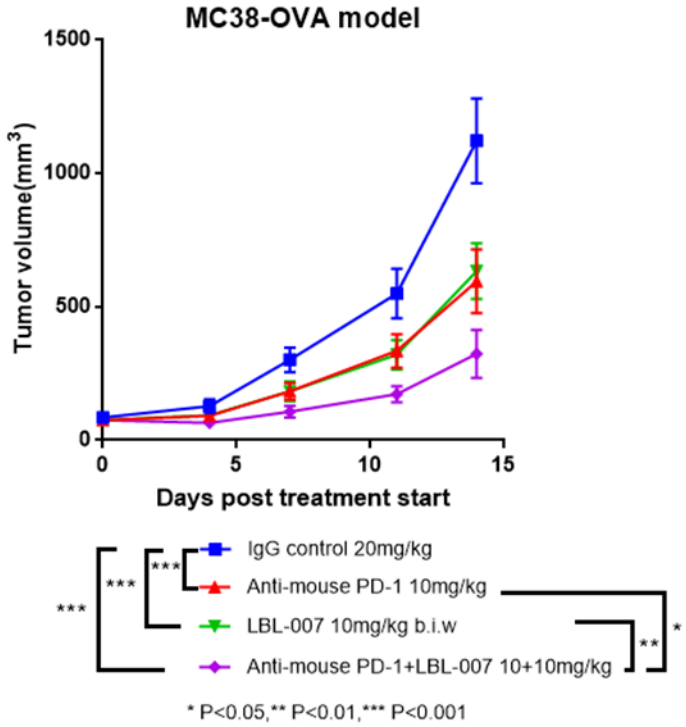
4.2. Scientific Rationale for Study Design

4.2.1. Rationale for LBL-007 in Combination With Tislelizumab

Coexpression of multiple immune checkpoint proteins occurs frequently on tumor-infiltrating T cells and is associated with their dysfunction state. LAG-3 was shown to be coexpressed 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 could further enhance antitumor immunity (Gettinger et al 2017; Hanna et al 2018; Johnson et al 2018; Kates et al 2021).

In preclinical mouse study, LBL-007 in combination with anti-PD-1 significantly improved antitumor effect with a 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 and Table 8). 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: b.i.w, twice weekly; PD-1, programmed cell death protein-1.

Table 8: Inhibitory Effect of LBL-007 on Tumor Growth in MC38-OVA Transplant Mouse Models

Group	# of Animals	Dose (mg/kg)	Tumor Volume (Mean ± STD mm^3)	Tumor Growth Inhibition (%)	p-value	
					vs Control	vs anti-mouse PD-1 + LBL-007

IgG Control	11	20	1120.24 ± 159.12	NA	NA	< 0.001
Anti-mouse-PD-1	12	10	595.09 ± 119.44	58.99	< 0.001	= 0.012
LBL-007	12	10	632.86 ± 104.46	56.10	< 0.001	= 0.003
Anti-mouse-PD-1 + LBL-007	12	10 + 10	323.20 ± 89.84	77.63	< 0.001	NA

Abbreviations: IgG, immunoglobulin G; NA, not applicable; PD-1, programmed cell death protein-1; STD, standard deviation; vs, versus.

The synergic antitumor efficacy for anti-LAG-3 antibody in combination with anti-PD-1 antibody has been preliminarily validated in clinical study. The first anti-LAG-3 antibody was recently approved by the US 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 (Study LBL-007-CN-002). A total of 32 evaluable patients had an 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.

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

4.2.2. Rationale for LBL-007 in Combination With Tislelizumab in the Treatment of Unresectable or Metastatic MSS/pMMR CRC

In CRC, T-cell infiltration into the tumor bed has long been associated with favorable outcomes, suggesting a possible role for immunoediting in controlling tumor growth (Galon et al 2006; Galon et al 2007; Pagès et al 2005). The beneficial effect of immune checkpoint inhibitors has been proved in patients with mCRC harboring dMMR and/or MSI-H status. However, the inhibition of the PD-1/PD-L1 axis alone has proven insufficient for pMMR/MSS mCRC: the response of PD-1 antibody in patients who have received at least 2 lines of treatment for MSS-CRC was only 0% to 5% (Le et al 2015; Overman et al 2018a). Combined blockade with immunotherapy strategies has been explored to overcome immune resistance in this setting.

In the MSS refractory setting, combined immune checkpoint inhibition with the anti-PD-L1 agent durvalumab plus the anti-CTLA-4 agent tremelimumab showed modest results in terms of response rate (0.8%) and a trend in OS benefit with a 2.5-month improvement for the combination over best supportive care (Chen et al 2020). To further explore the clinical benefit

of immunotherapy in MSS-CRC, novel combinations of checkpoint inhibitors are under development. LAG-3 antibody in combination with PD-1 antibody showed a promising clinical benefit in pretreated patients with MSS-CRC. The Phase 3 studies are ongoing to assess anti-PD-1 antibody plus anti-LAG-3 antibody in patients with MSS-CRC whose disease has progressed after at least 2 lines of chemotherapies.

In a Phase 1 first-in-human study containing favezelimab (anti-LAG-3 antibody sponsored by Merck & Co's) in the combination with pembrolizumab for patients with metastatic MSS-CRC whose disease has progressed after prior standard of care (Garralda et al 2021). Among the total of 80 patients who received favezelimab in combination with pembrolizumab, patients with PD-L1 CPS ≥ 1 (n = 36) presented promising anticancer activity compared with the patients with PD-L1 CPS < 1 (n = 35). ORR was 11.0% in the PD-L1 CPS ≥ 1 group compared with 2.9% in the PD-L1 CPS < 1 group. Median duration of response was 10.6 month in patients with response in the combination immunotherapy. Median PFS was 2.2 months versus 2.0 months and median OS was 12.7 months versus 6.7 months in the PD-L1 CPS ≥ 1 group and PD-L1 CPS < 1 group, respectively.

In another Phase 1 study evaluating BI 754111, an anti-LAG-3 antibody, in combination with BI 754091, an anti-PD-1 antibody, in patients with advanced solid tumors, the clinical outcomes from metastatic MSS-CRC also demonstrated that the combination of anti-LAG-3 and anti-PD-1 antibodies has preliminary anticancer activity and a tolerable safety profile (Bendell et al 2019). Of a total of 40 patients who received ≥ 2 lines of prior therapy and were treated with BI 754111 in combination with BI 754091, 3 patients had confirmed PR and 11 patients had stable disease. Significant and durable responses had been observed in some patients. Five (12.5%) patients had ≥ Grade 3 TRAE and no Grade 5 AE had been reported.

Therefore, LAG-3 represents an ideal target with the potential to significantly improve and/or extend the therapeutic benefit of anti-PD-1 therapy in patients with MSS/pMMR CRC.

Given the promising antitumor activity of anti-LAG-3 antibodies in combination with anti-PD-1 antibody reported in patients with MSS-CRC and given the scientific rationale that LAG-3 may improve the therapeutic benefit of anti-PD-1 therapy, the combination of LBL-007 plus tislelizumab in combination with backbone treatment in maintenance setting may bring significant clinical benefit and support further clinical development.

4.2.3. Rationale for LBL-007 Plus Tislelizumab Plus Backbone Treatment as Maintenance Therapy of CRC

Administration of maintenance treatment with fewer cytotoxic drugs until progression, as opposed to complete treatment breaks in the face of accumulating toxicity, has become a broadly accepted treatment approach. Only those patients who experience disease response or disease control during induction will proceed to further treatment in the maintenance treatment phase of the study.

The maintenance setting post-induction treatment may be ideal to evaluate the efficacy of immunotherapy, which is aimed at boosting the ability of the patient's immune system to eliminate cancer cells. Induction treatment often induces initial tumor shrinkage followed by eventual PD as the tumors find mechanisms to bypass the induction therapy induced growth inhibition.

Induction chemotherapy and targeted therapy-induced cell death can enhance the ability of the immune system to recognize and respond to the tumor through enhanced antigen release and presentation which, in turn, aids in the priming of immune cells to recognize and eliminate tumor cells.

Therefore, triggering or augmenting an antigenic antitumor response with induction treatment and following this treatment with immunotherapy, which acts to preserve ongoing immune responses by blocking an immunosuppressive signal, theoretically may result in enhanced antitumor activity.

Although the current clinical data showed that PD-1/L1 antibodies in combination with chemotherapy had not demonstrated solid clinical benefit as the front-line therapy, a delayed treatment effect was observed in the AtezoTRIBE study, which suggests the benefit of immunotherapy following induction treatment should be considered.

The Phase 2/3 study CheckMate-9X8 evaluated the efficacy of nivolumab in combination with the first-line standard of care (mFOLFOX6/bevacizumab) for patients with mCRC (Lenz et al 2022). Although the median PFS was 11.9 months for both treatment regimen (nivolumab + the standard of care versus the standard of care), which did not reach the statistically significant level for the study, at 15 months, the PFS rate for nivolumab plus the standard of care was 45% (95% CI: 35.4% to 54.8%) compared with that for the standard of care at 21.5% (95% CI: 9.7% to 36.4%). At 18 months, the PFS was 28% (95% CI: 19.0% to 38.4%) for nivolumab plus the standard of care versus 9.0% (95% CI: 2.4% to 21.8%) for the standard of care. Delayed treatment effects suggesting immunotherapy may have a potential benefit in maintenance therapy.

Taking into consideration that the treatment effect of the immunotherapy potentially be enhanced by effective cytotoxic therapy, and a delayed treatment effect was shown in the front-line treatment of anti-PD-1 plus backbone chemotherapy and bevacizumab, LBL-007 plus tislelizumab in combination with well-acceptable cytotoxic therapy as maintenance therapy is expected to bring more clinical benefit for patients with MSS-CRC than it in combination with cytotoxic therapy which from initial treatment in the first-line therapy.

4.2.4. Rationale for PD-L1 Expression Enrichment Strategy

The study will enroll the patients with unresectable or metastatic MMS/pMMR CRC who have no disease progression after induction treatment. The enrolled patients consist of a PD-L1 TAP ≥ 1% (PD-L1 positive) population and a PD-L1 TAP < 1% (PD-L1 negative) population.

According to the Phase 1 study containing favezelimab plus pembrolizumab in MSS-CRC, a better clinical benefit has been demonstrated in patients with PD-L1 CPS ≥ 1 status versus the PD-L1 CPS < 1 group.

In the Phase 3 IMblaze370 study, atezolizumab plus cobimetinib or atezolizumab monotherapy had not improved survival compared with regorafenib. In a post-hoc subgroup analysis of patients with PD-L1 expression (IC ≥ 1% by SP142 assay), the proportion of patients achieving an objective response in this subgroup was higher in atezolizumab-containing groups than in the control regorafenib monotherapy group. ORR was 4% in atezolizumab plus cobimetinib, and 3% in atezolizumab, compared with no response in regorafenib.

Patients with PD-L1 positive or negative status will be enrolled, given that PD-L1 expression might be a predictive marker for clinical efficacy of immunotherapy in CRC, the study will focus on the PD-L1 positive population. Consequently, the primary objective for Phase 2 is to evaluate LBL-007 plus tislelizumab in combination with the maintenance backbone versus maintenance backbone alone by PFS in PD-L1 positive population, and PD-L1 negative population will be analyzed as the secondary objective.

To assess the contribution of the component for the experimental arm with LBL-007 plus tislelizumab in combination with the maintenance backbone, one arm with LBL-007 in combination with the maintenance backbone is assessed in the PD-L1 positive population of this Phase 2 study.

4.2.5. Biomarker Strategy Rationale

Biomarker analyses will be performed to explore the following aspects: 1) target engagement, 2) pharmacodynamic effects in patients, and 3) biomarkers predictive of response or resistance (exploratory).

Receptor occupancy of LAG-3, soluble LAG-3 on peripheral blood cells will be used to demonstrate LAG-3 target engagement by LBL-007. LBL-007 plus tislelizumab in combination with bevacizumab plus fluoropyrimidine can enhance immune cell activation and increase the secretion of effector molecules. Markers of these immune cells and cytokines/chemokines or other soluble proteins secreted by these immune cell subsets will be evaluated through fluorescence-activated cell sorting and serum analysis in blood. Treatment effects will be evaluated by comparing these immune cell subsets, cytokines/chemokines, or other soluble proteins. Blood TMB/ctDNA monitoring/DNA mutation may be explored in peripheral blood as potential biomarkers predictive of response or resistance before, during, and after treatment.

In the tumor tissue, the planned biomarker analyses may include PD-L1 expression, LAG-3 expression, LAG-3 ligands expression (MHCII, LSECtin, Gal-3, and FGL-1)**,** GEP, TMB/DNA mutation.

PD-L1 is expressed in tumor cells and tumor-infiltrating immune cells, and its expression was shown to correlate with clinical efficacy of favezelimab plus pembrolizumab in MSS-CRC in Study MK-4280-001, in which a larger magnitude median OS improvement and numerically higher objective response were observed in patients with PD-L1 CPS ≥ 1 compared with PD-L1 negative population (CPS < 1). In the present study, PD-L1 expression status will be assessed centrally by the Ventana PD-L1 (SP263) assay and its predictive role will be analyzed.

LAG-3 is predominantly expressed in tumor-infiltrating lymphocytes, and its expression was shown to positively correlate with the clinical efficacy of anti-LAG-3 regimen containing studies (Luke et al 2020). Its predictive role will be analyzed in the present study. Apart from LAG-3, LAG-3 ligands (MHCII, LSECtin, Gal-3, and FGL-1) will also be explored to investigate their role in predicting response.

Highly mutated tumors can produce many neoantigens and these may increase T-cell reactivity. For this reason, high TMB may be associated with improved response to treatment with immune checkpoint blockade, including anti-PD-1 agents. Study KEYNOTE-158 demonstrated that, irrespective of tumor type, higher ORR with pembrolizumab treatment was observed in

TMB-high patients (≥ 10 mutations per megabase) compared with that in TMB-low patients (29% versus 6%) (Marabelle et al 2020). The positive association of high TMB with clinical efficacy of favezelimab plus pembrolizumab has been observed (Gutierrez et al 2021). Therefore, TMB levels along with any specific genetic alterations merit further exploration for the association with clinical outcomes.

GEP panels have been designed to investigate immune features (tumor immunogenicity, interferon gamma signature, immune cell population abundance, etc) and tumor features (epithelial-mesenchymal transition, angiogenesis, hypoxia, cell adhesion, etc). IFN-γ signature has been shown to be positively correlated with response to anti-PD-L1 monotherapy across tumor types (Cristescu et al 2018). IFN-γ and T-cell inflamed signature have demonstrated positive association with clinical efficacy of anti-LAG-3 regimen containing studies (Gutierrez et al 2021; Luke et al 2020). Apart from their potential predictive value, GEP panels can be designed to explore underlying resistance mechanisms such as immunosuppressive cytokines and cells to guide potential therapeutic strategies. In summary, the role of GEP in predicting response/resistance will be explored.

4.2.6. Patient Input Into Design

No patient/patient organization input has been obtained for this study.

4.3. Justification for Dose

4.3.1. Rationale for Dose Selection

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

In the single-agent dose-escalation study of WLZB-LBL-007-AST-001 (AST-001), doses of LBL-007 (0.05, 0.25, 1, 3, 6, and 10 mg/kg every 2 weeks) were evaluated. Concentration-time profiles from 0.05 mg/kg up to 1 mg/kg exhibit a typical TMDD pattern, suggesting a lack of target saturation. Once doses reach 3 mg/kg and above, PK of LBL-007 becomes linear, indicative of target saturation. The observed mean trough concentration of 5.63 µg/mL at 3 mg/kg was selected at a target concentration that overcomes TMDD.

A preliminary population PK analysis was conducted by pooling PK data from Study AST-001 LBL-007-CN-002, LBL-007-CN-004, and BGB-900-102. Result of this analysis reveals that LBL-007 has a clearance of 0.022 L/hr with half-life of approximately 11 days. Simulation using this model suggests that at 600 mg every 3 weeks, approximately 88% of patients will achieve steady-state trough concentration of 5.63 µg/mL.

The highest dose of 10 mg/kg (every 2 weeks) in Study AST-001 was tested in 7 patients with no DLT and generally well tolerated. Little accumulation was observed at steady-state due to its short half-life. The dose of 10 mg/kg (every 2 weeks) provides exposure coverage up to 600 mg LBL-007 dosed every 3 weeks, and 600 mg LBL-007 (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 (every 3 weeks) for Phase 2.

As of 15 February 2023, a total of 12 patients have received LBL-007 at 600 mg in combination with tislelizumab at 200 mg once every 3 weeks in 2 ongoing clinical Studies LBL-007-CN-004

(11 patients) and BGB-900-102 (1 patient). Though the exposure is limited, the safety profile of the combination of LBL-007 at 600 mg and tislelizumab at 200 mg once every 3 weeks is considered as tolerable and manageable in advanced solid tumors.

In Study LBL-007-CN-004, the safety profile of LBL-007 in 300 and 600 mg was comparable. As of 11 January 2023, all 21 patients who were treated with LBL-007 (n = 10 in 300 mg, n = 11 in 600 mg) in combination with tislelizumab 200 mg every 3 weeks experienced ≥ 1 TEAEs. No DLTs were reported at either dose, and no new safety signal was observed.

In Study BGB-900-102, no DLTs were reported. No ≥ Grade 3 TEAEs or serious TEAEs have been reported from the patient given 600 mg of LBL-007 and 200 mg of tislelizumab.

Since there is no clinical data regarding LBL-007 plus tislelizumab in combination with maintenance backbone (bevacizumab plus fluoropyrimidine), LBL-007 at 150 mg every 3 weeks or 100 mg every 2 weeks, are selected as the initial dose for safety run-in and PK analysis. This is in consideration of the safety and tolerability of this combination, which is one dose level below the highest tested LBL-007 dose (ie, 600 mg every 3 weeks, 400 mg every 2 weeks) as mentioned above.

In Phase 1b, the initial dose of LBL-007 will be 150 mg every 3 weeks or 100 mg every 2 weeks to the intermediate dose of 300 mg every 3 weeks or 200 mg every 2 weeks. This targets the planned dose of 600 mg every 3 weeks and 400 mg every 2 weeks in the combination treatment cohorts. The SMC will evaluate the safety profiles of the quadruplet containing each dose of LBL-007. The dose for LBL-007 in Phase 2 will be based on the emerging clinical data from Phase 1b and the recommendation from the SMC, to further evaluate tolerability, PK, and efficacy.

4.3.1.2. Rationale for the Selection of Tislelizumab Dose

The PK, safety, and efficacy data obtained from the first-in-human study BGB-A317_Study_001, as well as other clinical study data, were analyzed in aggregate to determine the recommended dose for studies of tislelizumab. The dose of 200 mg intravenously once every 3 weeks was selected for further evaluation.

Rates of treatment-related AEs and SAEs observed in patients receiving 2 mg/kg and 5 mg/kg once every 2 weeks and once every 3 weeks were comparable, suggesting no clear dose-dependence across these regimens. Similarly, confirmed ORRs in patients treated with tislelizumab 2 mg/kg and 5 mg/kg once every 2 weeks ranged between 10% and 15%, compared to a range of 15% to 38% for patients treated at 2 mg/kg and 5 mg/kg once every 3 weeks.

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

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

tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg every 3 weeks.

Tislelizumab 200 mg administered intravenously every 3 weeks is the approved dosage for tislelizumab in China. This dosage has been demonstrated to be tolerable with a clinically manageable safety profile in previously treated CRC patients.

The alternate regimen of 300 mg once every 4 weeks is selected by matching dose and exposure (AUC) with that of the 200 mg once every 3 weeks regimen. Exposure-response assessment of available clinical data from studies including BGB-A317_Study_001, BGB-A317-102, and BGB-A317-203 suggested no clinically significant relationships observed between tislelizumab exposure and efficacy (ORR) or safety across tumor types. Thus, the 300 mg once every 4 weeks regimen is not expected to be clinically different from the 200 mg once every 3 weeks in terms of safety or efficacy outcomes. The higher C_{max} of the 300 mg once every 4 weeks regimen compared with the 200 mg once every 3 weeks is covered by the available safety data at higher doses (up to 10 mg/kg once every 2 weeks were used in Study BGB-A317_Study_001).

