CLINICAL STUDY PROTOCOL

Protocol Title:	A Single-Arm, Multicenter, Open-Label, Phase 2 Study to Investigate the Efficacy and Safety of Tislelizumab (BGB-A317) as Neo-Adjuvant Treatment in Patients With Early-Stage (Stage II-III) Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Colorectal Cancer
Protocol Identifier:	BGB-A317-214
Phase:	2
Investigational Products:	Tislelizumab (BGB-A317)
Indication:	Neo-adjuvant treatment of Stage II or III Colorectal Cancer
Sponsors:	BeiGene (Shanghai) Co., Ltd. 4th floor, Building D, 780 Cailun Road, China (Shanghai) Pilot-Free Trade Zone Shanghai, 201203 China
Sponsor Medical Monitor:	[redacted] Telephone: [redacted] Email: [redacted]
Original Protocol Version 0.0:	31 March 2021
Amendment 1.0:	06 June 2022
Amendment 2.0:	25 July2022

FINAL PROTOCOL APPROVAL SHEET

Protocol Title: A Single-Arm, Multicenter, Open-Label, Phase 2 Study to Investigate the Efficacy and Safety of Tislelizumab (BGB-A317) as Neo-Adjuvant Treatment in Patients With Early-Stage (Stage II-III) Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Colorectal Cancer

BeiGene (Shanghai) Co., Ltd. Approval:

_____ _____

[redacted] Date

Sponsor Medical Monitor

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Single-Arm, Multicenter, Open-Label, Phase 2 Study to Investigate the Preliminary Efficacy and Safety of Tislelizumab (BGB-A317) as Neo-Adjuvant Treatment in Patients With Early-Stage (Stage II-III) Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Colorectal Cancer

Protocol Identifier: BGB-A317-214

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

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

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SYNOPSIS

Name of Sponsor/Company: BeiGene (Shanghai) Co., Ltd.

Investigational Products: Tislelizumab (also known as BGB-A317)

Title of Study: A Single-Arm, Multicenter, Open-Label, Phase 2 Study to Investigate the Efficacy and Safety of Tislelizumab (BGB-A317) as Neo-Adjuvant Treatment in Patients With Early-Stage (Stage II-III) Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Colorectal Cancer

Protocol Identifier: BGB-A317-214

Phase of Development: 2

Number of Patients: Approximately 38

Study Centers: Approximately 8 sites in China

Study Objectives:

Primary:

- To evaluate major pathological response (MPR) rate in patients receiving tislelizumab as neo adjuvant treatment.

Secondary:

- To evaluate pathological complete response (pCR) rate in patients receiving tislelizumab as neo-adjuvant treatment.
- To evaluate event-free survival (EFS) in patients receiving tislelizumab as neo-adjuvant treatment.
- To explore potential biomarkers that may correlate with clinical responses/resistance to tislelizumab as neo-adjuvant treatment.
- To evaluate the safety and tolerability of neo-adjuvant treatment with tislelizumab in patients with early-stage (Stage II-III) Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) colorectal cancer.

Exploratory:

- To evaluate R0 resection rate in patients receiving tislelizumab as neo-adjuvant treatment
- To evaluate perioperative events (including but not limited to treatment related surgery delay, postoperative complication) in patients receiving tislelizumab as neo-adjuvant treatment.

Study Endpoints:

Primary:

- MPR rate is defined as the proportion of patients with ≤ 10% residual viable tumor in the resected primary tumor after completion of neo-adjuvant therapy in an efficacy analysis set.

Secondary:

- The pCR rate is defined as the proportion of patients with absence of residual tumor in the resected primary tumor and all resected lymph nodes after completion of neo-adjuvant therapy in

an efficacy analysis set.