Therefore, both the approved regimen of 200 mg once every 3 weeks and the alternative regimen of 300 mg once every 4 weeks of tislelizumab will be utilized in this study.

4.3.1.3. Rationale for the Dose Selection of Bevacizumab and Fluoropyrimidine as the Maintenance Backbone

As mentioned in Section 2.1.2.2, a regimen of fluoropyrimidine with or without bevacizumab is the currently recommended maintenance therapy according to several clinical guidance (CSCO 2019; NCCN 2022; Yoshino et al 2018).

Bevacizumab is the first approved angiogenesis inhibitor targeting VEGFs, especially VEGF-A, which has been identified as a key factor for inducing tumor angiogenesis. By binding to VEGF-A, bevacizumab prevents the interaction of VEGF-A with VEGFR and thereby inhibits the activation of VEGF signaling pathways that promote neovascularization (Garcia et al 2020).

Bevacizumab in combination with fluorouracil-based chemotherapy has been approved in first- or second-line treatment for patients with metastatic colorectal cancer. The potential for drug-drug interaction between tislelizumab and bevacizumab is very low because both are therapeutic monoclonal antibodies. Bevacizumab and tislelizumab are expected to be degraded into amino acids and recycled into other proteins and are unlikely to influence drug-metabolizing enzymes or transporters. The different therapeutic targets of immune checkpoint and VEGF may suggest different safety profiles and different spectrums of related AEs. The combination is not expected to exacerbate the known safety risk of either study treatment.

The NCCN Panel has agreed that an FDA-approved biosimilar may be substituted for bevacizumab wherever these therapies are recommended within the NCCN Guidelines for CRC. Moreover, the same dosage of bevacizumab and its biosimilar was administered in combination with other anti-PD-1/PD-L1 inhibitors (DeClue et al 2021) where it seemed tolerable and clinical manageable.

The dose of fluoropyrimidine for maintenance treatment has not been established yet. The maintenance strategies with fluoropyrimidines after induction chemotherapy do not include oxaliplatin or irinotecan.

The dose of capecitabine monotherapy as a systemic treatment for advanced or metastatic CRC is from 850 to 1250 mg/m^2 orally twice daily for 14 days (repeated every 3 weeks per NCCN guidelines); or 625 mg/m² orally twice daily which is based on the Cairo 3 study, or is consistent with the dose in the induction treatment. Taking into consideration that the intention of maintenance therapy should be less intensive to reduce the treatment associated side effects without compromising clinical activity, the dose of capecitabine in this study is set at 850 mg/m^2.

In 5-FU based regimens, including (m)FOLFOX, FOLFIRI, FOLFIRINOX, the dose of 5-FU, an intravenous fluoropyrimidine, is 400 mg/m^2 bolus on Day 1, followed by 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46 to 48 hours) through continuous infusion. The regimens repeat every 2 weeks. To compensate for the relatively short half-life of 5-FU and to increase its activity, modified dose schedules and combinations with biochemical modulators, such as leucovorin or levoleucovorin, have been used.

Clinically, 5-FU-related toxicities also vary depending on dose schedule. The bolus dose adds substantial toxicity and is often withheld in patients with limited functional status or high-risk comorbidities, but it does not appear to add efficacy to regimens utilizing 5-FU infusion (Peng et al 2023). In this trial, the initial dose of 5-FU in the maintenance therapy kept only the infusion dose within 1600 to 2400 mg/m^2 to eliminate the safety risk from 5-FU bolus administration.

4.4. Start of Study and End of Study Definitions

The start of the study is defined as the date that the first patient signs the ICF.

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 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 that indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory
- The sponsor's decision on the overall development of the study treatment
- 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 IRBs/IECs of the early termination of the study.

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- GCP noncompliance
- Completion of study activity (ie, all patients have completed the study, and all obligations have been fulfilled)

5. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 5.1 and Section 5.2. The sponsor will not grant any eligibility waivers.

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all the following criteria:

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the SoA.
2. Aged ≥ 18 years on the day of signing the ICF (or the legal age of consent in the jurisdiction in which the study is taking place).
3. Has a histologically confirmed colorectal adenocarcinoma with metastatic or unresectable disease (Stage IV as defined by American Joint Committee on Cancer [AJCC] 8th edition).
4. Patient must have measurable disease as defined per RECIST version 1.1.
5. No prior systemic therapy for CRC in the metastatic setting except for the induction treatment of first-line therapy.

   Note: Local regional treatment performed during induction systemic treatment is allowed.
6. Patients who have completed the first-line induction treatment, which is defined as 6 to 12 cycles of a 2-week regimen of chemotherapy ([m]FOLFOX or FOLFIRI or [m]FOLFIRINOX) + bevacizumab, or 4 to 8 cycles of the 3-week regimen of chemotherapy (CapeOX + bevacizumab), with an overall response of stable disease or better. The duration of induction treatment (the first dose from the first cycle to the last cycle) should be completed within approximately 6 months. The first dose of study treatment needs to occur within 2 weeks (for 2-week regimen) or 3 weeks (for 3-week regimen) to 6 weeks after Day 1 of the last cycle of induction therapy.

   Note: Bevacizumab must be administered with ≥ 75% of cycles of induction therapy with treatment ongoing at the start of maintenance.
7. Availability of tumor tissue (archival tumor tissues as FFPE) blocks or approximately 16 freshly cut unstained slides) that is of good quality and acceptable sample type for the determination of PD-L1 levels, MSI-H/dMMR status assessment (for patients without local MSS/pMMR information)/confirmation and other exploratory biomarkers. Patients may be permitted to be enrolled on a case-by-case basis after discussion with the medical monitor if fewer than 16 unstained slides of suitable quality are provided.
   a. For the Phase 2 study, PD-L1 expression status must be available before randomization. Patients with unevaluable PD-L1 expression status are not eligible for the study.
   b. For MSI-H/dMMR status assessment (for patients without local MSS/pMMR information)/confirmation, approximately 2 mL peripheral whole blood will be collected as MSI test control.

c. A fresh biopsy is mandatory in the absence of archival tumor tissues. For fresh biopsies, acceptable samples include core needle biopsies for nonsuperficial tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

8. Have an ECOG PS of 0 or 1.
9. Adequate organ function as indicated by laboratory values during screening and within 7 days before the first dose of study treatment(s).
   a. Patients must not have required blood transfusion or growth factor support ≤ 14 days before sample collection for the following:
      – ANC ≥ 1.5 x 10^9/L
      – Platelet count ≥ 75 x 10^9/L
      – Hemoglobin ≥ 90 g/L, without blood transfusion or growth factor support ≥ 14 days before sample collection
   b. Estimated GFR ≥ 60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or creatinine clearance ≥ 60 mL/min by Cockcroft-Gault formula as specified in Appendix 8.
   c. Proteinuria < 2 + (within 7 days of randomization). Patients discovered to have ≥ 2+ proteinuria at baseline should undergo a 24-hour urine collection and must demonstrate < 1 g of protein in 24 hours.
   d. Serum total bilirubin ≤ 1.5 x ULN (less than 3 x ULN for patients with Gilbert syndrome).
   e. AST and ALT ≤ 2.5 x ULN (≤ 5 x ULN in patients with known liver metastases).
10. Women of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and for 6 months after the last dose of study treatment and have a negative urine or serum pregnancy test ≤ 7 days before starting the study treatment.
11. Nonsterile men must be willing to use a highly effective method of birth control for the duration of the study and for 6 months after the last dose of the study treatment.
    a. A sterile man 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 “sub-fertility”) are not to be considered sterile for the purposes of this study.

5.2. Exclusion Criteria

Patients are excluded from the study if they meet any of the following criteria:

1. Have locally or centrally confirmed MSI-H by PCR method or dMMR by immunohistochemistry method. Local result is recommended and acceptable for enrollment.

Note: CRC patients with tumors without MMR deficiency or MSI-H status are categorized as pMMR or MSS.

2. Patients whose disease has become resectable at the investigator's discretion during or after induction treatment are not eligible.
3. Progressive disease occurred less than 6 months from completion of any prior neoadjuvant therapy (ie, chemotherapy ± radiotherapy) or adjuvant therapy (ie, chemotherapy ± radiotherapy), whichever occurred later.
4. Toxicities (as a result of induction therapy) that have not recovered to baseline or Grade 1, except for the toxicity not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities).
5. Patients with BRAF V600E mutations.

   Note: The result of local BRAF testing is needed for all patients and a prior BRAF testing result is acceptable.
6. Patients who have been treated with anti-EGFR antibody in the induction treatment.
7. Patients intend to have palliative surgery or local regional therapy for metastases lesions after randomization (palliative local regional therapy for bone metastases is allowed).
8. Any prior therapy targeting T-cell stimulation or checkpoint pathways.
9. Have received an investigational agent during the induction treatment.
10. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation).
11. Significant vascular disease (eg, aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months before starting the study treatment.
12. Surgical procedure (including open biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity) or significant traumatic injury within 28 days before start of study treatment, or anticipation of the need for a major surgical procedure during the course of the study.
13. Minor surgical procedure including placement of a vascular access device, within 2 days of starting the study treatment.
14. History of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess, or active GI bleeding within 6 months before start of the study treatment.

    Note: If the affected area was surgically resected, and there is no further risk to the area, patients may be enrolled after more than 28 days of the surgery.
15. Inadequately controlled hypertension (defined as systolic blood pressure ≥ 150 mmHg and/or diastolic blood pressure > 100 mmHg) that cannot be managed by standard anti-hypertension medications ≤ 28 days before starting the study treatment, or a history of hypertensive crisis or hypertensive encephalopathy.
16. Active, symptomatic or untreated CNS metastases; history of or known carcinomatous meningitis.

Note: Treatment of brain metastases, either by surgical or radiation techniques, must have been completed > 4 weeks before start of study treatment. Patients requiring anticonvulsants or corticosteroids for symptom control and patients with evidence of interim progression between the completion of CNS-directed therapy and study baseline disease assessments are excluded from the study.

Note: Patients without measurable disease outside the CNS are excluded from the study.

17. Requirement for treatment with any medicinal product that contraindicates the use of any of the study medications, may interfere with the planned treatment, affects patient compliance or puts the patient at high risk for treatment-related complications.
18. Active autoimmune diseases or history of autoimmune diseases that may relapse.

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

    a. Controlled Type I diabetes
    b. Hypothyroidism (provided it is managed with hormone replacement therapy only)
    c. Controlled celiac disease
    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
19. Any active malignancy ≤ 2 years before starting the study treatment except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast).
20. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before starting the study treatment.

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

    a. Adrenal replacement steroid (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) or for the treatment of a nonautoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)
21. With uncontrolled diabetes; > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management; or ≥ Grade 3 hypoalbuminemia ≤ 14 days before starting the study treatment.
22. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence within 2 weeks of intervention).
23. History of interstitial lung disease, noninfectious pneumonitis, or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc. Patients with significantly

impaired pulmonary function or who require supplemental oxygen at baseline must undergo an assessment of pulmonary function at screening.

24. Infection (including tuberculosis) requiring systemic antibacterial, antifungal, or antiviral therapy within 14 days of randomization. Patients receiving prophylactic antibiotics (eg, for prevention of urinary tract infection, chronic obstructive pulmonary disease, or for dental extraction) are eligible.

    Note: Antiviral therapy is permitted for chronic HBV or HCV infection.

25. Untreated chronic hepatitis B or chronic HBV carriers with HBV DNA > 200 IU/mL (or > 1000 copies/mL) at screening.

    Note: Inactive HBsAg carriers, and treated and stable hepatitis B patients (HBV DNA < 200 IU/mL or < 1000 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 starting the study treatment.

26. Known history of HIV infection.
27. Prior allogeneic stem cell transplantation or organ transplantation.
28. 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 starting the study treatment
    b. Pulmonary embolism ≤ 28 days before starting the study treatment
    c. Any history of acute myocardial infarction ≤ 6 months before starting the study treatment
    d. Any history of heart failure meeting the New York Heart Association (NYHA) (Appendix 9) Classification ≥ II within 6 months before starting the study treatment
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before starting the study treatment
    f. Any history of cerebrovascular accident ≤ 6 months before starting the study treatment
    g. Inadequately controlled hypertension (defined as systolic blood pressure ≥ 150 mmHg and/or diastolic blood pressure > 100 mmHg), based on an average of ≥ 3 blood pressure readings on ≥ 2 sessions) that cannot be managed by standard anti-hypertension medications ≤ 28 days before starting the study treatment
    h. Any episode of syncope or seizure ≤ 28 days before starting the study treatment
29. A history of hemoptysis (≥ 2.5 mL of bright red blood per episode) within 28 days of starting the study treatment.
30. Current or recent (within 10 days of randomization) use of aspirin (≥ 325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, or cilostazol.
31. Current or recent (within 10 days of starting the study treatment) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose.

Note: Prophylactic anticoagulation for the patency of venous access devices is allowed provided that the activity of the agent results in an INR < 1.5 x ULN and activated partial thromboplastin time is within normal limits within 14 days of starting the study treatment. For prophylactic use of anticoagulants or thrombolytic therapies, local label-approved dose levels may be used.

32. History of intestinal obstruction and/or clinical signs or symptoms of gastrointestinal obstruction including sub-occlusive disease related to the underlying disease or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding before induction treatment.

    Note: Patients with signs/symptoms of sub-/occlusive syndrome/intestinal obstruction at the time of initial diagnosis may be enrolled if they had received definitive (eg, surgical) treatment for symptom resolution.

33. Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure.
34. Serious, nonhealing or dehiscing wound, active ulcer, or untreated bone fracture.
35. History of severe hypersensitivity reactions to other monoclonal antibodies.
36. Was administered a live vaccine ≤ 28 days before starting the study treatment.

    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.

37. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study treatment, or affect the explanation of drug toxicity or AEs, or result in insufficient or impaired compliance with study conduct.
38. Women who are pregnant or are breastfeeding.
39. 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.

40. Known dihydropyrimidine dehydrogenase deficiency.
41. Active inflammatory bowel disease, eg, Crohn’s disease or ulcerative colitis.
42. The lowest dose level of fluoropyrimidine during the induction treatment was lower than the predefined initial dose of the study treatment.
43. Patients who had experienced any toxic effects from bevacizumab or fluoropyrimidine during the induction treatment that would prevent its safe continuation in maintenance setting.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

No meal or dietary restrictions are required.

5.3.2. Caffeine, Alcohol, and Tobacco

Patients should not abuse alcohol during the study. No caffeine or tobacco restrictions are required.

5.3.3. Physical Activity

No activity restrictions are required.

5.3.4. Other Restrictions

Patients should not abuse other drugs during the study.

5.4. Screen Failures

A screen failure occurs when a patient who has consented to participate in the clinical study does not meet the criteria required and therefore is not subsequently assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patient to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under limited conditions after consultation with the sponsor. Rescreening may be considered when a patient's laboratory result narrowly misses a laboratory criterion that is correctable and not due to a rapidly deteriorating condition or progressive disease. Rescreening is allowed only once. If a patient is rescreened, the patient should be assigned a new patient number for every rescreening event and a new informed consent will not be required.

5.5. Procedures for Handling Incorrectly Enrolled Patients

Incorrect enrollment of patients is defined as enrollment using incorrect baseline information, ineligible patients being enrolled, multiple enrollments being performed for the same patient, and patients receiving the incorrect treatment after enrollment.

The sponsor should be notified as soon as the enrollment error is discovered, and the investigator should ensure clear documentation of the error and provision of relevant information to the sponsor. The sponsor will promptly provide a decision how to manage the patient (eg, continuation of treatment, discontinuation from the study). Until then the investigator should ensure the patient continues to be managed according to the incorrect enrollment and the protocol.

The incorrect enrollment of patients is deemed a protocol deviation.

5.6. Criteria for Temporarily Delaying Enrollment/Administration of Study Treatment

There are no predefined criteria for this study for temporarily delaying enrollment or administration of the first dose of study treatment. Refer to Section 6.6 for details on the dose modification of study treatment.

6. STUDY DRUG/TREATMENT(S) AND CONCOMITANT THERAPY

6.1. Study Drug/Treatment(s) Administered and Dosage

The first dose of study treatments is to be administered within 3 business days of randomization.

Dosing schedules for all arms, broken out by individual treatment arm, are provided in Table 9. Dosing administration and monitoring times, broken out by individual treatment arm, are provided in Table 10.

For all cohorts and arms containing 5-FU in combination with LV:

- The dose of 5-FU should not exceed the lowest dose level in induction treatment.
- The dose of leucovorin or levoleucovorin will follow the relevant local guidance and/or prescribing information, where applicable, and should be no less than the lowest dose level in induction treatment.

Phase 1b

Cohort -1 (LBL-007 + tislelizumab + bevacizumab + capecitabine)

- LBL-007 will be administered at a dose of 150 mg intravenously once every 3 weeks.
- Tislelizumab will be administered at a dose of 200 mg intravenously once every 3 weeks.
- Bevacizumab or its biosimilar will be administered at a dose of 7.5 mg/kg intravenously once every 3 weeks.
- Capecitabine 850 mg/m^2 will be administered twice daily orally for 2 weeks, followed by a one-week treatment break every 3 weeks.

Cohort -1b (LBL-007 + tislelizumab + bevacizumab + 5-FU):

- LBL-007 will be administered at a dose of 100 mg intravenously once every 2 weeks.
- Tislelizumab will be administered at a dose of 300 mg intravenously once every 4 weeks.
- Bevacizumab or its biosimilar will be administered at a dose of 5 mg/kg intravenously once every 2 weeks.
- 5-FU 1600 to 2400 mg/m^2 (continuous infusion over 46 to 48 hours) in combination with LV will be administered intravenously once every 2 weeks.

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

Cohort 1a (LBL-007 + tislelizumab + bevacizumab + capecitabine)

- LBL-007 will be administered at a dose of 300 mg intravenously once every 3 weeks.
- Tislelizumab will be administered at a dose of 200 mg intravenously once every 3 weeks.

- Bevacizumab or its biosimilar will be administered at a dose of 7.5 mg/kg intravenously once every 3 weeks.
- Capecitabine 850 mg/m^2 will be administered twice daily orally for 2 weeks, followed by a one-week treatment break every 3 weeks.

Cohort 1b (LBL-007 + tislelizumab + bevacizumab + 5-FU):

- LBL-007 will be administered at a dose of 200 mg intravenously once every 2 weeks.
- Tislelizumab will be administered at a dose of 300 mg intravenously once every 4 weeks.
- Bevacizumab or its biosimilar will be administered at a dose of 5 mg/kg intravenously once every 2 weeks.
- 5-FU 1600 to 2400 mg/m^2 (continuous infusion over 46 to 48 hours) in combination with LV will be administered intravenously once every 2 weeks.

Cohort 2 (LBL-007 + tislelizumab + bevacizumab + fluoropyrimidine):

- LBL-007 will be administered at a dose of 600 mg intravenously once every 3 weeks, or 400 mg intravenously once every 2 weeks. The doses between 300 mg and 600 mg once every 3 weeks, or 200 mg to 400 mg once every 2 weeks, may be assessed based on a review of tolerability and exposure data by the SMC.
- Tislelizumab will be administered at a dose of 200 mg intravenously once every 3 weeks or 300 mg intravenously once every 4 weeks.
- Bevacizumab or its biosimilar will be administered at a dose of 7.5 mg/kg intravenously once every 3 weeks or 5 mg/kg intravenously once every 2 weeks.
- Capecitabine 850 mg/m^2 will be administered twice daily orally for 2 weeks, followed by a one-week treatment break every 3 weeks. Alternatively, 5-FU 1600 to 2400 mg/m^2 (continuous infusion over 46 to 48 hours) in combination with LV will be administered intravenously once every 2 weeks.

Phase 2

Arm A and Arm D (LBL-007 + tislelizumab + bevacizumab + fluoropyrimidine):

- LBL-007 will be administered at a dose of 600 mg intravenously once every 3 weeks, or 400 mg intravenously once every 2 weeks. A lower dose than 600 mg once every 3 weeks or 400 mg once every 2 weeks may be determined as the recommended dose for Phase 2 based on tolerability, safety, and PK data from Phase 1b and the SMC recommendation.
- Tislelizumab will be administered at a dose of 200 mg intravenously once every 3 weeks or 300 mg intravenously once every 4 weeks.
- Bevacizumab or its biosimilar will be administered at a dose of 7.5 mg/kg intravenously once every 3 weeks or 5 mg/kg intravenously once every 2 weeks.
- Capecitabine 850 mg/m^2 will be administered twice daily orally for 2 weeks, followed by a one-week treatment break every 3 weeks. Alternatively, 5-FU 1600 to 2400 mg/m^2

(continuous infusion over 46 to 48 hours) in combination with LV will be administered intravenously once every 2 weeks.

Arm B (LBL-007 + bevacizumab + fluoropyrimidine)

- LBL-007 will be administered at a dose of 600 mg intravenously once every 3 weeks, or 400 mg intravenously once every 2 weeks. A lower dose than 600 mg once every 3 weeks or 400 mg once every 2 weeks may be determined as the recommended dose for Phase 2 based on tolerability, safety, and PK data from Phase 1b and the SMC recommendation.
- Bevacizumab or its biosimilar will be administered at a dose of 7.5 mg/kg intravenously once every 3 weeks or 5 mg/kg intravenously once every 2 weeks.
- Capecitabine 850 mg/m^2 will be administered twice daily orally for 2 weeks, followed by a one-week treatment break every 3 weeks. Alternatively, 5-FU 1600 to 2400 mg/m^2 (continuous infusion over 46 to 48 hours) in combination with LV will be administered intravenously once every 2 weeks.

Arm C and Arm E (bevacizumab + fluoropyrimidine):

- Bevacizumab or its biosimilar will be administered at a dose of 7.5 mg/kg intravenously once every 3 weeks or 5 mg/kg intravenously once every 2 weeks.
- Capecitabine 850 mg/m^2 will be administered twice daily orally for 2 weeks, followed by a one-week treatment break every 3 weeks. Alternatively, 5-FU 1600 to 2400 mg/m^2 (continuous infusion over 46 to 48 hours) in combination with LV will be administered intravenously once every 2 weeks.

Table 9: Planned Dose, Frequency of Administration, and Route of Administration for Study Treatments

Study Treatments	Dose	Timing of Administration	Route of Administration	Duration of Treatment
LBL-007	100 mg 200 mg 400 mg (or intermediate dose levels)	Once every 2 weeks on Day 1 of each 14-day cycle	Intravenous	Refer to Section 4.1.1.3
	150 mg 300 mg 600 mg (or intermediate dose levels)	Once every 3 weeks on Day 1 of each 21-day cycle		
Tislelizumab	200 mg	Once every 3 weeks on Day 1 of each 21-day cycle	Intravenous	Refer to Section 4.1.1.3
	300 mg	Once every 4 weeks, on Day 1 of every other 14-day cycle		
Bevacizumab or its biosimilar [a]	5 mg/kg	Once every 2 weeks on Day 1 of each 14-day cycle	Intravenous	Refer to Section 4.1.1.3
	7.5 mg/kg	Once every 3 weeks on Day 1 of each 21-day cycle		
Capecitabine [b]	850 mg/m^2	Twice a day for the first 2 weeks of each 21-day cycle	Oral	Refer to Section 4.1.1.3
5-FU	1600-2400 mg/m^2	Once every 2 weeks on Day 1 of each 14-day cycle	Intravenous	Refer to Section 4.1.1.3
LV	Per local guidance and/or prescribing information	Once every 2 weeks on Day 1 of each 14-day cycle	Intravenous	Refer to Section 4.1.1.3

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin or levoleucovorin.
[a] Bevacizumab or its biosimilar products of bevacizumab (POBEVCY® or MVASI®) will be used in this study.
[b] Capecitabine will be administered with water within 30 minutes after a meal twice daily orally, from the morning of Day 1 to the evening of Day 14 or from the evening of Day 1 to the morning of Day 15 of each 21-day cycle.

Table 10: Administration of Study Treatments and Monitoring Time

Cycle	LBL-007, Tislelizumab, and Bevacizumab Combination
Day 1, Cycle 1	LBL-007 infusion over 60 (± 5) minutes, followed by tislelizumab infusion over 60 (± 5) minutes, followed by bevacizumab over 30 (± 5) minutes (or follow local guidelines, if applicable) (Phase 1b and Arm A and Arm D in Phase 2) Or LBL-007 infusion over 60 (± 5) minutes, followed by bevacizumab over 30 (± 5) minutes (or follow local guidelines, if applicable) (Arm B in Phase 2) Patient monitoring for ≥ 120 minutes
Day 1, Cycle 2 onwards, if tolerated	LBL-007 infusion over 60 (± 5) minutes, followed by tislelizumab infusion over 30 (± 5) minutes, followed by bevacizumab over 30 (± 5) minutes (Phase 1b and Arm A and Arm D in Phase 2) Or LBL-007 infusion over 60 (± 5) minutes, followed by bevacizumab over 30 (± 5) minutes (Arm B in Phase 2) Patient monitoring for ≥ 60 minutes

Capecitabine 850 mg/m^2 will be administered twice daily orally for 2 weeks, followed by a one-week treatment break every 3 weeks for all applicable patients.

5-FU 1600 to 2400 mg/m^2 (continuous infusion over 46 to 48 hours) in combination with LV will be administered intravenously, once every 2 weeks on Day 1 of each 14-day cycle for all applicable patients. The dose of 5-FU should not exceed the lowest dose level in induction treatment. The dose of leucovorin or levoleucovorin will follow the relevant local guidance and/or prescribing information, where applicable, and should be no less than the lowest dose level in induction treatment.

Treatment Administration

The dose of bevacizumab will be based on the baseline weight, defined as the weight of the patient (in kilograms) measured ≤ 14 days before the initiation of study treatment, and will remain the same throughout the study unless there is a weight change of > 10%. Baseline body weight is used to calculate the required capecitabine doses. If re-assessment of baseline weight is needed, the latest baseline weight should always be used to calculate percent change in weight for all subsequent doses.

As described below, LBL-007, tislelizumab, and bevacizumab must be prepared and administered as separate infusions and must not be concurrently administered with any other drug (Section 6.9). Specific instructions for product preparation and administration are provided in the pharmacy manual.

LBL-007 and tislelizumab must be administered by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2- or 0.22-micron in-line or add-on filter. Use of a volumetric pump is recommended to control the infusion speed and to avoid potential infusion reactions associated with too rapid administration. The pump may not be needed if the infusion speed is controlled through alternative means and is consistent with approved institutional procedures. At the end of the infusion period, the line should be flushed

with enough normal saline to make sure that all of the study treatments are administered to the patient.

Regardless of the infusion completion time, patients must be monitored in an area with resuscitation equipment and emergency agents. All patients will be monitored continuously for AEs. Treatment modifications (eg, dose delay, interruption, or discontinuation) will be based on specific laboratory and AE criteria, as described in Section 6.6. Guidelines for dose modification, treatment interruption, or discontinuation and for managing imAEs and infusion-related reactions are provided in Section 6.10.4, Appendix 13, Section 6.10.3, and Appendix 11.

6.2. Preparation, Handling, Storage, and Accountability

6.2.1. Formulation, Packaging, and Handling

6.2.1.1. LBL-007

LBL-007 is a monoclonal antibody formulated for intravenous infusion and is provided as a preservative-free, single-use vial containing a minimum of 5 mL of a 17 mg/mL concentrated solution (85 mg) or 17.65 mL of a 17 mg/mL concentrated solution (300 mg) of antibody in a buffered isotonic solution. LBL-007 is aseptically filled in single-use vials (6 mL or 20 mL; USP Type I glass) with a coated butyl rubber stopper and sealed with an aluminum flip-off cap.

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

The study drug must be kept at the temperature and light conditions as specified on the label.

Refer to the pharmacy manual for details regarding intravenous administration, accountability, and disposal. Please also refer to the LBL-007 Investigator's Brochure for other details regarding LBL-007.

6.2.1.2. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous injection in a single-use vial (20R glass, USP type I), containing a total of 100 mg of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in single-use vials with a Flurotec-coated butyl rubber stopper and an aluminum 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 conditions as specified on the label. Shaking should be avoided.

Refer to the pharmacy manual for details regarding intravenous administration, accountability, and disposal. Refer to the Tislelizumab Investigator's Brochure for other details regarding tislelizumab.

6.2.1.3. Bevacizumab and Fluoropyrimidine

Management (ie, labeling, handling, storage, administration, and disposal) of these products will be in accordance with the relevant local guidelines and/or prescribing information.

For further details, see the manufacturer's prescribing information for the respective products.

Bevacizumab or the regional health authority approved biosimilar (POBEVCY®, Bio-Thera Solutions, Ltd.; or MVASI®, Amgen Inc.) will be used in the study. Depending on the region in which the drug is approved, POBEVCY® will be used in the sites in China, MVASI® will be used in the sites in the region of ex-China. Each patient should receive either bevacizumab or the same biosimilar during the treatment period; switching between bevacizumab or different biosimilars is not allowed in the study.

6.2.2. Study Treatment Accountability

The study treatments required for completion of this study (LBL-007, tislelizumab, bevacizumab, capecitabine, and 5-FU/LV) will be provided by the sponsor. The investigational site will acknowledge receipt of the study treatments. Any damaged shipments will be replaced. Accurate records of all study treatment received, dispensed, returned, and disposed of should be recorded.

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study treatments. This includes acknowledgment of receipt of each shipment of study treatments (quantity and condition), patient drug dispensation records, and returned or destroyed study treatments. 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 treatment disposal/destruction to ensure that it complies with the requirements of the sponsor specified in the Pharmacy Manual. At appropriate timepoints during the conduct of the study or at the end of the study after the final treatment inventory reconciliation by the medical monitor, the study site will dispose of and/or destroy all unused study treatment 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 treatment supplies.

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

Refer to the Pharmacy Manual for details on managing study treatments.

6.3. Assignment to Study Treatment

All patients will be centrally assigned to the study drug using an IRT system. Before the study is initiated, the telephone number and call-in directions and/or the log-in information and directions for the IRT system will be provided to each site.

Study drugs will be dispensed at the study visits as summarized in the SoA (Section 1.3).

Returned study drugs/treatments should not be redispensed to the patients. Sites will be given the option to return drug or destroy study drugs on site.

6.4. Blinding

No blinding or masking is required.

6.5. Study Treatment Compliance

When patients are dosed at the site, they will receive treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

The dose of study treatment and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

6.6. Dose Modification

A dose interruption is an interruption of an infusion. A dose delay is a deviation from the prescribed dosing schedule (ie, the drug is withheld beyond the visit window).

Every effort should be made to administer the study treatments in a synchronized manner according to the planned dose and schedule as described in Section 6.1. In the event of significant toxicities, dosing of one or more study treatments may be delayed and/or interrupted based on the guidelines provided below. Reasons for dose interruptions or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

When treatment is temporarily interrupted because of toxicity, treatment cycles should be restarted such that the LBL-007 ± tislelizumab and bevacizumab infusions remain synchronized and aligned with the capecitabine schedule. However, if it is anticipated that fluoropyrimidine will be delayed by ≥ 2 weeks, then LBL-007 ± tislelizumab and bevacizumab should be given without fluoropyrimidine if there is no contraindication.

Bevacizumab and LBL-007 ± tislelizumab do not need to be held together or given together. For example, if there is a bevacizumab-related adverse effect, the bevacizumab may need to be held, while LBL-007 ± tislelizumab may be able to be continued. However, in cases in which the adverse effect may be related to either bevacizumab or LBL-007 ± tislelizumab, both drugs may need to be held.

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

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

Management guidelines for infusion-related reactions, imAEs, and AEs related to bevacizumab and fluoropyrimidine in patients are presented in Section 6.10.3, Appendix 11, Section 6.10.4, Appendix 13, and Appendix 14.

6.6.1. Dose Interruption or Delay for LBL-007 and Tislelizumab

If a dose delay is required, both study treatments are to be delayed (ie, LBL-007 and tislelizumab must both be delayed and if applicable restarted at the same time). Exceptions may be considered following consultation between the investigator and the medical monitor.

Patients who temporarily withhold or permanently discontinue a study treatment due to related AEs may continue on the other study treatment(s) (eg, bevacizumab and/or fluoropyrimidine) as long as the patients are experiencing clinical benefit in the opinion of the investigator.

If treatment is delayed due to TEAEs, treatment may resume only after the AEs have returned to baseline or ≤ Grade 1 severity except for alopecia or AEs that, in the opinion of the investigator, are not considered a safety risk to the patient. If a treatment delay is due to laboratory results worsening, eg, hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated. In general, dose delays for reasons other than management of AEs are prohibited.

A dose delay of ≤ 12 weeks is allowed under the following guidance and at the discretion of the investigator after consultation with the medical monitor or designee.

Treatment with immunotherapy will need to be resynchronized with chemotherapy at the subsequent cycles according to the chemotherapy dose administration date, but the time between 2 consecutive cycles of immunotherapy should be at least 10 days.

If imAEs are persistent without any improvement for more than 12 weeks, permanent discontinuation of the study treatment should be considered. In arms containing both LBL-007 and tislelizumab, the treatment discontinuation in response to imAEs should be applied to both LBL-007 and tislelizumab because the causality of imAEs may not be distinguished from one study treatment to the other.

If the patient recovers from the treatment-related AE after 12 weeks, re-initiation of LBL-007 with or without tislelizumab is permitted only in patients who are deemed to be deriving clinical benefit per the opinion of the investigator following agreement between the investigator and the medical monitor. The tumor assessment schedule will not be altered even if the administration of the study treatment is delayed.

6.6.2. Dose Reduction for LBL-007 and Tislelizumab

There will be no dose reductions allowed for LBL-007 or tislelizumab in this study.

6.6.3. Dose Modification for Bevacizumab and Fluoropyrimidine

No dose reduction of bevacizumab is foreseen for an individual patient. Skipped doses or termination of treatment will be based on the observed toxicities specified in prescribing information for bevacizumab. No dose adjustments are allowed except for body weight changes of more than 10%.

For toxicity management, the doses of bevacizumab can only be held.

Dose modifications for fluoropyrimidine and bevacizumab should be performed per applicable local prescribing information and per local practice according to the investigator's clinical judgment.

Recommended dose modifications for bevacizumab and fluoropyrimidine are outlined in Appendix 14.

If chemotherapy-related toxicities warrant a dosing delay, chemotherapy administration may restart as soon as is feasible. Chemotherapy may be delayed up to 3 weeks to allow sufficient

time for recovery. Upon recovery, chemotherapy is recommended to be administered according to the dose as Section 6.1.

Toxicities related to fluoropyrimidine must be resolved to baseline or ≤ Grade 1 before administering the next dose of chemotherapy, with the exception of alopecia, Grade 2 fatigue, or other AEs, which, in the opinion of the investigator, would not affect the safety evaluation of the study treatments.

A maximum of 2 dose level reductions of fluoropyrimidine due to toxicity are permitted throughout the induction and maintenance treatment. If additional reductions are required, then fluoropyrimidine must be discontinued. Once the dose has been decreased, it should remain reduced for all subsequent administrations or further reduced if necessary. There will be no dose escalations and/or re-escalations in this study.

If capecitabine is vomited due to an AE after oral administration or the dose is interrupted by any reasons, there is no need to have additional dose as supplement. The cycle for capecitabine need to be no less than 21 days and the time interval between the last dose and the first dose of the next cycle should not be less than 7 days.

If the patient is unable to resume fluoropyrimidine within 6 weeks after the last dose of chemotherapy, then discontinuation for fluoropyrimidine should be considered. If the patient is not able to resume chemotherapy within 6 weeks after the last dose for unforeseen non-drug-related reasons, continued treatment may be allowed if approved by the medical monitor.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, patient vacation, and holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the patient's study record.

Patients may also discontinue capecitabine following multiple cycles if, in the investigator’s judgment, cumulative toxicity is likely to increase over time and become problematic. Recommended guidance regarding dose modifications of chemotherapy for certain toxicities is presented in Appendix 14. For toxicities not listed, dose modifications are permitted per local standards.

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

The Extended IP Access Period is established to provide continued access to study treatment for ongoing patients after the sponsor’s decision of enrollment termination. The Extended IP Access Period will begin when Protocol Amendment 4.0 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 any discontinuation criterion specified in Section 7.1 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 resign 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 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 8.6.4.

Samples for PK, ADA, and biomarker assessments will not be collected during the Extended IP Access Period.

6.8. Treatment of Overdose

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

An incorrect administration or overdose of study treatment(s) is not itself an AE, but it may result in an AE. AEs associated with an incorrect administration or overdose of study treatments will be recorded on the AE eCRF. Any SAEs associated with an incorrect administration or overdose must be reported within 24 hours of awareness via the SAE reporting process as described in Section 8.6.4. Supportive-care measures should be administered as appropriate.

6.9. Prior and Concomitant Therapy

6.9.1. Prior Therapy

Prior medication use, including any protocol-specified washout requirement, and prior medications taken by the patient within 28 days of first dose of study medication should be recorded. Prior anticancer treatment for CRC including systemic treatments, radiation, and surgeries should be recorded separately and not listed as a prior medication.

The exclusion criteria (Section 5.2) specify that patients should not have received any anticancer therapy for CRC in the metastatic setting except for the induction treatment of the first-line treatment, and any prior therapies targeting T-cell stimulation or checkpoint pathways.

6.9.2. Concomitant Therapy

6.9.2.1. Permitted Concomitant Medications/Procedures

Unless noted otherwise, most concomitant medications and therapies are allowed at the discretion of the investigator if they are deemed necessary and are in keeping with local standards of medical care for supportive care (eg, antiemetics, antidiarrheals, hematopoietic growth factors, and red blood cell/platelet transfusions) and in a patient's interest. Opiates and other medication required for palliative management of patients are allowed. Ongoing therapies such as oral contraceptives, hormone-replacement therapy, or thyroid replacement therapy should continue their use. Patients must notify the investigator of all concurrent medications used during the study.

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

All concomitant medications will be recorded on the eCRF, including all prescription and over-the-counter medicines, herbal supplements, and intravenous medications and fluids, taken by or administered to the patient within 28 days before randomization and within 30 days after the last dose of study treatment(s) and relevant concomitant medications/procedures (if appropriate, ie, is associated with an imAE or is a new anticancer therapy within 90 days after the last dose of study treatment(s) will be recorded.

6.9.2.1.1. Systemic Corticosteroids

Systemic corticosteroids administered for the control of imAEs must be tapered gradually (see Appendix 13) and must be administered at nonimmunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next administration of LBL-007 with or without tislelizumab. The short-term use of steroids as prophylactic treatments (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

6.9.2.1.2. Hepatitis B Treatment

Patients with active hepatitis B, defined as HBV DNA ≥ 200 IU/mL at screening, must initiate antiviral treatment > 2 weeks before the first dose of study treatment. These patients would not be eligible unless HBV DNA decreases to < 200 IU/mL. If the patients are treated and eligible, antiviral treatment must continue until 6 months after the last dose of study treatment. Patients should continue effective antiviral treatment during the study to decrease potential viral reactivation risk. Tenofovir and entecavir are recommended in the American Association for the Study of Liver Disease (AASLD) guideline 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 on study.

Management of prophylactic antiviral therapy for patients with inactive, treated, and stable hepatitis B (HBV DNA < 200 IU/mL at screening) is at the discretion of the investigator, as aligned with local guidance. Such medications must be documented in the patient's chart and recorded in the eCRF. Patients receiving antivirals at screening should be treated for > 2 weeks before enrollment and continue treatment during the study and for 6 months after study treatment discontinuation.

6.9.2.1.3. Hepatitis C Treatment

The sponsor does not require patients with active hepatitis C to receive treatment with antiviral therapy. Patients with detectable HCV RNA who are receiving treatment at screening should remain on continuous, effective antiviral therapy during the study. Investigators can consider

treatment with antiviral agents, in accordance with international or local guidelines. However, interferon-based therapy for HCV is not permitted during the study. Patients who are given antiviral therapy must initiate treatment > 2 weeks before the first dose of study treatment and continue treatment during the study and for 6 months after study treatment discontinuation.