- EFS is defined as the time from first dose until any of the following events, whichever occurs first: radiographic disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, local or distant recurrence, or death due to any cause in an efficacy analysis set. 2-year/3-year EFS rate is defined as the proportion of patients free from EFS events at 2 years and 3 years estimated using the Kaplan-Meier method.
- Potential biomarkers including immune cell infiltration, programmed cell death protein ligand-1 (PD-L1) expression, tumor mutational burden (TMB) and DNA mutation, gene expression profile (GEP) and the association of biomarkers with disease status, response/resistance to tislelizumab as neo-adjuvant treatment.
- Incidence and severity of treatment-emergent adverse events (TEAEs), including serious adverse events and immune-mediated adverse events (imAEs), with severity determined according to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0) in a safety analysis set.

Exploratory:

- R0 resection rate - defined as the proportion of patients with R0 resection
- To evaluate perioperative events (including but not limited to treatment related surgery delay, postoperative complication) in patients receiving tislelizumab as neo-adjuvant treatment.

Study Design:

This is an open-label, multicenter Phase 2 study designed to investigate the preliminary efficacy and safety of tislelizumab monotherapy as neo-adjuvant treatment in approximately 38 patients with early-stage (Stage II-III) Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR)colorectal cancer.

The study consists of a prescreening and/or screening phase, a treatment phase that includes a neo-adjuvant phase, surgery and disease follow-up phase.

The study schema is presented in Figure 1, Section 3.1

Neo-adjuvant Phase:

During the neo-adjuvant phase, patients who are found to have disease progression at scheduled tumor assessments (before Cycle 3 and surgery) or at any time during neo-adjuvant treatment and are still deemed resectable and non-metastatic will proceed to receive surgery if amenable and will remain eligible for all on-study evaluations based on investigator's judgement.

Patients who discontinue neo-adjuvant treatment early because of urgent surgery (eg., because of intestinal obstruction, intestinal perforation, or intestinal bleeding), disease progression or intolerable AEs and do not proceed to a complete resection will proceed to receive other treatment as determined by the investigator. Further in-clinic study procedures of these patients should be discussed with the medical monitor.

Surgery:

Upon completion of neo-adjuvant therapy, patients will undergo surgical resection of their tumor. Surgical specimens will be assessed for pathological response (MPR and pCR). In addition, exploratory biomarker analysis of surgical specimens (primary tumor tissue and dissected lymph nodes) will be performed.

Before surgery, the investigator will reassess the patient to reconfirm disease resectability. The presurgical visit and associated assessments should occur within 14 days of surgery and in accordance with local institutional practice.

The surgical procedure should be performed within 10 weeks from the first administered dose of study treatment. If surgery cannot be performed within this time window (eg, because of a prolonged AE), the medical monitor should be consulted. The investigator and the medical monitor will determine the acceptable length of this time window. Complete resection (R0) should be performed.

Disease Follow-up Phase:

Patients will continue adjuvant treatment and perform follow-up which will be determined by the investigator according to the stage of disease and benefit-risk assessment in accordance with the relevant clinical practice (eg. Colon and Rectal Cancer NCCN (National Comprehensive Cancer Network) guidelines, Chinese Society of Clinical Oncology (CSCO)guideline). Patients will continue to undergo tumor assessments following the original plan until the patient experiences disease progression or recurrent according to RECIST v 1.1, withdraws consent, is lost to follow up, death, begins a new anticancer therapy or until the study terminates, whichever occurs first.

Study Assessments:

Patients with the diagnosis of Stage II-III colorectal cancer and with unknown MSI and MMR status are required to provide blood and tumor tissues for central laboratory confirmation of MSI status during the prescreening period (defined as within 56 days prior to the first dose of the study drug). Approximately 2 mL peripheral whole blood together with tumor tissues (archival formalin-fixed paraffin-embedded [FFPE] blocks or at least 10 freshly cut unstained slides) are required for central laboratory confirmation of MSI status.