6.9.2.1.4. Radiation Therapy

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

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

Additionally, palliative radiation or other focally ablative therapy for other nontarget sites of the disease is permitted if clinically indicated per the investigator's discretion and after consultation with the medical monitor. Whenever possible, these patients should have a tumor assessment of the lesion(s) before receiving the radiation therapy to rule out progressive disease. It is not required to withhold study treatments during palliative radiotherapy.

6.9.2.2. Prohibited Concomitant Medications/Procedures

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

- Any other concurrent anticancer therapy (ie, chemotherapy other than capecitabine, hormonal therapy [except supportive care], or immunotherapy) that are standard or investigational agents.

  Note: if the tumor presents a deep regression due to study treatment during the maintenance therapy compared with the tumor after the completion of induction treatment and is assessed to be resectable in the intent of curative purpose at the investigator's discretion, it should be discussed with the medical monitor before making decision. Post-surgery treatment with the study treatment should be discussed with the medical monitor further if the investigators consider it will derive additional benefit and is in the interest of the patients.
- Herbal remedies for the treatment of cancer or Chinese patent medicines with approval from the NMPA for use as anticancer treatment (regardless of the type of cancer) used ≤ 14 days before the first dose of study treatment(s).
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 28 days or 5 half-lives (whichever is longer) of randomization and during the study.
- Herbal remedies with immune-stimulating properties or that are known to potentially interfere with liver or other major organ functions.

The following medication/therapies are prohibited during treatment of LBL-007 with or without tislelizumab:

- Live vaccines administered ≤ 28 days before starting the study treatment through the 60 days after the last dose of LBL-007 or tislelizumab, whichever is later.

The following medication/therapies are prohibited during treatment of bevacizumab:

- Use of warfarin or Coumadin-like products (including for prophylactic use) is prohibited
  - Prophylactic use of low-dose anticoagulants, unfractionated heparin, or low-molecular-weight heparin is permitted.
- Current use of full-dose anticoagulants, thrombolytic therapy at therapeutic doses, or anti-platelet therapy are prohibited. However, if a patient experiences a venous thromboembolism event while still receiving the study treatment, it may still be possible for the patient to remain on study medication despite anticoagulation treatment (See Section 5.2)
- Concomitant chronic use of NSAIDs while receiving study treatments is prohibited. However, for the symptomatic relief of medical conditions (eg, headache, fever), sporadic or short-term intake of oral NSAIDs is allowed, when co-administered with proton-pump inhibitors to reduce potential gastrointestinal damage.

6.9.2.3. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

- Patients should not abuse alcohol or other drugs during the study.
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored.
- Radiation therapy is not allowed, except for palliative radiation therapy, as described in Section 6.9.2.1.4.

The following medications are restricted during the treatment of LBL-007 with or without tislelizumab

- Immunosuppressive agents (except to treat a drug-related AE).
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control an AE (per protocol) or for short-term use as prophylactic treatment.

6.9.2.4. Potential Interactions Between the Study Treatments and Concomitant Medications

Information regarding clinical drug interactions with LBL-007 is not available and no dedicated drug-drug interaction studies are planned. However, the potential for drug-drug interaction between the study treatments (LBL-007 and tislelizumab) and other drug products is very low because LBL-007 and tislelizumab are therapeutic monoclonal antibodies. Because LBL-007 and tislelizumab are expected to be degraded into amino acids and recycled into other proteins, they are unlikely to influence drug-metabolizing enzymes or transporters.

Refer to the drug-drug interaction section in manufacturer's prescribing information for the influence of the respective chemotherapy agents on drug-metabolizing enzymes or transporters. Formal drug-drug interaction studies between capecitabine and phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the cytochrome P450 (CYP) 2C9 isoenzyme by capecitabine and/or its metabolites. Other than warfarin, no formal drug-drug interaction studies between capecitabine and other CYP2C9 substrates have been conducted. Care should be exercised when capecitabine is co-administered with CYP2C9 substrates. While PK data are not available to assess the effect of 5-FU administration on warfarin PK, the elevation of coagulation times that occurs with the 5-FU prodrug capecitabine is accompanied by an increase in warfarin concentrations. This interaction may be due to inhibition of CYP2C9 by 5-FU or its metabolites.

6.9.3. Rescue Medication

Not applicable.

6.10. Safety Management for Adverse Events

6.10.1. Risks Associated with Study Treatments

6.10.1.1. Risks Associated With LBL-007 and Tislelizumab

LBL-007 and tislelizumab are investigational agents that are currently in clinical development. Limited safety data are available for patients, and the full safety profile has not been characterized. The following recommendation is based on results from clinical studies with LBL-007 in combination with another PD-1 antibody (toripalimab), and published data on other molecules within the same biologic class.

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

The PD-L1/PD-1 and LAG-3 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 Section 6.10.4.

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. Suggested workup procedures for suspected imAEs are provided in Appendix 13.

6.10.1.2. Risks Associated With Bevacizumab and Fluoropyrimidine

Bevacizumab as a single agent or in combination with other anticancer therapies at a rate > 10% were epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, hemorrhage, lacrimation disorder, back pain, and exfoliative dermatitis. The most frequent SAEs for bevacizumab include gastrointestinal perforations, hemorrhage, and arterial thromboembolism.

As an intravenous fluorouracil drug, 5-FU has common toxicities, including myelosuppression with leukopenia, thrombocytopenia and anemia, nausea/vomiting and other gastrointestinal tract toxicity, hepatic impairment, fatigue, anorexia, and constipation. It also has specific toxicities, such as neutropenia and neurotoxicity.

Capecitabine as an oral fluorouracil drug can produce 5-FU-like side effects. The most common adverse reactions (≥ 30%) were diarrhea, hand-and-foot syndrome, nausea, vomiting, abdominal pain, fatigue/weakness, and hyperbilirubinemia. Compared with fluorouracil, capecitabine was associated with more hand-foot syndrome but less stomatitis, alopecia, neutropenia requiring medical management, diarrhea, and nausea. The commonly reported Grade 3-4 AEs include hyperbilirubinemia, hand-and-foot syndrome.

Regarding the combination of bevacizumab and fluoropyrimidine, the safety profile is well tolerated and manageable. All AEs will be monitored during the study and need to be managed with standard symptomatic treatment.

The investigator should refer to the prescribing information for detailed information of potential side effects.

6.10.2. General Plan to Manage Safety Concerns

6.10.2.1. 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 LBL-007 and tislelizumab, as well as the nonclinical/clinical data from other LAG-3 and PD-L1/PD-1 inhibitors, were considered. Specifically, patients who are at risk for treatment-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 viral vaccine ≤ 28 days before starting the study treatment are excluded from the study.

Refer to Section 5.2 for the full list of exclusion criteria.

6.10.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE v5.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Section 1.3.

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, recording of AEs (see Table 12), physical examinations, laboratory measurements (hematology, clinical chemistry, etc), and other assessments including those listed in Section 1.3. In addition, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions or infection.

At the start of each cycle, study treatment(s) will be administered only after clinical laboratory results have been reviewed. Administration of study treatments will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (for additional information, see Section 6.1).

During the Extended IP Access Period, safety assessments 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. 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 8.6.4.

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in Section 6.10.3, Section 6.10.4, and Section 6.10.5.

6.10.3. Infusion-Related Reactions and Anaphylaxis

As a routine precaution, after infusion of the study treatments, patients must be monitored. Refer to Section 6.1 for the administration of study treatments and monitoring time.

Patients should be closely monitored for infusion-related reactions. Immediate access to an Intensive Care Unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

See Appendix 11 and Appendix 12 for management of infusion-related reactions and anaphylaxis reactions, as well as treatment modifications.

6.10.4. Immune-Mediated Adverse Events

If the events listed below or similar events occur, the investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic, toxin, progressive disease, or other neoplastic causes) with appropriate diagnostic tests that may include but are not limited to serologic, immunologic, and histologic (biopsy) data. If alternative causes have been ruled out, the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy and is consistent with an immune-mediated mechanism of action, the imAE indicator on the eCRF AE page should be checked.

A list of potential imAEs is shown in Table 14. All conditions similar to those listed should be evaluated in patients to determine whether they are immune-mediated.

Recommendation for diagnostic evaluation and management of imAEs is based on European Society for Medical Oncology and American Society of Clinical Oncology guidelines (Haanen et al 2017; Brahmer et al 2018) and common immune-mediated toxicities are detailed in Appendix 13. For any AEs not included in Appendix 13, refer to the American Society of Clinical Oncology Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Recommendations for managing imAEs are detailed in Appendix 13.

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

6.10.5. Hepatic Function Abnormalities

When a hepatic event, such as liver function laboratory abnormalities, is observed, the investigator must evaluate for reactivation of viral hepatitis, consider other drug-related toxicities, and exclude disease progression involving the liver. When an elevated ALT or AST level (> 3 x ULN) in combination with either an elevated total bilirubin level (> 2 x ULN), clinical jaundice in the absence of cholestasis, or other causes of hyperbilirubinemia are observed, it is an indicator of severe liver injury (Hy's law case). For diagnosis and management of patients with abnormal ALT or AST levels, refer to Section 6.10.4 and Appendix 13.

7. DISCONTINUATION OF STUDY TREATMENT AND PATIENT WITHDRAWAL

7.1. Discontinuation of Study Treatment

Patients have the right to discontinue study treatment(s) at any time for any reason. In addition, the investigator has the right to discontinue a patient from study treatment(s) at any time. Patients who discontinue the study treatment(s) for reasons other than progressive disease should be followed for an assessment of antitumor activity (Section 8.4), safety (Section 8.5) and survival (Section 8.12.3), if possible.

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

- Radiographic progressive disease per RECIST v1.1
- AE
- 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(s)
- Use of any concurrent anticancer therapy (ie, chemotherapy, hormonal therapy [except supportive care], 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) (Section 6.9.2.2)
- Patient noncompliance

  Investigative site staff should first counsel patients who are significantly noncompliant (eg, missing 2 treatment cycles) on the importance of study treatment compliance and drug accountability. The investigator may discontinue patients from treatment if they are consistently noncompliant.
- Completion of study treatment(s)

7.2. Patient Withdrawal From the Study

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

- Patient withdrawal of consent
- Death
- Loss to follow-up
- The sponsor's decision to terminate the study

7.3. Loss to Follow-up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls, and if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, the patient will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomized, including those who did not receive study treatment. Hospital records and public sources may be searched for vital status information where local laws allow. If vital status is determined as deceased, this will be documented, and the patient will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. STUDY ASSESSMENTS AND PROCEDURES

A table of scheduled study assessments for Phase 1b and Phase 2 is provided in Section 1.3. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented in the medical record for each patient.

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

8.1. Administrative and Screening Assessments and Procedures

8.1.1. Prescreening Period

Prescreening period is optional at the investigator's discretion. The evaluation may start during the induction treatment before the screening if the patient is considered eligible for the clinical study. The purpose of the Prescreening Period in Phase 2 is to allow time for determination of the PD-L1 levels and MSI-H/dMMR status. In addition, the Prescreening Period allows early exclusion for the patients who experienced disease progression during induction treatment. The details for collection, storage, shipment, and analysis of tumor and blood are detailed in the laboratory manual.

Patients who agree to participate in the clinical study will sign the prescreening ICF before undergoing any prescreening procedure.

The overall duration for prescreening is 56 days before the randomization. A longer Prescreening Period may be granted on a case-by-case basis following approval from the medical monitor. This will not have an impact on the screening timeframe of 28 days before the randomization.

The following tasks will be performed during the Prescreening Visit:

- Obtain written informed consent (prescreening ICF) to obtain tumor samples (archival tissue/biopsy) and blood
- Collect MSS/pMMR documentation if known; obtain consent to have central MSI-H/dMMR assessment if unknown
- Prepare tumor samples/blood and ship to the qualified central lab for analysis.

Refer to Section 8.8 for detailed tumor tissue and biomarker assessment procedure.

Site staff should plan prescreening activities in advance to ensure that all subsequent screening activities can be completed within the allowed period with a maximum duration of 28 days before the randomization.

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

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

8.1.1.1. PD-L1/MSI/BRAF Test

Local result for MSI-H/dMMR status (if appropriate) is recommended and acceptable, followed by retrospective confirmation by test lab. If the site could not provide local results, the tumor tissue sample and blood sample will be sent for central laboratory assessment of MSI-H/dMMR status by an MSI assay (Promega Corporation).

Central laboratory determination of PD-L1 levels by SP263 assay is required.

BRAF status will be tested locally. A prior BRAF testing result is acceptable for confirming the status.

8.1.2. Screening Period

Screening evaluations will be performed ≤ 28 days before starting the study treatment (for Phase 1b) or randomization (for Phase 2). A patient who agrees to participate in this study will sign the ICF before undergoing any screening assessment. The screening period begins on the first day that a screening assessment is conducted. Screening evaluations may be repeated as needed within the screening period. The investigator is to assess patient eligibility according to the latest screening assessment results.

Results of standard-of-care tests or examinations performed before informed consent has been obtained and within 28 days before starting the study treatment (for Phase 1b) or randomization (for Phase 2) may be used for the purposes of screening rather than repeating the standard-of-care tests, unless otherwise indicated.

Rescreening under limited conditions may be allowed after consultation with the sponsor. Refer to Section 5.4 for details related to rescreening.

Procedures conducted only during the Screening Visit are described in this section. For the description of other assessments that are conducted during screening as well as throughout the study, refer to the safety assessments (Section 8.5), tumor and response evaluations (Section 8.4), and tumor tissue and biomarker assessment procedures (Section 8.8) sections.

8.1.2.1. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before any study-specific procedures are performed. The ICFs for enrolled patients and for patients who are prescreened or 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 starting the study treatment. The investigator will maintain a prescreening and screening log to record the details of all patients screened and to confirm eligibility or record reasons for not meeting screening criteria, as applicable.

8.1.2.2. 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.

8.1.2.3. Demographics

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 2018) 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. 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.

8.1.2.4. Women of Childbearing Potential and Contraception

Childbearing potential is defined as the physiological ability to become pregnant. Refer to Appendix 2 for contraception guidelines and definitions of "women of childbearing potential" and "women of no childbearing potential."

8.1.2.5. Pulmonary Function Tests

Patients who are suspected of having or known to have serious and/or severe respiratory conditions, or who exhibit significant respiratory symptoms unrelated to the underlying cancer, or who have a history of thoracic radiotherapy will undergo pulmonary function testing that may include, but is not limited to, spirometry and assessment of diffusion capacity performed during the screening period to assist the determination of suitability for the study. The test may be repeated as clinically indicated while on study (refer to Section 1.3 for details).

The medical monitor needs to be consulted to confirm eligibility if test results indicate significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, absolute forced expiratory volume (FEV1) value < 1L, FEV1 of age and sex adjusted predicted performance levels < 50%, diffusing capacity of the lungs for carbon monoxide (if performed) < 40% of age and sex adjusted predicted performance levels (Pellegrino et al 2005).

8.1.2.6. HIV Serology Test

Where required by the Health Authority or local guidance: An HIV serology test (including antigen and/or antibodies) will be conducted at baseline for patients with unknown HIV status.

8.1.2.7. COVID-19 Test

A COVID-19 test may be conducted according to local practice.

8.2. Enrollment

8.2.1. Confirmation of Eligibility

Before 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.

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

8.2.2. Randomization

In Phase 2, site personnel will access the IRT system to randomize PD-L1 positive patients and assign study treatments by permuted block stratified randomization, and randomize PD-L1 negative patients and assign study treatments by block randomization.

All patients should receive the study treatment(s) within 3 business days after randomization and treatment assignment.

8.3. Study Treatment Dispensation

Patients enrolled by the sponsor will be treated as described in Section 6.1, starting from Day 1 of Cycle 1.

8.4. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

Tumor imaging will be performed ≤ 28 days before the first dose date (Phase 1b) or randomization (Phase 2). Results of standard-of-care tests or examinations performed before obtaining informed consent and ≤ 28 days before starting the study treatment may be used for the purposes of screening rather than repeating the standard-of-care tests.

During the study, tumor response will be evaluated by the investigator every 9 weeks (63 days ± 7 days) from Day 1 of Cycle 1, in accordance with RECIST v1.1. Tumor assessments must be performed on schedule regardless of whether the study treatment(s) have been administered or withheld, ie, they should not be adjusted for delays in cycles.

Screening assessments and each subsequent assessment must include CT scans (with oral/intravenous contrast) of the chest, abdomen, and pelvis. If a contraindication exists, other modalities can be allowed after consultation with the medical monitor (eg, MRI or CT without contrast); a bone scan or PET is required if clinically indicated. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc). For patients who are suspected to have CNS metastases, CT/MRI of the head is required at baseline. MRI may be used when it is the standard of care at a site, regardless of whether or not CT is contraindicated.

All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to

assess disease sites at screening must be used throughout the study (eg, the same contrast protocol for CT scans).

- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a noncontrast 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 [TC-99m]) or PET should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans, TC-99m or PET bone scans should be repeated when a CR is suspected in a target lesion or when progression in bone is suspected.
- CT scans of the head, neck, or extremities should be performed at screening only if clinically indicated and should be repeated throughout the study if there is evidence of metastatic disease in these regions at screening.
- At the investigator's discretion, other methods of assessment of target lesion and nontarget lesions per RECIST v1.1 may be used.

Response will be assessed by the investigator using RECIST v1.1 (see Appendix 10). The same evaluator should perform the assessments, if possible, to ensure internal consistency across visits.

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

If a patient discontinues study treatment(s) due to any reason other than progressive disease (eg, toxicity), tumor assessments will be performed according to the original schedule until progressive disease, death, loss to follow-up, withdrawal of consent, start a new anticancer therapy, or study termination, whichever occurs first.

8.5. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.5.1. Physical Examinations

Assessments will be performed according to the SoA (Section 1.3).

During the Screening Visit, a complete physical examination will be conducted, including evaluations of the head, eyes, ears, nose, and throat and of the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified during screening will be graded according to the 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 8.6 and Appendix 3 regarding AE definitions and reporting and follow-up requirements.

8.5.2. Vital Signs, Height, and Weight

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

If coinciding with administration of study treatments, the patient's vital signs should be recorded within 60 minutes before the study treatment administration.

Height should only be measured and recorded during screening. Weight will be measured before study treatment administration in every cycle.

8.5.3. Eastern Cooperative Oncology Group Performance Status

ECOG PS (Appendix 7) will be assessed during the study. Each patient's ECOG PS will be assessed at the Screening Visit, at pretreatment on Day 1 of each treatment cycle, and at the EOT/Safety Follow-up Visits.

8.5.4. Electrocardiograms

Assessments will be performed according to the SoA (Section 1.3).

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

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

8.5.5. Clinical Safety Laboratory Tests

Local laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Table 11 per the SoA (Section 1.3).

If laboratory tests at screening are not performed ≤ 7 days before Day 1 of Cycle 1, these tests should be repeated and reviewed before starting the study treatment. After Cycle 1, laboratory tests are to be conducted and results are to be reviewed within 48 hours before study treatment administration.

Thyroid assessments will be performed as specified in Section 1.3.

For central laboratory assessments, details regarding sample collection and shipment will be provided in a separate laboratory manual.

Table 11: Protocol-Required Safety Laboratory Tests

Clinical Chemistry	Hematology	Coagulation	Urinalysis	Thyroid function
Alkaline phosphatase	Hematocrit	Prothrombin time	pH	Free triiodothyronine
ALT	Hemoglobin	Partial thromboplastin time or activated partial thromboplastin time	Specific gravity	Free thyroxine Thyroid stimulating hormone
AST	Platelet counts	International normalized ratio	Glucose	
Albumin	White blood cell count		Protein	
Total bilirubin	Neutrophil count		Ketones	
Direct bilirubin	Lymphocyte count		Blood	
Blood urea nitrogen or urea			24-hour protein [a]	
Potassium				
Sodium				
Calcium				
Phosphorus				
Magnesium				
Chloride				
Creatinine				
Glucose				
Lactate dehydrogenase				
Total protein				
Creatine kinase/CK-MB [b]				

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

[a] Urinalysis will be conducted at Screening, Day 1 (-3 days) of each cycle, Safety Follow-up Visits, and as clinically indicated. On routine urinalysis, if urine protein is ≥ 2+ then obtain a 24-hour urine sample for total protein or a random urine sample for total protein and creatinine to determine a protein-to-creatinine ratio.

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

8.5.6. Pregnancy Testing

Urine or serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented with a negative result within 7 days before Day 1 of Cycle 1. Urine pregnancy tests will be performed at each visit before dosing, and at the EOT/Safety Follow-up Visits. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

8.5.7. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune checkpoint inhibitors, serum CK and CK-MB are monitored in all tislelizumab studies to protect study patients and to quantify the risk of muscle inflammation (see Section 1.3 for the blood collection schedule and Appendix 13 for guidelines for management of suspected immune-mediated myocarditis).

CK and CK-MB testing will be implemented for all patients at screening, repeated at all scheduled visits during the first 3 treatment cycles, all predose assessments from Cycle 4 onwards, the EOT Visit, and the Safety Follow-up Visit (30 days [± 7 days] after the last dose). If CK-MB fractionation is not available, serum troponins (troponin I and/or T) may be tested instead.

8.5.8. Hepatitis B and C Testing

Viral hepatitis B and C serologic markers and viral load (if applicable) will be tested by a central laboratory or the local laboratory. HBV testing will include HBsAb, HBsAg, and HBcAb. In addition, HBV DNA will be quantified in patients positive for HBsAg. HCV testing will consist of HCV antibody plus HCV RNA in patients positive for HCV antibody.

For patients who have detectable HBV DNA at screening, a respective viral load test will be performed every 4 cycles (ie, Day 1 of Cycle 5, 9, 13, etc) starting from Cycle 5.

8.5.9. 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 and Appendix 3.

8.5.10. Suicidal Ideation and Behavior Risk Monitoring

No suicidal ideation and behavior risk monitoring is required.

8.5.11. Other Safety Assessments

No other tests are required.

8.6. Adverse Event, Serious Adverse Event, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, SAE) and remain responsible for following up of all AEs (see Section 7). This includes events reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.6.1. Time Period for Collecting and Recording Adverse Events and Serious Adverse Event Information

After the ICF has been signed, but before the administration of the study treatments, only SAEs associated with protocol-defined procedure should be reported to the sponsor.

After initiation of study treatments, all AEs and SAEs, regardless of relationship to study treatments, will be reported until either 30 days after last dose of study treatments or initiation of subsequent anticancer therapy, whichever occurs first. Serious or nonserious imAEs should be reported until 90 days after the last dose of study treatments, regardless of whether the patient starts a subsequent anticancer therapy. All SAEs considered related to the study treatment(s) that are brought to the attention of the investigator should be reported, regardless of time since the last dose of treatment.

AEs and SAEs should be recorded as described in Table 12. For the follow-up period for AEs, see Section 8.6.3. For the definition of TEAEs, see Section 9.3.5.2.

Table 12: Guidance for Duration of Recording New or Worsening Adverse Events in Both Arms

Event type	Record new or worsening events that occur during this period	
	Begin	**End**
SAE associated with protocol-defined procedure	Signing of informed consent	First dose of study drug
All AEs, SAEs [a]	First dose of study drug	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
ImAEs	First dose of study drug	Up to 90 days after last dose (regardless of initiation of new anticancer therapy), death, withdrawal of consent, or loss to follow-up, whichever occurs first

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

8.6.2. Method of Detecting 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?

8.6.3. Follow-up of Adverse Events

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

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

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

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any 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 8.6.4.

8.6.4. Reporting Serious Adverse Events

8.6.4.1. 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 (within 24 hours) to the sponsor or designee as described in Table 13.

Table 13: Time Frames and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

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

Abbreviations: EDC, electronic data capture; IP, investigational product; SAE, serious adverse event.

[a] Report follow-up information that is clinically relevant and pertaining to the SAE which includes but is not limited to the following: Update to the SAE, new additional SAE, outcome, seriousness criteria, investigator causality, event start date/date of onset, date of death, relationship to each study treatment. 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 EDC. If the electronic submission is not available for any reason, a paper SAE form should be submitted by email or fax.

8.6.4.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours, as outlined above in Section 8.6.4.1. The SAE report should always be completed as thoroughly as possible, including all available details of the event, and forwarded to the sponsor or designee within the designated time frames.

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

The investigator must always provide an assessment of causality for each SAE as described in Appendix 3.

The sponsor will provide contact information for SAE receipt.

8.6.4.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.4.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a drug under clinical investigation.

The investigator, or other 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 Appendix 3) will be submitted to all applicable regulatory authorities and investigators for LBL-007 and tislelizumab studies.

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

8.6.4.4. 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 the following reference safety information documents:

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

8.6.5. Pregnancy

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

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should always be reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study treatments should be recorded and reported as an SAE.

8.6.6. Death on Study

Deaths that occur during the AE recording period that are attributed by the investigator solely to disease progression should not be reported as an AE but recorded on the End of Study eCRF page (see Section 8.6.7). For other deaths which occurred during the study safety reporting period (refer to Section 8.6.1), regardless of relationship to the study drug(s), the primary cause of death must be reported as a fatal SAE on the Adverse Event eCRF and immediately reported to the sponsor (see Section 8.6.4).

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

8.6.7. Disease Progression

Disease progression, which is expected in this study population and measured as an efficacy endpoint, should not be recorded as an AE. 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 reported as an AE. However, if there is any uncertainty as to whether an AE is due to disease progression, it should be recorded as an AE (see Section 8.6.4).

8.6.8. Adverse Events of Special Interest

Not applicable.

8.7. Patient-Reported Outcomes

Patients will be asked to complete the EORTC QLQ-C30 (Appendix 4), EORTC QLQ-CR29 (Appendix 5) module and the PRO-CTCAE questionnaires (Appendix 6) according to the schedule in Section 1.3. The questionnaires will be provided in the patient's preferred language.

8.8. Biomarkers

Instructions for the processing, storage, and shipping of samples will be provided in the study laboratory manual. Refer to the SoA (Section 1.3) for sample collection timepoints.

Blood samples will be collected at specified times as described in Section 1.3 for the evaluation of biomarkers that may include receptor occupancy of LAG-3 and soluble LAG-3; subpopulations and phenotype of immune cells; concentrations of cytokines, chemokines, or soluble proteins; bTMB/ctDNA monitoring/DNA mutation. Approximately 2 mL of peripheral whole blood will be required for collection to work as the MSI test control during the Prescreening or Screening Period. Other assessments may be conducted as allowed by local regulations. Written patient consent is required for blood sample collections.

Archival tumor tissues (FFPE blocks or approximately 16 freshly cut unstained FFPE slides) need to be sent for central laboratory determination of PD-L1 levels (during the [pre]screening period for Phase 2, and retrospective analysis for Phase 1b), for central laboratory assessment (during the [pre]screening period for patients without local MSS/pMMR information) or retrospective confirmation of MSI-H status, and for retrospective analyses of other exploratory biomarkers related to response and resistance for all patients in a sponsor-designated central/test laboratory. These exploratory biomarkers may include but are not limited to LAG-3, LAG-3 ligands (MHCII, LSECtin, Gal-3, and FGL-1), GEP, and TMB/DNA mutation. Other assessments may be conducted as allowed by local regulations. Patients may be permitted to be enrolled on a case-by-case basis after discussion with the medical monitor if fewer than 16 unstained slides of suitable quality are provided.

A fresh tumor biopsy at a tumor lesion is mandatory if there are no available archival tumor samples during the screening period. Optional fresh biopsy samples in patients who have

confirmed progressive disease will also be collected during the study from accessible tumor sites. If feasible, any follow-up biopsy should ideally be taken from the same tumor lesion as the baseline biopsy sample.

Written patient consent is required for any tumor biopsies. For fresh biopsies, acceptable samples include core needle biopsies for nonsuperficial tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

Blood or tissue samples for biomarker analyses will not be collected during the Extended IP Access Period (see Section 6.7).

8.9. Medical Resource Utilization and Health Economics

Not applicable.

8.10. Visit Windows

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted (see Section 1.3). 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 any study treatment is given unless otherwise noted. Laboratory results must be reviewed before dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled for the nearest feasible date (the visit window is provided in Section 1.3), with subsequent visits conducted according to the latest schedule date. This minor change in visit scheduling due to operational feasibility is permitted and will not be considered a protocol deviation.

8.11. Unscheduled Visit

Unscheduled visits may be performed at any time at the patient's or the investigator's request and may include vital signs/physical examination, ECOG PS, AE review, concomitant medications and procedure reviews, radiographic assessments, physical examination of the liver, spleen, and lymph nodes, disease-related constitutional symptoms, and hematology and clinical 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 progressive disease, then diagnostic tests may be performed based on the investigator's assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

8.12. Treatment Period

8.12.1. End-of-Treatment Visit

The EOT Visit is conducted when the investigator determines to discontinue the study treatment (including all drugs) regardless of any reasons. If routine laboratory tests (eg, hematology, serum

chemistry) were completed within 7 days before the EOT Visit, these tests do not need to be repeated.

Tumor assessment is required at the EOT Visit if the investigator determines that the study treatment(s) must be discontinued. However, the tumor assessment may be omitted at the EOT Visit provided that ≤ 9 weeks have passed since the last assessment. Patients who discontinue study treatment(s) for reasons other than progressive disease (eg, toxicity) will continue to undergo tumor assessments following the original schedule until the patient experiences progressive disease, death, loss to follow-up, withdrawal of consent, start a new anticancer therapy, or study termination, whichever occurs first.

See Section 1.3 for assessments to be performed at the EOT Visits.

8.12.2. Safety Follow-up Visit

Patients will be asked to return to the clinic for a Safety Follow-up Visit to occur 30 days (± 7 days) after the last dose of study drug, or before the initiation of a new anticancer treatment, whichever occurs first.

If the decision to discontinue study treatment is taken ≥ 23 days after the last dose of any study medicine, the EOT Visit and the Safety follow-up Visit should be conducted concurrently within 7 days of the decision to end treatment.

In addition, patients who discontinue LBL-007 and tislelizumab in Phase 1b and Arm A and Arm D of Phase 2, or LBL-007 in Arm B of Phase 2, will be asked to return to the clinic or will be contacted via telephone to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE) at 60 and 90 (± 14) days after the last dose of LBL-007 or tislelizumab, whichever is later, regardless of whether they start a subsequent anticancer therapy. If patients report a suspected imAE at a follow-up visit or a telephone contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

All AEs, including SAEs, will be collected as described in Section 8.6 and Appendix 3. Patients will be asked for any subsequent anticancer therapy information at the EOT/Safety Follow-up Visits or telephone contacts.

See Section 1.3 for assessments to be performed at the Safety Follow-up Visits.

8.12.3. 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 Safety Follow-up Visit, until death, withdrawal of consent, loss to follow up, 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 4.4.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypothesis

Not applicable.

9.1.1. Multiplicity Adjustment

Not applicable.

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Patient Analysis Set	Description
ITT Analysis Set	All randomized patients.
Safety Analysis Set	All patients who have received ≥ 1 dose of any component of study treatment.
DLT-Evaluable Analysis Set	Patients who received ≥ 70% of fluoropyrimidine and full dose of other assigned study treatment (LBL-007, tislelizumab, and bevacizumab) and remain on the study for the 21-day DLT observation period for safety assessments or who have experienced any DLT during the 21-day DLT observation period.

The Intent-to-Treat Analysis Set will be primary analysis set used for Phase 2 efficacy analysis. Patients will be analyzed according to their randomized treatment arm.

The Safety Analysis Set will be the analysis set used for safety analyses.

The DLT-Evaluable Analysis Set will be used in DLT evaluation period.

9.3. Statistical Analyses

9.3.1. Randomization Methods

Patients in Phase 2 will be randomized using the IRT system by permuted block stratified randomization with a stratification factor of liver metastases (absent versus present) for PD-L1 positive patients, and by block randomization for PD-L1 negative patients.

9.3.2. Patient Disposition

The number (percentage) of patients randomized, treated, discontinued from the study, reasons for discontinuation from the study, and the duration of study follow-up will be summarized in the ITT Analysis Set. The patients who discontinued treatment and the primary reason for the end of treatment will be summarized among patients who were treated.

9.3.3. Patient Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by treatment arm in all randomized patients using descriptive statistics in the ITT Analysis Set. Continuous variables include age and weight. Categorical variables include age (< 65 and ≥ 65), sex, geographical region, ethnicity, race, liver metastases, etc.

9.3.4. Efficacy Analyses

Efficacy endpoints are assessed by the investigator according to RECIST v1.1. The following efficacy endpoints will be analyzed and summarized in order to evaluate the antitumor activities of LBL-007 plus tislelizumab in combination with the maintenance backbone. These analyses are intended to be descriptive in nature as preliminary efficacy evidence.

- PFS is defined as the time from the date of randomization to the date of the first documentation of disease progression or death, whichever occurs first.
- ORR is defined as the proportion of randomized patients with a confirmed CR or PR from the time of randomization.
- DOR is defined as the time from the first determination of an objective confirmed response after randomization until the first documentation of disease progression or death, whichever comes first.

9.3.4.1. Primary Efficacy Analysis for Phase 2

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

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

The median and other quartiles of PFS will be estimated using the Kaplan-Meier method. The 2-sided 95% CIs will be constructed with the generalized Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). Event-free rates at selected timepoints for PFS will be estimated using the Kaplan-Meier method with the corresponding 95% CI constructed using Greenwood's formula (Greenwood 1926). The PFS censoring rule will follow the US FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2018).

9.3.4.2. Secondary Efficacy Analysis for Phase 2

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

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

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

9.3.5. Safety Analyses

Safety will be assessed by monitoring and recording of AEs and laboratory values (hematology, clinical chemistry), and ECG findings will also be used in determining the safety profile. The severity of AEs will be graded according to NCI-CTCAE v5.0. The incidence of DLT events and TEAEs will be reported as the number (percentage) of patients with TEAEs by MedDRA SOC and PT.

Safety data will be summarized using descriptive statistics and will be performed in the Safety Analysis Set in Phase 1b and Phase 2, respectively.

9.3.5.1. Extent of Exposure

Extent of exposure to a study treatment will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure, cumulative total dose received per patient (mg), dose intensity (mg/day) and relative dose intensity (%).

Patient-level listings will be provided for all dosing.

9.3.5.2. Adverse Events

The AE verbatim descriptions (as recorded by the investigator on the eCRF) will be classified into standardized medical terminology using the MedDRA®. AEs will be coded to the MedDRA lowest level term closest to the verbatim term, preferred term, and primary SOC.

DLTs will be summarized for the Phase 1b safety run-in period.

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 treatment(s) and up to 30 days after last dose of study treatment(s), or initiation of new anticancer therapy, whichever occurs first. All SAEs considered related to the study treatment(s) that are brought to the attention of the investigator should be reported, regardless of the time since the last dose of study treatment. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient-level listings.

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 study treatment and up to 90 days from the last dose of study treatment, regardless of whether the patient starts a new anticancer therapy.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and PT. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 within an SOC and PT, even if the patient experienced > 1 TEAE within a specific SOC and PT.

All TEAEs, SAEs, deaths, ≥ Grade 3 TEAEs, imAEs, and TEAEs that led to treatment discontinuation will be summarized.

9.3.5.3. Laboratory Analyses

Clinical laboratory (eg, hematology, clinical chemistry) 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 included in the CSR for this protocol.

In the summary of laboratory parameters by NCI-CTCAE grade, parameters with NCI-CTCAE grading in both high and low directions will be summarized.

9.3.5.4. Electrocardiograms

ECG results will be listed by patient.

9.3.6. Other Safety Analyses

Not applicable.

9.3.7. Other Analyses

Not applicable.

9.4. Interim Analysis

No formal interim analyses were planned.

9.5. Sample Size Determination

The study plans to enroll approximately 226 patients:

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

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

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

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory and Ethical Considerations

This study will be conducted by the principal investigator and the study center in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will also comply with the requirements of the ICH E2A guideline (ICH E2A 1994).

10.1.1. Regulatory Authority Review

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

10.1.2. 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/other information and the approved amended ICF/other information must be forwarded to the sponsor promptly.

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

10.1.3. Protocol Amendments

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

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

10.2. Financial Disclosure

Investigators are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of clinical investigators and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure that financial interests and arrangements of 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).

10.3. Informed Consent Process

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 be reconsented 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.

10.4. Study Committees Structure

Safety Monitoring Committee

An SMC will be established and include both the sponsor (including the medical monitor and study team members from Pharmacovigilance/Drug Safety, Clinical Pharmacology, and Biostatistics with other members as appropriate) and investigators. The SMC will review all available safety, PK, and exploratory data and make recommendations on dose modification and

dose selection of LBL-007 to ensure that the study treatment is tolerable and that patients are adequately monitored.

The SMC will make recommendations on safety management (including resumption of enrollment, or de-escalation of LBL-007, or termination of enrollment, etc) and will assess whether it is suitable to continue the clinical study without change according to the study design.

The SMC may also be called upon by the sponsor on an ad hoc basis where applicable to the conduct of the study. The details of SMC membership, responsibilities, and meeting schedule are outlined in a separate SMC Charter.

10.5. Confidentiality and Data Protection

Patient Confidentiality and Data Protection

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

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

- Names or initials (full or partial);
- Full dates of birth;
- Contact information (such as phone numbers or home or email addresses);
- Numerical identifiers (eg, hospital or medical record, government, health insurance, or financial account numbers) other than patient identification numbers assigned as part of this study;
- Geographic identifiers smaller than a state, province, or local equivalent (such as city, county, zip code, or other equivalent geographic identifiers); or
- Information about marital status, family, or household members; employment, sex life, sexual orientation, or other sensitive data that is not relevant to the study.

Patient personal and medical information obtained during this study is confidential and may only be disclosed to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law.

In limited circumstances, such as in connection with insurance purposes or patient support services ancillary to certain study sites (eg, for patient travel or reimbursement), the investigator and site may provide certain of this personal information to the sponsor or its representatives. Such personal information may not be provided as part of the study protocol (eg, as part of the eCRF, on samples or reports submitted to the central lab, on safety reporting forms [except in China], or on product dispensing logs provided to the sponsor, etc).

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

In the event of a breach of the confidentiality of a patient's personal and 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, affiliates, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

BeiGene Confidential Information

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

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

10.6. Data Collection and Management Responsibilities

10.6.1. Data Entry in the Electronic Case Report Form

Data entry in eCRF will not be required as no data will be collected in the eCRFs during the Extended IP Access Period. 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.

10.6.2. Data Collection and Management Responsibilities

No data will be collected in the eCRFs during the Extended IP Access Period. 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 prior written permission from the sponsor, except for authorized representatives of the sponsor or appropriate regulatory authorities.

10.6.3. 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 course of the study, a study monitor 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, giving due consideration 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 Lowest Level Term, PT, and primary SOC. 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.

10.6.4. Data Integrity and In-house Blinding

Due to the open-label design of the study, access to the unblinded patient-level clinical data in the EDC system will only be assigned to predefined study personnel. Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate

unnecessary listings/summaries that may introduce unwanted bias, or share such outputs or the unblinded data 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 treatment assignment and actual treatment received will be limited and documented.

10.6.5. Study Records Retention

The investigator must maintain adequate and accurate records so that the conduct of the study can be fully documented and the study data can be subsequently verified. These documents should be classified into at least 1 of the following 2 categories: the investigator's study file or the 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, but not be limited to, documents such as the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, x-ray, pathology and special assessment reports, consultant letters, and screening and enrollment log, 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 or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements including, but not limited to, the following: archival at an off-site facility or transfer of ownership of 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 at a separate location so that they can be sealed and returned to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

At the conclusion of this study, biological samples may be retained as outlined in the agreement with the contract research organization managing the biological samples, for a period of up to 10 years or as allowed by the IRB/IEC, whichever is shorter.

10.7. 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 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. In accordance with established IRB/IEC policies and procedures, the investigator must promptly report any important deviations that might impact patient safety and/or data integrity to the sponsor and to the IRB/IEC.

10.8. Data Quality Assurance

- No data will be collected in the eCRFs during the Extended IP Access Period.
- All patient data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the EDC system.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant source data and documents (see Section 10.9.2) and to allocate their time and the time of their personnel to the auditor/inspector to discuss findings and any relevant issues.
- The Risk-Based Quality Management process identifies factors that are critical to patient protection, reliability of the study results, and/or compliance with requirements. A fit-for-purpose application of risk management is used to identify, evaluate, and control the risks. Controls applied, including types of monitoring, are proportionate to the level of risk, with higher risks receiving more or significant actions. The quality management approach implemented in the study and a summary of quality tolerance limits deviation (as applicable) will be summarized in the clinical study report.
- Monitoring details describing strategy, methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Site Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.9. Source Documents

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

10.9.1. Access to Information for Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation 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.

10.9.2. Access to Information for Auditing and 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 to representatives of a regulatory agency or the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.10. Site 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/provide all study data to the sponsor;
- Resolution and closure of all data queries;
- Accountability, reconciliation, and arrangements for unused study treatments;
- Review of study records for completeness;
- Collection of all study documents for the study master file filing according to GCP and local regulation; and

- Shipment of samples (including but not limited to those for PK, ADA, and biomarkers) to the designated laboratory for 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 reasons. 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 and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the 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 all unused study treatments in accordance with the applicable sponsor procedures for the study.

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

10.11. Publications and Data Presentation Policy

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 ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). An abbreviated or synoptic 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. For a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication, or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors or stricter local criteria (International Committee of Medical Journal Editors 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 sponsors 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. 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.

10.12. Data Disclosure and Transparency and Data Sharing With External Researchers

BeiGene publicly discloses study drug/treatment clinical studies in compliance with BeiGene policy and applicable regulations. When the study is completed and analysis is conducted, results are published on clinical study databases like https://www.ClinicalTrials.gov and BeiGene's Clinical Studies webpage. The facility name, contact information, and other study information for this study may be searched by entering the protocol ID.

BeiGene may make redacted clinical study documents and deidentified patient-level data from this study available to external researchers for scientific analyses or to conduct further research that may help advance medical science and lead to better research and treatments for all people. "Deidentified" means that all direct and indirect identifiers, including the study patient identification numbers, have been removed before the data are made available. "Redacted" documents means that personal data and commercially confidential information are no longer visible.

Information Disclosure and Inventions

All rights, title, and interests in any inventions, expertise, 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:

- 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 10.11.

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

11. REFERENCES

AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015;62(3):932-54.

Andreae S, Piras F, Burdin N, et al. Maturation and activation of dendritic cells induced by lymphocyte activation gene-3 (CD223). J Immunol. 2002;168(8):3874-80.

Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683-91. doi:10.1136/gutjnl-2015-310912

Avice MN, Sarfati M, Triebel F, et al. Lymphocyte activation gene-3, a MHC class II ligand expressed on activated T cells, stimulates TNF-alpha and IL-12 production by monocytes and dendritic cells. J Immunol 1999;162:2748-53.

Bailey CE, Hu CY, You YN, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010 [published correction appears in JAMA Surg. 2015 Mar 1;150(3):277]. JAMA Surg. 2015;150(1):17-22.

Bendell J, Ulahannan SV, Chu Q, et al. Abstract C027: A Phase I, dose finding study of BI 754111, an anti-LAG-3 antibody, in combination with BI 754091, an anti-PD-1 antibody, in patients with advanced solid tumors: preliminary results from the microsatellite stable (MSS) metastatic colorectal cancer (mCRC) cohort. Mol Cancer Ther. 2019;18(suppl 12):C027.

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

Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [published correction appears in CA Cancer J Clin. 2020 Jul;70(4):313]. CA Cancer J Clin. 2018;68(6):394-424.

Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet. 2014;383(9927):1490-502.

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

Camisaschi C, Casati C, Rini F, et al. LAG-3 expression defines a subset of CD4(+)CD25(high)Foxp3(+) regulatory T cells that are expanded at tumor sites. J Immunol. 2010;184(11):6545-51.

Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012;487(7407):330-7.

Chen EX, Jonker DJ, Loree JM, et al. Effect of combined immune checkpoint inhibition vs best supportive care alone in patients with advanced colorectal cancer: the Canadian Cancer Trials Group CO.26 study. JAMA Oncol. 2020;6(6):831-38.

Clinical Trials Facilitation Group. Recommendations related to contraception and pregnancy testing in clinical trials. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. Accessed 15 April 2020.

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

Cristescu R, Mogg R, Ayers M, et al. Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy [published correction appears in Science. 2019 Mar 1;363(6430):]. Science. 2018;362(6411):eaar3593.

Data Elements and Standards for Drug Dictionaries: M5. Recommended for Adoption at Step 2 of the ICH Process on 10 May 2005 by the ICH Steering Committee. ICH Consensus Guideline. Released for Consultation on 10 May 2005 at Step 2 of the ICH Process.

Datar I, Sanmamed MF, Wang J, et al. Expression analysis and significance of PD-1, LAG-3, and TIM-3 in human non-small cell lung cancer using spatially resolved and multiparametric single-cell analysis. Clin Cancer Res. 2019;25(15):4663-73.

DeClue RW, Rhodes W, Accortt NA, et al. Demographics and clinical characteristics of metastatic colorectal cancer patients treated with bevacizumab-awwb in real-world oncology clinics. Presented at: ASCO GI Cancers Symposium 2021.

Diagnosis And Treatment Guidelines For Colorectal Cancer Working Group CSOCOC. Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for colorectal cancer 2018 (English version). Chin J Cancer Res. 2019;31(1):117-134.

Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; 1994.

E17 General Principles for Planning and Design of Multiregional Clinical Trials. Guidance for Industry. US Department of Health and Human Services Food and Drug Administration. July 2018. ICH.

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

Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol. 2007;25(13):1670-76.

Food and Drug Administration Center for Drug Evaluation Research CDER and Center for Biologics Evaluation and Research. FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018). https://www.fda.gov/media/71195/download. Accessed July 3, 2022.

Fridericia LS. The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease. Acta Medica Scandinavica. 1920;53:469-86.

Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science. 2006;313(5795):1960-4.

Galon J, Fridman WH, Pagès F. The adaptive immunologic microenvironment in colorectal cancer: a novel perspective. Cancer Res. 2007;67(5):1883-6.

Garcia J, Hurwitz HI, Sandler AB, et al. Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. Cancer Treat Rev. 2020;86:102017.

Garralda E, Sukari A, Lakhani NJ, et al. A phase 1 first-in-human study of the anti-LAG-3 antibody MK4280 (favezelimab) plus pembrolizumab in previously treated, advanced microsatellite stable colorectal cancer. J Clin Oncol. 2021;39(suppl 15):3584.

Gettinger S, Choi J, Hastings K, et al. Impaired HLA Class I antigen processing and presentation as a mechanism of acquired resistance to immune checkpoint inhibitors in lung cancer. Cancer Discov. 2017;7(12):1420-35.

Ghosh S, Sharma G, Travers J, et al. TSR-033, a novel therapeutic antibody targeting LAG-3, enhances T-cell function and the activity of PD-1 blockade in vitro and In vivo. Mol Cancer Ther. 2019;18(3):632-41.

Greenwood M. The natural duration of cancer. In: Reports on Public Health and Medical Patients. Her Majesty's Stationery Office. 1926;33:1-26.

Gutierrez M, Lam WS, Hellmann M, et al. KEYNOTE-495/KeyImPaCT: interim analysis of a randomized, biomarker-directed, phase 2 trial of pembrolizumab-based combination therapy for non–small cell lung cancer (NSCLC). J. Immunother. Cancer. 2021;9.

Haanen, JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. Ann Oncol. 2017:28(suppl_4):iv119-iv142.

Hanna GJ, Lizotte P, Cavanaugh M, et al. Frameshift events predict anti-PD-1/L1 response in head and neck cancer. JCI Insight. 2018;3(4):e98811.

He Y, Rivard CJ, Rozeboom L, et al. Lymphocyte-activation gene-3, an important immune checkpoint in cancer. Cancer Sci. 2016;107(9):1193-7.

Huang CT, Workman CJ, Flies D, et al. Role of LAG-3 in regulatory T cells. Immunity. 2004;21(4):503-13.

International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. 2018. Available online: http://www.icmje.org. Accessed 01 September 2020.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use. Clinical safety data management: definitions and standards for expedited reporting E2A. 1994

Johnson DB, Nixon MJ, Wang Y, et al. Tumor-specific MHC-II expression drives a unique pattern of resistance to immunotherapy via LAG-3/FCRL6 engagement. JCI Insight. 2018;3(24):e120360.

Kasi PM, Shahjehan F, Cochuyt JJ, et al. Rising proportion of young individuals with rectal and colon cancer. Clin Colorectal Cancer. 2019;18(1):e87-e95.

Kates M, Nirschl TR, Baras AS, et al. Combined next-generation sequencing and flow cytometry analysis for an anti-PD-L1 partial responder over time: an exploration of mechanisms of PD-L1 activity and resistance in bladder cancer. Eur Urol Oncol. 2021;4(1):117-20.

Kemeny N. Management of liver metastases from colorectal cancer. *Oncology (Williston Park)*. 2006;20(10):1161-86.

Kloor M, von Knebel Doeberitz M. The immune biology of microsatellite-unstable cancer. Trends Cancer. 2016;2(3):121-33.

Koopman M, Kortman GA, Mekenkamp L, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. Br J Cancer. 2009;100(2):266-73.

Labrijn A, Buijsse A, van den Bremer E, et al. Therapeutic IgG4 antibodies engage in Fab-arm exchange with endogenous human IgG4 in vivo. Nat Biotechnol. 2009;27(8): 767-71.

Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372(26):2509-20.

Lenz H, Parikh A, Spigel D, et al. Nivolumab (NIVO) + 5-fluorouracil/leucovorin/oxaliplatin (mFOLFOX6)/bevacizumab (BEV) versus mFOLFOX6/BEV for first-line (1L) treatment of metastatic colorectal cancer (mCRC): phase 2 results from CheckMate 9X8. J Clin Oncol. 2022;40(suppl 4):8.

Levey A, Stevens L, Schmid C, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

Lichtenegger FS, Rothe M, Schnorfeil FM, et al. Targeting LAG-3 and PD-1 to enhance T cell activation by antigen-presenting cells. Front Immunol. 2018;9:385.

Long L, Zhang X, Chen F, et al. The promising immune checkpoint LAG-3: from tumor microenvironment to cancer immunotherapy. Genes Cancer. 2018;9(5-6):176-89.

Luke JJ, Ratel MR, Hamilton EP, et al. A phase I, first-in-human, open-label, dose-escalation study of MGD013, a bispecific DART molecule binding PD-1 and LAG-3, in patients with unresectable or metastatic neoplasms. J Clin Oncol. 2020;38(suppl 15):3004.

Lythgoe MP, Liu DSK, Annels NE, et al. Gene of the month: lymphocyte-activation gene 3 (LAG-3). J Clin Pathol. 2021;74(9):543-7.

Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 2020;21(10):1353-65.

McDermott DF, Atkins MB. PD-1 as a potential target in cancer therapy. *Cancer Med*. 2013;2(5):662-73.

Mimura K, Kua LF, Xiao JF, et al. Combined inhibition of PD-1/PD-L1, Lag-3, and Tim-3 axes augments antitumor immunity in gastric cancer-T cell coculture models. Gastric Cancer. 2021;24(3):611-23.

Muratore A, Zorzi D, Bouzari H, et al. Asymptomatic colorectal cancer with un-resectable liver metastases: immediate colorectal resection or up-front systemic chemotherapy? *Ann Surg Oncol*. 2007;14(2):766-70.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer, version 1.0.2022.

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

Overman MJ, Ernstoff MS, Morse MA. Where we stand with immunotherapy in colorectal cancer: deficient mismatch repair, proficient mismatch repair, and toxicity management. Am Soc Clin Oncol Educ Book. 2018b;38:239-47.

Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol 2018a; 36: 773-79.

Pagès F, Berger A, Camus M, et al. Effector memory T cells, early metastasis, and survival in colorectal cancer. N Engl J Med. 2005;353(25):2654-66.

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

Peng CW, Saffo S, Shusterman M, et al. Analysis of the impact of eliminating bolus 5-fluorouracil in metastatic colorectal cancer. Journal of Clinical Oncology. 2023;41(suppl 4): 59.

Riley JL. PD-1 signaling in primary T cells. Immunol Rev. 2009;229(1):114-25.

Rosello S, Blasco I, Garcia Fabregat L, et al. Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines. Annals of Oncology. 2017;28 (suppl 4):100-18.

Sawicki T, Ruszkowska M, Danielewicz A, et al. A review of colorectal cancer in terms of epidemiology, risk factors, development, symptoms and diagnosis. Cancers (Basel). 2021;13(9):2025.

Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020;70(3):145-64.

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

Solinas C, Migliori E, De Silva P, et al. LAG3: The biological processes that motivate targeting this immune checkpoint molecule in human cancer. Cancers (Basel). 2019;11(8):1213.

Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.

Tabernero J, Grothey A, Arnold D, et al. MODUL cohort 2: an adaptable, randomized, signal-seeking trial of fluoropyrimidine plus bevacizumab with or without atezolizumab maintenance therapy for BRAFwt metastatic colorectal cancer. ESMO Open. 2022;7(5):100559.

Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med. 2022;386(1):24-34.

Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63(1):261-83.

US Department of Health and Human Services Food and Drug Administration. National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. 2017.

US Food and Drug Administration. Guidance for industry: Immunogenicity assessment for therapeutic protein products. Accessed August, 2014. https://www.fda.gov/media/85017/download

Van Cutsem E, Huijberts S, Grothey A, et al. Binimetinib, encorafenib, and cetuximab triplet therapy for patients with BRAF V600E-mutant metastatic colorectal cancer: safety lead-in results from the Phase III BEACON colorectal cancer study. J Clin Oncol. 2019;37(17):1460-9.

Westergaard MCW, Milne K, Pedersen M, et al. Changes in the tumor immune microenvironment during disease progression in patients with ovarian cancer. Cancers (Basel). 2020;12(12):3828.

Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68:250-81.

Woo SR, Turnis ME, Goldberg MV, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. Cancer Res. 2012;72(4):917-27.

World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and colorectal cancer. 2018. Diet, nutrition, physical activity and colorectal cancer (wcrf.org)

Yang ZZ, Kim HJ, Villasboas JC, et al. Expression of LAG-3 defines exhaustion of intratumoral PD-1+ T cells and correlates with poor outcome in follicular lymphoma. Oncotarget. 2017;8(37):61425-39.

Yoshino T, Arnold D, Taniguchi H, et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol. 2018;29(1):44-70.

Zhou YH, Lee JJ, Wang SG, et al. Incorporating historical information to improve phase I clinical trial designs. arXiv. 2020;2004:12972.

12. APPENDICES

APPENDIX 1. PROTOCOL AMENDMENT HISTORY

The Summaries of Changes for Protocol Amendments 1.0 and 2.0 were provided as standalone documents, which are available upon request.

Protocol Amendment 3.0 (26 September 2024)

This Protocol Amendment 3.0 replaces Protocol Amendment 2.0. This amendment is considered substantial according to BeiGene standard operating procedure and working instruction based on the criteria set forth in regulatory references from ICH and local regulations (eg, IND Application Reporting: Protocol Amendments issued by the FDA, and Drug Registration Regulation and Technical Guidelines for Protocol Changes During Drug Clinical Trials [Interim] issued by the CDE of the NMPA).

The primary purposes of Protocol Amendment 3.0 are as follows:

- To update the delivery period of LBL-007 infusion to over 60 (± 5) minutes for all cycles.
- To add the 300-mg vial strength for LBL-007.
- To clarify the maximum number of cycles and duration for the induction treatment, as well as the time window between Day 1 of the last cycle of induction therapy and the first dose of study treatment.
- To clarify the dose of leucovorin and levoleucovorin.
- To clarify that the local MSS/pMMR information is acceptable for patient enrollment, and to update the requirement for the minimum number of FFPE slides.
- To update and add the tables of PK and immunogenicity sampling schedules to accommodate different cycle lengths.

In addition, the latest information contained in the LBL-007 Investigator's Brochure Edition 4.0 and the Tislelizumab Investigator's Brochure Edition 11.0 are presented, and protocol template-related updates are included.

The changes made in this amendment are described in the table below. Editorial and formatting changes are not included in this summary.

Protocol Amendment Summary of Changes Table

Section Number and Title	Summary of Change	Brief Rationale for Change
Section 1.3.1 Schedule of Activities (formerly Appendix 1) Footnote #10 (formerly Footnote #25) Section 6.1 Study Drug/Treatment(s) Administered and Dosage (formerly Section 5.2)	Updated the delivery period of LBL-007 infusion to over 60 (± 5) minutes for all cycles.	To minimize the risk of patients being exposed to endotoxin levels above the US Pharmacopeia 85 limit.

Section Number and Title	Summary of Change	Brief Rationale for Change
Section 6.2.1 Formulation, Packaging, and Handling (formerly Section 5.1)	Updated that LBL-007 will also be provided as a preservative-free, single-use vial containing a minimum of 17.65 mL of a 17 mg/mL concentrated solution (300 mg) of antibody in a vial of 20 mL.	Revised to add the 300-mg vial strength of LBL-007 to enhance the clinical and operational convenience.
Section 5.1 Inclusion Criteria (formerly Section 4.1) Inclusion Criterion #6	• Updated the maximum number of cycles for first-line induction treatment to 12 cycles for 2-week regimen of chemotherapy and 8 cycles for 3-week regimen of chemotherapy. • Clarified that the duration of induction treatment should be completed within approximately 6 months. • Clarified that the first dose of study treatment needs to occur within 2 weeks (for 2-week regimen) or 3 weeks (for 3-week regimen) to 6 weeks after Day 1 of the last cycle of induction therapy.	Revised to accommodate global treatment guidelines and to be able to recruit a broader population.
Section 1.2 Study Schema (formerly Figure 2) Section 1.3.1 Schedule of Activities (formerly Appendix 1) Footnote #14 (formerly Footnote #29) Section 4.3.1.3 Rationale for the Dose Selection of Bevacizumab and Fluoropyrimidine as the Maintenance Backbone (formerly Section 1.5.5.3) Section 6.1 Study Drug/Treatment(s) Administered and Dosage (formerly Section 5.2) Table 16 (formerly Table 5)	Clarified that the dose of leucovorin or levoleucovorin will follow the relevant local guidance and/or prescribing information, where applicable, and should be no less than the lowest dose level in induction treatment.	Considering there may be no influence between different doses on survival or safety profile, incorporated suggestion from the investigator to allow flexibility on the leucovorin or levoleucovorin dose.
Section 1.3.1 Schedule of Activities (formerly Appendix 1) Footnote #30 (formerly	• Clarified that central laboratory assessment of MSI-H/dMMR status during the (pre)screening period is applicable for patients without local MSS/pMMR	Revised for clarity and flexibility.

Section Number and Title	Summary of Change	Brief Rationale for Change
Footnote #22) Section 5.1 Inclusion Criteria (formerly Section 4.1) Inclusion Criterion #7 Section 8.9 Biomarkers (formerly Section 7.8)	information, which also indicates that local MSS/pMMR information is allowed and acceptable for patient enrollment. • Updated the requirement for the minimum number of FFPE slides and clarified that patients who provided fewer than 16 unstained FFPE slides of suitable quality may be permitted to be enrolled on a case-by-case basis after discussion with the medical monitor.	
Section 1.3.2 Pharmacokinetic and Immunogenicity Sampling Schedules (formerly Appendix 2, Appendix 3, and Appendix 4)	Updated and added the tables of PK and immunogenicity sampling schedules for 2-week regimens and 3-week regimens.	Revised to accommodate different cycle lengths: When 5-FU is used, cycle length is 2 weeks; when capecitabine is used, cycle length is 3 weeks.
Section 1.3.1 Schedule of Activities (formerly Appendix 1) Footnote #8 (*new footnote*) Section 1.3.2 Pharmacokinetic and Immunogenicity Sampling Schedules (formerly Appendix 2, Appendix 3, and Appendix 4) Section 1.3.3 Blood Biomarker Sampling Schedule (formerly Appendix 5) Section 8.14 Visit Windows (formerly Section 7.10)	Added a footnote to clarify visit windows permit minor changes in visit scheduling due to operational feasibility (eg, visit window falls on a nonworking day such as a weekend or public holiday), and this will not be considered a protocol deviation.	Revised for clarity.
Section 6.1 Study Drug/Treatment(s) Administered and Dosage (formerly Section 5.2) Table 16 (formerly Table 5) Section 6.2.1.3 Bevacizumab and Fluoropyrimidine (formerly Section 5.1.3)	Clarified that bevacizumab or its biosimilar can be used in this study.	Revised to better accommodate study drug supply.
Section 1.3.1 Schedule of Activities (formerly	Clarified that the delivery period for the bevacizumab infusion on Day 1 of	Revised for clarity.

Section Number and Title	Summary of Change	Brief Rationale for Change
Appendix 1) Footnote #12 (formerly Footnote #27) Section 6.1 Study Drug/Treatment(s) Administered and Dosage (formerly Section 5.2)	Cycle 1 may follow local guidelines, if applicable.	
Section 5.1 Inclusion Criteria (formerly Section 4.1) Inclusion Criterion #9a	Revised the criterion for platelet count to ≥ 75 x 10^9/L.	Revised to be consistent with NCI-CTCAE v5.0.
Section 5.2 Exclusion Criteria (formerly Section 4.2) Exclusion Criterion #3	Clarified the exclusion criterion from the perspective of progressive disease, rather than the induction treatment.	Revised for clarity.
Section 5.2 Exclusion Criteria (formerly Section 4.2) Exclusion Criterion #15	Update the parameter of systolic blood pressure to ≥ 150 mmHg to be consistent within the document.	Revised for clarity and consistence.
Section 8.1.1.1 PD-L1/MSI/BRAF Test (formerly Section 7.1.1)	Added the assay information for MSI-H/dMMR central assessment.	Revised to include the biomarker assay information.
Section 1.3.1 Schedule of Activities (formerly Appendix 1) Footnote #20 (formerly Footnote #15)	• Clarified that laboratory tests at screening should be repeated if they are not performed ≤ 7 days before Day 1 of Cycle 1 rather than from the time of randomization. • Clarified the window for the coagulation test on Day 1 of Cycle 1: ≤ 7 days before Day 1 of Cycle 1. • Clarified the window for urinalysis on Day 1 of each cycle: ≤ 7 days before Day 1 of Cycle 1, ≤ 2 days before Day 1 of Cycle 2, and ≤ 3 days before Day 1 of Cycle 3 and subsequent cycles.	Revised for clarity and consistency.
Section 1.3.1 Schedule of Activities (formerly Appendix 1) Footnote #23 (formerly Footnote #18)	Clarified the window for thyroid function tests on Day 1 of every cycle starting from Cycle 2: ≤ 2 days before Day 1 of Cycle 2, ≤ 3 days before Day 1 of Cycle 3 and subsequent cycles.	

Section Number and Title	Summary of Change	Brief Rationale for Change
Section 1.3.1 Schedule of Activities (formerly Appendix 1) Footnote #28 (formerly Footnote #23) Section 8.7 Patient-Reported Outcomes (formerly Section 7.9)	Removed the description that the EORTC QLQ-C30, EORTC QLQ-CR29, and PRO-CTCAE questionnaires should be completed before any clinical activities during on-study site visits.	Revised to reduce redundancy.
Section 1.3.1 Schedule of Activities (formerly Appendix 1) Footnote #15 (formerly Footnote #21) Section 4.1.1.3 Treatment Period (formerly Section 3.4) Section 8.4 Efficacy Assessments (formerly Section 7.6)	Corrected that the schedule of tumor assessment should start from Day 1 of Cycle 1.	Revised for clarity and correction.
Section 1.3.1 Schedule of Activities (formerly Appendix 1) Footnote #22 (formerly Footnote #17) Section 8.5.6 Pregnancy Testing (*new section*)	Corrected that the time window of pregnancy test should be "within 7 days before Day 1 of Cycle 1" rather than "within 7 days of randomization".	Revised for clarity and correction.
Section 1.3.1 Schedule of Activities (formerly Appendix 1) Footnote #1	Clarified that the Prescreening Period allows early exclusion for the patients who experienced disease progression during induction treatment.	Revised for clarity and consistency.
Section 1.3.1 Schedule of Activities (formerly Appendix 1)	Added a footnote to indicate that the visit on Day 15 of Cycle 2 applies only to the 3-week regimens.	Revised for clarity.
Section 4.1.1.3.2 Dose-Limiting Toxicities (formerly Section 3.4)	For the criterion of febrile neutropenia, clarified that the single temperature should be ≥ 38.3°C, and the sustained temperature should be ≥ 38°C for > 1 hour.	Revised for clarity and to be consistent with NCI-CTCAE v5.0.
Section 4.1.1.1 Prescreening Period (formerly Section 3.2) Section 8.1.1 Prescreening Period (formerly Section 7.1)	Clarified that the prescreening period may start during the induction treatment before the screening if the patient is considered eligible for the clinical study.	Revised for clarity.
Section 1.3.1 Schedule of	Clarified that the screening evaluations	Revised for clarity and

Section Number and Title	Summary of Change	Brief Rationale for Change
Activities (formerly Appendix 1) Footnote #2 Section 4.1.1.2 Screening Period (formerly Section 3.3) Section 8.1.2 Screening Period (formerly Section 7.2)	will be performed ≤ 28 days before starting the study treatment (for Phase 1b) or randomization (for Phase 2).	consistency.
Section 1.3.1 Schedule of Activities (formerly Appendix 1) Footnote #2 Section 8.1.2 Screening Period (formerly Section 7.2)	Clarified that the results of standard-of-care tests or examinations performed before informed consent has been obtained and within 28 days before starting the study treatment (for Phase 1b) or randomization (for Phase 2) may be used for the purposes of screening rather than repeating the standard-of-care tests, unless otherwise indicated.	
Section 8.1.1.1 PD-L1/MSI/BRAF Test (formerly Section 7.1.1)	Removed the below sentence: During the Prescreening Period, patients may undergo PD-L1, MSI, and BRAF testing. For patients without the Prescreening Period, MSI and BRAF tests will be performed during the Screening Period, if applicable.	Revised to reduce redundancy.
Section 8.1.2 Screening Period (formerly Section 7.2)	Simplified and added a reference to the section providing details on rescreening.	Revised for clarity.
Section 8.1.2.1 Informed Consent and Screening Log (formerly Section 7.2.1)	Clarified that the ICFs for patients who are prescreened but not enrolled will also be maintained at the study site.	Revised for clarity.
Section 8.1.2.4 Women of Childbearing Potential and Contraception (formerly Section 7.2.4)	Removed the description for pregnancy testing in this section.	Revised to reduce redundancy.
Section 8.2.1 Confirmation of Eligibility (formerly Section 7.3.1)	Removed the description for sponsor verification.	Revised to be consistent with the actual conduct; sponsor verification is no longer allowed.
Section 8.2.2 Randomization (formerly Section 7.3.2)	Clarified that the study treatment(s) should be received within 3 calendar days after randomization and treatment assignment rather than the timing being a requirement.	Revised to allow flexibility.

Section Number and Title	Summary of Change	Brief Rationale for Change
Section 8.5.2 Vital Signs, Height, and Weight (formerly Section 7.5.1) (*renamed section*)	Revised the section name to indicate vital signs, height, and weight.	Revised for clarity.
Section 1.3.1 Schedule of Activities (formerly Appendix 1) Footnote #18 (formerly Footnote #11)	Corrected the schedule of ECG assessments for Phase 1b and Phase 2. Clarified that triplicate 12-lead ECG is applicable for Phase 1b and single 12-lead ECG is applicable for Phase 2.	Revised for clarity.
Section 8.5.4 Electrocardiograms (formerly Section 7.5.5)	Simplified and added a reference to the SOA for details on ECG assessments.	
Section 9.3.5.4 Vital Signs (formerly Section 9.3.4)	Removed the respiratory rate.	Revised for consistency.
Appendix 14 Recommended Dose Modification of Bevacizumab and Fluoropyrimidine	Removed the below sentence: The use of vitamin B6 is not permitted for symptomatic or secondary prophylactic treatment of hand-foot syndrome, since impaired efficacy has been reported with concomitant use of vitamin B6 and cisplatin.	Revised for clarity since cisplatin is not used in this study.
Section 2.2 Background (formerly Section 1.3) Section 2.3 Benefit/Risk Assessment (formerly Section 1.6)	Updated the clinical experience of LBL-007 and tislelizumab according to the latest investigator's brochure.	To incorporate information from the latest LBL-007 Investigator's Brochure and Tislelizumab Investigator's Brochure.
Section 4.1 Overall Design (formerly Section 3.1)	Updated the text to be consistent with other sections. • Added "versus bevacizumab plus fluoropyrimidine" in the study design. • Corrected Cohort 1 to Cohort -1.	Revised for consistency.
Section 4.2.1 Rationale for LBL-007 in Combination With Tislelizumab (formerly Section 1.5.1)	Correct the footnote of "b.i.w" from biweekly to twice weekly.	Revised for correction.
Section 6.1 Study Drug/Treatment(s) Administered and Dosage (formerly Section 5.2)	Corrected the dose of tislelizumab for Phase 2 Arm B, from 400 mg once every 3 weeks to 400 mg once every 2 weeks.	Revised for correction.
Section 2.1 Study Rationale (formerly Section 1.1 and	Simplified the study rationale and background parts.	To comply with BeiGene Global Protocol Template.

Section Number and Title	Summary of Change	Brief Rationale for Change
Section 1.2) Section 2.2 Background (formerly Section 1.3)		
Section 2.2.3 Regulatory Status (*new section*)	Added the section for regulatory status of the IMPs and AxMPs.	To comply with BeiGene Global Protocol Template.
Section 3.2 Estimands (*new section*)	Added the section for estimands.	To comply with BeiGene Global Protocol Template.
Section 4.1.2 Duration of the Study (*new section*)	Added the section for duration of study.	To comply with BeiGene Global Protocol Template.
Section 4.2.6 Patient Input Into Design (*new section*)	Added the section for patient input into design.	To comply with BeiGene Global Protocol Template.
Section 5.3 Lifestyle Considerations (*new section*)	Added the section for lifestyle considerations.	To comply with BeiGene Global Protocol Template.
Section 5.4 Screen Failures (*new section*)	Added the section for screen failures.	To comply with BeiGene Global Protocol Template.
Section 5.5 Procedures for Handling Incorrectly Enrolled Patients (*new section*)	Added the section for procedures for handling incorrectly enrolled patients.	To comply with BeiGene Global Protocol Template.
Section 5.6 Criteria for Temporarily Delaying Enrollment/Administration of Study Treatment (*new section*)	Added the section for criteria for temporarily delaying enrollment/administration of study treatment.	To comply with BeiGene Global Protocol Template.
Section 6.3 Assignment to Study Treatment (*new section*)	Added the section for assignment to study treatment.	To comply with BeiGene Global Protocol Template.
Section 6.4 Blinding (*new section*)	Added the section for blinding.	To comply with BeiGene Global Protocol Template.
Section 6.5 Study Treatment Compliance (*new section*)	Added the section for study treatment compliance.	To comply with BeiGene Global Protocol Template.
Section 6.7 Continued Access to Study Treatment After the End of the Study (*new section*)	Added the section for continued access to study treatment after the end of the study.	To comply with BeiGene Global Protocol Template.
Section 6.9.3 Rescue Medication (*new section*)	Added the section for rescue medication.	To comply with BeiGene Global Protocol Template.
Section 7.3 Loss to Follow-up (*new section*)	Added the section for loss to follow-up.	To comply with BeiGene Global Protocol Template.
Section 8.5.6 Pregnancy	Added the section for pregnancy	To comply with BeiGene

Section Number and Title	Summary of Change	Brief Rationale for Change
Testing (*new section*)	testing.	Global Protocol Template.
Section 8.5.10 Suicidal Ideation and Behavior Risk Monitoring (*new section*)	Added the section for suicidal ideation and behavior risk monitoring.	To comply with BeiGene Global Protocol Template.
Section 8.5.11 Other Safety Assessments (*new section*)	Added the section for other safety assessments.	To comply with BeiGene Global Protocol Template.
Section 8.6.8 Adverse Events of Special Interest (*new section*)	Added the section for adverse events of special interest.	To comply with BeiGene Global Protocol Template.
Section 8.10 Pharmacodynamics (*renamed section*)	Added the section for pharmacodynamics.	To comply with BeiGene Global Protocol Template.
Section 8.11 Genetics (*new section*)	Added the section for genetics.	To comply with BeiGene Global Protocol Template.
Section 8.12 Immunogenicity Analyses (*renamed section*)	Added the section for immunogenicity analyses.	To comply with BeiGene Global Protocol Template.
Section 8.13 Medical Resource Utilization and Health Economics (*new section*)	Added the section for medical resource utilization and health economics.	To comply with BeiGene Global Protocol Template.
Section 9.1 Statistical Hypothesis (*new section*)	Added the section for statistical hypothesis.	To comply with BeiGene Global Protocol Template.
Section 9.3.9 Other Safety Analyses (*new section*)	Added the section for other safety analyses.	To comply with BeiGene Global Protocol Template.
Section 9.3.10 Other Analyses (*new section*)	Added the section for other analyses.	To comply with BeiGene Global Protocol Template.
Section 9.4 Interim Analysis (*new section*)	Added the section for interim analysis.	To comply with BeiGene Global Protocol Template.
Section 10.8 Data Quality Assurance (*new section*)	Added the section for data quality assurance.	To comply with BeiGene Global Protocol Template.
Appendix 1 Protocol Amendment History (*new appendix*)	Added the appendix for protocol amendment history.	To comply with BeiGene Global Protocol Template.
Section 2.3 Benefit/Risk Assessment (formerly Section 1.6)	Added template language about benefit/risk assessment.	To comply with BeiGene Global Protocol Template.
Section 4.4 Start of Study and End of Study Definitions (*renamed section*)	Added the definition of the start of study.	To comply with BeiGene Global Protocol Template.
Section 8.4 Efficacy	Added template language about the	To comply with BeiGene

Section Number and Title	Summary of Change	Brief Rationale for Change
Assessments (*renamed section*) Section 8.5 Safety Assessments (formerly Section 7.5)	planned timepoints for assessments.	Global Protocol Template.
Section 8.6 Adverse Event, Serious Adverse Event, and Other Safety Reporting (*renamed section*)	Added template language and references to sections providing additional details regarding definitions, methods of recording, evaluation, and causality assessment of AEs and SAEs and the procedures for completing and transmitting SAE reports.	To comply with BeiGene Global Protocol Template.
Section 10.12 Data Disclosure and Transparency and Data Sharing With External Researchers (*renamed section*)	Added template language about data disclosure and transparency and data sharing with external researchers.	To comply with BeiGene Global Protocol Template.
Appendix 13 Evaluation and Management of Immune-Mediated Adverse Events (formerly Appendix 12)	Added template language about management of imAEs, and updated the description for grade of hypophysitis.	To comply with BeiGene Global Protocol Template.
Section 8.1.2.3 Demographics (formerly Section 7.2.3)	Updated the references for ICH guidance.	To comply with BeiGene Global Protocol Template.
Formerly Section 10.2 Communication (*deleted section*)	This section is removed.	To comply with BeiGene Global Protocol Template.
Formerly Section 12.3 Study Site Inspections (*deleted section*)	This section is removed.	To comply with BeiGene Global Protocol Template.
Throughout document	Updated the title page and signature page, reorganized the protocol, and added and/or revised headings and text in accordance with BeiGene Global Protocol Template.	To comply with BeiGene Style Guide and Global Protocol Template.

APPENDIX 2. CONTRACEPTIVE AND BARRIER GUIDANCE

Contraception Guidelines

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical studies include the use of highly effective forms of birth control. 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
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized male partner, provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment[s]).

  NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle.

  Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence for the duration of exposure to study treatments, 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 combined with another acceptable method listed above.

Definitions of "Women of Childbearing Potential," "Women of No Childbearing Potential"

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

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

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:

- ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
- < 55 years of age with no spontaneous menses for ≥ 12 months AND with a postmenopausal follicle-stimulating hormone concentration > 30 mIU/mL

Adapted from: Recommendations related to contraception and pregnancy testing in clinical trials

APPENDIX 3. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definitions of Adverse Event

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 study treatments, whether considered related to study treatments or not.

Examples of AEs include:

- Worsening of a chronic or intermittent preexisting condition, including an increase in severity, frequency, duration, and/or an association with a significantly worse outcome.
- New conditions detected or diagnosed after study treatment administration even though the condition might have been present before the start of the study.
- Signs, symptoms, or clinical sequelae of a suspected interaction.
- Signs, symptoms, or clinical sequelae of a suspected overdose of any of the study treatments or a concurrent medication (overdose per se should not be reported as an AE or SAE).

Definition of a Serious Adverse Event

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

a. Results in death

b. 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.

c. Requires hospitalization or prolongation of existing hospitalization

- Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

d. 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.

e. Is a congenital anomaly/birth defect

f. Is considered a significant medical AE by the investigator or sponsor based on medical judgment (eg, may jeopardize the patient or may require medical/surgical intervention to prevent the outcomes listed above)

The following are NOT considered SAEs:

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

Definition of a Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the study treatment's reference safety information [RSI]) and meets the definition of a serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the LBL-007 Investigator's Brochure and Tislelizumab Investigator's Brochure.

Recording and Follow-Up of Adverse Events and Serious Adverse Events

Adverse Event, Serious Adverse Event, and Recording

- 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) related to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be obscured on the copies of the medical records before submission to the sponsor.
- 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 that worsen significantly during the study. The definition of clinically significant is based on 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 treatment 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 AE eCRF.
- 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 AE eCRF unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

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 per NCI-CTCAE v5.0.

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

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

Note: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (eg, grade of a specific AE, such as 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 8.6.4.

Assessment of Causality

The investigator is obligated to assess the relationship between the study treatments and the occurrence of each AE or SAE using their best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, and other risk factors, and the temporal relationship of the AE or SAE to the study treatments should be considered and investigated. The investigator should consult the LBL-007 Investigator's Brochure and Tislelizumab Investigator's Brochure in the determination of their assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the

investigator always assesses causality for every SAE before transmission of the SAE report to the sponsor because the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change their opinion of causality after considering follow-up information, amending the SAE report accordingly.

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

- Temporal relationship of the AE to the administration of study treatment(s) or the study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study treatments
- Biological plausibility

An AE should be considered "related" to study treatments if any of the following are met; otherwise, the event should be assessed as "not related" if:

- 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[s]). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

Recording Immune-Mediated Adverse Events

Because treatment with anti-PD-1 or immune checkpoint inhibitors can cause autoimmune disorders, AEs considered by the investigator to be immune-mediated (see Section 6.10.4) should be classified as imAEs and identified as such on the eCRF AE page until Day 90 after treatment discontinuation.

Investigators should consult the guidance on diagnostic evaluation and management of imAEs, that are commonly seen with immune checkpoint inhibitors, in Appendix 13.

An extensive list of potential imAEs appears in Table 14. All conditions like those listed should be evaluated to determine whether they are imAEs based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 13.

Table 14: Examples of Immune-Mediated Adverse Events

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

Recording Infusion-Related Reactions

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

Any event occurring during or within 24 hours of study drug administration and considered related to the infusion of study treatment should be recorded as a diagnosis (Infusion-related reaction) on the Adverse Event eCRF.

Refer to the eCRF completion guidelines for details. See Appendix 11 for management of infusion-related reactions.

Recording Anaphylaxis

Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. It is characterized by the rapid development of airway and/or breathing and/or circulation problems. Intramuscular adrenaline is the most important treatment. Rechallenge is contraindicated. The definition currently accepted by the FDA relies on clinical diagnostic criteria and does not specify a particular immunologic mechanism (US FDA 2014).

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

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

See Appendix 12 for management of anaphylaxis.

APPENDIX 4. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE CANCER QUESTIONNAIRE QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 5. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE QUESTIONNAIRE-COLORECTAL CANCER MODULE QLQ-CR29

ENGLISH

EORTC QLQ – CR29

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Have you had any unintentional release (leakage) of urine?	1	2	3	4
34. Did you have pain when you urinated?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had blood in your stools?	1	2	3	4
39. Have you had mucus in your stools?	1	2	3	4
40. Did you have a dry mouth?	1	2	3	4
41. Have you lost hair as a result of your treatment?	1	2	3	4
42. Have you had problems with your sense of taste?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
43. Were you worried about your health in the future?	1	2	3	4
44. Have you worried about your weight?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4
48. Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes		No	

ENGLISH

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue below:				
49. Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50. Have you had leakage of stools from your stoma bag?	1	2	3	4
51. Have you had sore skin around your stoma?	1	2	3	4
52. Did frequent bag changes occur during the day?	1	2	3	4
53. Did frequent bag changes occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your stoma?	1	2	3	4
55. Did you have problems caring for your stoma?	1	2	3	4

Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG:				
49. Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50. Have you had leakage of stools from your back passage?	1	2	3	4
51. Have you had sore skin around your anal area?	1	2	3	4
52. Did frequent bowel movements occur during the day?	1	2	3	4
53. Did frequent bowel movements occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your bowel movement?	1	2	3	4

During the past 4 weeks:	Not at All	A Little	Quite a Bit	Very Much
For men only:				
56. To what extent were you interested in sex?	1	2	3	4
57. Did you have difficulty getting or maintaining an erection?	1	2	3	4

For women only:				
58. To what extent were you interested in sex?	1	2	3	4
59. Did you have pain or discomfort during intercourse?	1	2	3	4

APPENDIX 6. NATIONAL CANCER INSTITUE PATIENT-REPORTED OUTCOMES VERSION OF THE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (PRO-CTCAE)

NCI- PRO-CTCAE™ ITEMS-ENGLISH

Item Library Version 1.0

Colorectal Cancer Treatment Side Effect items

As individuals go through treatment for their cancer, they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days

8: PRO-CTCAE™ Symptom Term: Decreased Appetite

a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

13: PRO-CTCAE™ Symptom Term: Bloating

a. In the last 7 days, how OFTEN did you have BLOATING OF THE ABDOMEN (BELLY)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
b. In the last 7 days, what was the SEVERITY of your BLOATING OF THE ABDOMEN (BELLY) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

24: PRO-CTCAE™ Symptom Term: Rash

a. In the last 7 days, did you have any RASH?	
O Yes	O No

28: PRO-CTCAE™ Symptom Term: Itching

a. In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

30: PRO-CTCAE™ Symptom Term: Hand-foot syndrome

a. In the last 7 days, what was the SEVERITY of your HAND-FOOT SYNDROME (A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS OR PAIN) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

50: PRO-CTCAE™ Symptom Term: Muscle pain

a. In the last 7 days, how OFTEN did you have ACHING MUSCLES?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
b. In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
c. In the last 7 days, how much did ACHING MUSCLES INTEREFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

51: PRO-CTCAE™ Symptom Term: Joint pain

a. In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
b. In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
c. In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTEREFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

53: PRO-CTCAE™ Symptom Term: Fatigue

a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

APPENDIX 7. EASTERN COOPERATIVE ONCOLOGY GROUP 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 housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

As published by Oken et al 1982.

APPENDIX 8. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION AND COCKCROFT AND GAULT EQUATION

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation

In adults, the most widely-used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al 2009) and the Modification of Diet in Renal Disease (MDRD) Study equation. The National Kidney Disease Education Program (NKDEP) calculators rely on creatinine determinations which are isotope dilution mass spectrometry (IDMS) traceable. All laboratories should be using creatinine methods calibrated to be IDMS traceable.

This CKD-EPI equation calculator should be used when serum creatinine (S_{cr}) is reported in mg/dL. This equation is recommended when eGFR 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 women and 0.9 for men,

α is -0.329 for women and -0.411 for men,

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/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators

Cockcroft and Gault Equation

For S_{cr} in mg/dL:

Creatinine Clearance (CrCl) = [((140-age) x weight)/(72 x S_{cr})] x 0.85 if female

For S_{cr} in µmol/L:

Creatinine Clearance (CrCl) = [((140-age) x weight)/(0.81x S_{cr})] x 0.85 if female

Note: CrCl is expressed in mL/min, age is expressed in years, and weight is expressed in kilograms.

Source: Cockcroft and Gault 1976

APPENDIX 9. 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, NYHA, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

APPENDIX 10. 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 trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

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

Measurable Disease

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

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical examination (when superficial).
- 20 mm by chest x-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT or MRI scan (CT/MRI scan slice thickness recommended to be ≥ 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

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

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

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph node" or "multiple liver metastases").

Guidelines for Evaluation of Measurable Disease

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

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

- Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, because CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: 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).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease-specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease to differentiate between response (or stable disease) and PD.

Response Criteria

Evaluation of Target Lesions

- CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
- PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
- Stable disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the “sum” of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, to qualify for CR, each node

must achieve a short axis < 10 mm. For PR, stable disease, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

- Target lesions that become "too small to measure." While on study, all lesions (nodal and nonnodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure."
- When this occurs, it is important that a value be recorded on the 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 should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Evaluation of Non-target Lesions

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

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

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

- When the patient has only nonmeasurable disease: This circumstance arises in some Phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept 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 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 non-measurable 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 PD; 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 trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD. An example of this is the patient who has visceral disease at baseline and while on trial has a CT or MRI brain scan ordered that reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

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

While fluorine-18 [F-18] 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 FDG-PET at baseline, with a positive FDG-PET at Follow-up, is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The BOR 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 BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "BOR."

The BOR is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all timepoints (for example, a patient who has stable disease at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When stable disease 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 stable disease is otherwise the best timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has stable disease at first assessment, PD at second and does not meet minimum duration for stable disease, will have a best response of PD. The same patient lost to follow-up after the first stable disease assessment would be considered inevaluable.

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

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

When 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" on the eCRF.

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

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

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of 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 at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Confirmation of Measurement/Duration of Response

Confirmation

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

In the case of stable disease, measurements must have met the stable disease criteria at least once after trial 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 disease or PD is objectively documented (taking as reference for PD 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 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 trial, the protocol should specify the minimal time interval required between 2 measurements for determination of stable disease.

Note: The DOR and stable disease as well as the PFS are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should consider many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be considered if comparisons between trials are to be made.

APPENDIX 11. MANAGEMENT OF INFUSION-RELATED REACTIONS

Patients should be closely monitored during and after study drug administration for infusion-related reactions and hypersensitivity reactions. See Table 10 for the monitoring periods required. Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

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

Table 15: Management of Infusion-Related Reactions

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

NCI-CTCAE Grade v5.0	Management
Grade 4 Life-threatening consequences; urgent intervention indicated	• Immediately stop the infusion. • Treatments include, but are not limited to, H1/H2 antagonists and corticosteroids. • Proper medical management should be instituted. • The patient should be withdrawn from study drug(s) treatment. • Hospitalization is recommended.

Abbreviations: H1/H2, histamine H1 and H2 receptors; IV, intravenously; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; NSAIDs, nonsteroidal anti-inflammatory drugs.

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

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

APPENDIX 12. MANAGEMENT OF ANAPHYLAXIS

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

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

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

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

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

APPENDIX 13. EVALUATION AND MANAGEMENT OF IMMUNE-MEDIATED ADVERSE EVENTS

Evaluation of Immune-Mediated Adverse Events

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

Criteria used to diagnose imAEs include blood tests, diagnostic imaging, histopathology, and microbiology assessments to exclude alternative causes such as infection, PD, 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 treatments and the AE?
- How did the patient respond to withdrawal of study treatments?
- Did the event recur when study treatments was/were reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is PD 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 should be checked.

Table 16: Recommended Diagnostic Tests in the Management of Possible Immune-Mediated Adverse Events

Immune-Mediated Toxicity	Diagnostic Evaluation Guideline
Thyroid disorders	Scheduled and repeated TFTs (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 PFT 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

Immune-Mediated Toxicity	Diagnostic Evaluation Guideline
	screen and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, CMV or other viral PCR, fecal calprotectin, *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 Grades 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 I and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, troponin I, and refer to a cardiologist.

Abbreviations: AE, adverse event; ANA, antinuclear antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FBC, full blood count; 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; 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

ImAEs can escalate quickly. Study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention as appropriate are required. ImAEs should improve

promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice, and contact the medical monitor.

If a toxicity does not resolve to ≤ Grade 1 within 12 weeks, study treatment 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 treatment should permanently discontinue study treatment.

For some Grade 3 toxicities that resolve quickly, rechallenge with study treatment 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 corticosteroid-refractory imAEs, consider use of corticosteroid-sparing agents (eg, MMF). Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy.

Table 17: Management of Immune-Mediated Adverse Events

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Treatment 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 Judgment)	Study Treatment 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. Taper corticosteroids over at least 1 month.	Continue study treatment.
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade 2 or less. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 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 ≥ 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2-4 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Treatment Management
Neurological toxicity	**1** Mild symptoms	–	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	Initiate treatment with oral prednisolone or IV methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/diarrhea	**1** Mild symptoms: < 3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days manage as a Grade 2 event.	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks, consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg; if no perforation, sepsis, TB, hepatitis, NYHA Grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/sigmoidoscopy.	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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Treatment Management
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgment: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: IV 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 IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3X ULN	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening. 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 3-5X 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 judgment.	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 Judgment)	Study Treatment Management
	3 ALT or AST 5-20X ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate IV (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment until improved to baseline grade; reintroduce only after discussion with the study medical monitor.
	4 ALT or AST > 20X ULN	Initiate IV methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over ≥ 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: If on oral prednisolone, change to pulsed IV methylprednisolone If on IV, add MMF 500-1000 mg twice a day If worsens on MMF, consider addition of tacrolimus Duration and dose of steroid required will depend on severity of event		
Nephritis	**1** Creatinine 1.5X baseline or > ULN to 1.5X ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5X-3X baseline or > 1.5X-3X ULN	Ensure hydration and review creatinine in 48-72 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 treatment, 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 treatment and resolved/improved to baseline grade: Restart study treatment if tapered to < 10 mg prednisolone.
	3 Creatinine > 3X baseline or > 3X-6X ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study treatment suspected: Discontinue study treatment.
	4 Creatinine > 6X ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Treatment Management
Diabetes/ hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
Ocular toxicity	**1** Asymptomatic eye exam/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 steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Treatment Management
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment manage as a Grade 3 event.	Continue treatment or, if symptoms continue worsens, hold study treatment until symptoms improve to baseline or Grade 0-1.
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 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 IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider IV corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2.	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 X ULN or worse initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	Hold study treatment until improved to Grade 0-1. Discontinue if any evidence of myocardial involvement.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Treatment Management
Myocarditis	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Admit to hospital and refer to a cardiologist. Transfer all patients with moderate/severe cardiac symptoms or any increase in cardiac serum markers to the coronary care unit. Initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab or anti-thymocyte globulin.	Hold study treatment until completely resolved or myocarditis has been ruled out.
	2 Symptoms on mild-moderate exertion		Discontinue study treatment unless cardiac involvement has been excluded and symptoms have completely resolved.
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CK, creatine kinase; CK-MB, creatine kinase-muscle-brain; CHF, congestive heart failure; INR, international normalized ratio; IV, intravenous; LFT, liver function test; MMF, mycophenolate mofetil; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.

APPENDIX 14. RECOMMENDED DOSE MODIFICATION OF BEVACIZUMAB AND FLUOROPYRIMIDINE

Bevacizumab and fluoropyrimidine dose modification scheme as described below are recommended for the management of adverse reactions.

Dosage Modifications of Bevacizumab

Adverse Reaction	Severity	Dosage Modification
Gastrointestinal Perforations and Fistulae .	• Gastrointestinal perforation, any grade • Tracheoesophageal fistula, any grade • Fistula, Grade 4 • Fistula formation involving any internal organ	Discontinue bevacizumab
Wound Healing Complications .	• Any	Withhold bevacizumab until adequate wound healing. The safety of resumption of bevacizumab after resolution has not been established.
	• Necrotizing fasciitis	Discontinue bevacizumab
Hemorrhage .	• Grade 3 or 4	Discontinue bevacizumab
	• Recent history of hemoptysis of 1/2 teaspoon (2.5 mL) or more	Withhold bevacizumab
Thromboembolic Events	• Arterial thromboembolism, severe	Discontinue bevacizumab
	• Venous thromboembolism, Grade 4	Discontinue bevacizumab
Hypertension	• Hypertensive crisis • Hypertensive encephalopathy	Discontinue bevacizumab
	• Hypertension, severe	Withhold bevacizumab if not controlled with medical management; resume once controlled
Posterior Reversible Encephalopathy Syndrome (PRES)	• Any	Discontinue bevacizumab
Renal Injury and Proteinuria	• Nephrotic syndrome	Discontinue beivacizumab
	• Proteinuria greater than or equal to 2 grams per 24 hours in absence of nephrotic syndrome	Withhold bevacizumab until proteinuria less than 2 grams per 24 hours
Infusion-Related Reactions	• Severe	Discontinue bevacizumab
	• Clinically significant	Interrupt infusion; resume at a decreased rate of infusion after symptoms resolve
	• Mild, clinically insignificant	Decrease infusion rate
Congestive Heart Failure	Any	Discontinue bevacizumab

Dose Reduction Level of Fluoropyrimidine

Drug	First Dose Level	Second Dose Level
Capecitabine	Reduce dose to 75%	Reduce dose to 50%
5-FU	Reduce dose to 75%	Reduce dose to 50%

Abbreviation: 5-FU, 5-fluorouracil.
Note: A maximum of 2 dose level reductions of fluoropyrimidine due to toxicity are permitted throughout the induction and maintenance treatment.

Dose Modification for Hematologic Toxicities of Fluoropyrimidine

Toxicities related to chemotherapy must be resolved to baseline or ≤ Grade 1 prior to administering the next dose of chemotherapy, with the exceptions of alopecia, Grade 2 fatigue, or other AEs, which, in the opinion of the investigator, would not affect the safety evaluation of the study drugs.

Adverse Event	Grade	Dose Modifications
Febrile neutropenia	3	First occurrence: First reduced dose level Second occurrence: Stop treatment permanently unless it is in the best interest of the patient to treat with second reduced dose level
	4	First occurrence: Stop treatment permanently unless it is in the best interest of the patient to treat with second reduced dose level Second occurrence: Stop treatment permanently
Neutrophil count decreased	1/2	Maintain dose level
	3/4	First occurrence: First reduced dose level Second occurrence: Second reduced dose level Third occurrence: Stop treatment permanently
Platelet count decreased	1	Maintain dose level
	≥ 2	First occurrence: First reduced dose level Second occurrence: Second reduced dose level Third occurrence: Stop treatment permanently

Note: If considered in the best interest of the patient and consistent with local practice, investigators may decide to use supportive measures/treatment and/or secondary prophylaxis instead of dose reductions for the next cycle. The provided triggers for dose modifications are recommendations only.

Dose Modification for Nonhematologic Toxicities of Capecitabine

	Grade 2	Grade 3	Grade 4
1st appearance	Interrupt treatment until resolved to ≤ grade 1 then continue at 100% of original capecitabine dose with prophylaxis where possible	Interrupt treatment until resolved to ≤ grade 1, then continue at 75% of original capecitabine dose, with prophylaxis where possible	Interrupt treatment, if the investigator considers it to be in the best interest of the subject to continue at 50% of original capecitabine dose, once toxicity has resolved to ≤ grade 1
2nd appearance of same toxicity	Interrupt treatment until resolved to ≤ grade 1, then continue at 75% of original capecitabine dose	Interrupt treatment until resolved to ≤ grade 1, then continue at 50% of original capecitabine dose	Discontinue treatment permanently
3rd appearance of same toxicity	Interrupt treatment until resolved to ≤ grade 1, then continue at 50% of original capecitabine dose	Discontinue treatment permanently	
4th appearance of same toxicity	Discontinue treatment permanently		

Capecitabine treatment interruptions are regarded as lost treatment days and the planned treatment schedule should be maintained. Missed doses due to treatment interruptions should not be replaced. A flat dosing is suggested.

Besides the guidance for dose modification on toxicities of capecitabine, some detailed guidance for dose modification and management for the specified toxicities are listed below.

Diarrhea

Careful consideration of which agent is most likely to be contributing is important for evaluation, treatment, and management, including appropriate dose modification(s). Persistent diarrhea despite standard antidiarrheal medications (eg, loperamide, octreotide, diphenoxylate, and atropine) or diarrhea that is associated with significant abdominal pain, bloody stools, or signs of systemic inflammation should be further investigated to rule out infectious etiologies as well as immunotherapy-associated colitis. Gastroenterology consultation and sigmoidoscopy with biopsy

should be strongly considered in such cases. Refer to Appendix 13 for recommendations on evaluation of suspected immune-mediated colitis.

For the first occurrence of Grade 2, 3, or 4 diarrhea, capecitabine should be interrupted immediately and should not be restarted until the diarrhea has resolved to Grade 0 or 1 with the last loperamide dose given at least 24 hours beforehand. Prophylactic antidiarrheal treatment (eg loperamide) could be considered when resuming capecitabine.

Following the occurrence of Grade 2 or higher diarrhea, subsequent doses of capecitabine should be decreased.

For the first occurrence of Grade 4 diarrhea or recurring Grade 3 diarrhea, discontinuation of capecitabine should be strongly considered. Alternatively, re-challenge with capecitabine with dose reduction by 2 dose levels, could be considered based on investigator's risk-benefit assessment and discussion with the sponsor's medical monitor.

Symptomatic treatment with loperamide is recommended, and prevention or reversal of fluid and electrolyte depletion should be taken into consideration. Diarrhea of > 2 days duration requires medical evaluation including relevant diagnostic procedures and alternative or additional antidiarrheal treatments.

Hand-Foot Syndrome

Hand-foot syndrome is a cutaneous toxicity which severity ranges from Grade 1 to 3 as follows:

- Grade 1: Minimal skin changes or dermatitis (eg, erythema) without pain.
- Grade 2: Skin changes (eg, peeling, blisters, bleeding, edema) or pain, not interfering with function.
- Grade 3: Ulcerative dermatitis or skin changes with pain interfering with function.

If Grade 2 or 3 hand-foot syndrome occurs, administration of capecitabine should be immediately interrupted until the event resolves or decreases in intensity to Grade ≤ 1. Subsequent doses of capecitabine should be decreased and administered as per Table 9. Hand-foot syndrome should be treated symptomatically (ie, use of emollients is recommended).

Stomatitis

If stomatitis ≥ Grade 2 occurs, the administration of capecitabine should be immediately interrupted until the event resolves or decreases in intensity to Grade ≤ 1. Treat symptomatically. Subsequent doses of capecitabine should be administered as per Table 9.

Cardiac Toxicity

For Grade ≥ 2 cardiac toxicity which is attributable to capecitabine, patients will be permanently discontinued from capecitabine and thus oxaliplatin therapy.

Dose Modification for Nonhematologic Toxicities of 5-FU

Dose modifications for specific toxicities are described below:

For Grade 3 to 4 diarrhea refractory to oral antidiarrheal medication, 5-FU will be held until the toxicity is Grade ≤ 1, then 5-FU will be reduced by 25%. One further dose reduction of 25% will be allowed. If Grade ≥ 3 diarrhea persists, then the patient will be withdrawn from 5-FU.

For Grade 3 to 4 mucositis or hand-foot syndrome, the 5-FU infusion will be interrupted. In the subsequent cycle, if the toxicity has improved to Grade ≤ 1, the 5-FU doses should be reduced by 25%. One further dose reduction of 25% will be allowed.

For Grade ≥ 2 cardiac toxicity which is attributable to 5-FU, patients will be permanently discontinued from 5-FU.

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Approved Date 2/26/2025

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