Patients with known MSI-H status by local laboratory must undergo central laboratory assessment of MSI-H during or after the screening period if tumor samples are obtainable. For patients with known dMMR status determined by local laboratory, central laboratory confirmation of MSI-H status will be performed during the screening period for enrollment. Approximately 2 mL peripheral whole blood together with tumor tissues (archival FFPE blocks or at least 10 freshly cut unstained slides) are required for central laboratory assessment/confirmation of MSI-H. Available paired tumor tissues need to be sent for retrospective analysis of other exploratory biomarkers related to response and resistance in sponsor designated central or test laboratory. A fresh biopsy is mandatory in the absence of archival tumor tissues. Tumor imaging will be performed ≤ 28 days before first dose. During the study, tumor assessment will be performed after neo-adjuvant treatment and before surgery (9 weeks ± 7 days after first dose). After surgery, the post-surgery treatment and the follow up will determined by investigator. During this period tumor assessment will be performed every 12 weeks (± 14 days) for the first 3 years, and then every 24 weeks (± 28 days) for a total 5 years, and then once (±28 days) each year thereafter based on RECIST v1.1. Patients will continue with the scheduled tumor assessments until radiographic disease progression or recurrent per RECIST v1.1, withdrawal of consent, loss to follow-up, study termination by the sponsor, start of a new anticancer therapy (excluding adjuvant therapy), or death, whichever occurs first.

Patients will be evaluated for adverse events (AEs) and immune-mediated adverse events (imAEs) (all grades according to NCI-CTCAE v5.0). Serious adverse events (SAEs) and any AEs that lead to treatment discontinuation will be followed and documented until the event is resolved, the investigators assess the event as stable, or the patient is lost to follow-up, whichever occurs first.

After initiation of study drug, all AEs and SAEs, regardless of the relationship to the study drug, will be reported until either 30 days after the last dose of study treatment or initiation of new anticancer therapy, whichever occurs first. All imAEs (serious or nonserious) should be reported up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy.

Duration of Patient Participation:

The duration of the study from the first enrolled patient to the final analysis for three-year EFS is estimated to be approximately 50 months and from the first enrolled patient to the time of primary analysis is estimated to be approximately 16 months

Study Population:

The study will enroll approximately 38 patients who meet the following inclusion/exclusion criteria.

Key Eligibility Criteria:

Key Inclusion Criteria:

- Age ≥18 years on the day of signing the ICF.
- ECOG Performance Status of 0 or 1.
- Pathologically (histologically) confirmed diagnosis of potentially resectable Stage II or Stage III (per the Eighth American Joint Committee on Cancer staging system for Colon/Rectal Cancer) colorectal cancer (CRC) with MSI-H confirmed by sponsor designated central laboratory or known MSI-H status by local laboratory. Patients should be eligible for an R0 resection with curative intent.
- Evaluable or measurable disease as assessed by the investigator per RECIST v1.1.
- With unknown MSI status by local laboratory, patients must provide blood (approximately 2 mL peripheral whole blood) and tumor tissues (archival FFPE blocks or at least 10 freshly cut unstained slides) for central laboratory MSI confirmation. Patients must be able to provide paired tumor tissues (pre-treatment and post-treatment tumor tissues as FFPE blocks or approximately 14 [≥ 10] freshly cut unstained slides) for retrospective analysis of other exploratory biomarkers related to response and resistance. A fresh biopsy is mandatory in the absence of pre-treatment archival tumor tissues.
- Adequate hematologic and organ function, defined by protocol-specified laboratory test results, obtained within 14 days before first dose

Key Exclusion Criteria:

- Any prior therapy for current CRC, including chemotherapy or radiotherapy or immunotherapy
- Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days before first dose.
- Active autoimmune diseases or history of autoimmune diseases that may relapse

Test Product, Dose, and Mode of Administration:

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

Reference Therapy, Dose, and Mode of Administration:

Not applicable.

Statistical Methods:

This study is designed to evaluate the safety and efficacy of neo-adjuvant treatment with Tislelizumab (BGB-A317) in patients with early-stage (Stage II-III) Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Colorectal Cancer. Details of statistical analyses will be described in Statistical Analysis Plan.

Analysis Sets:

The Safety Analysis Set (SAS) includes all enrolled patients who received ≥ 1 dose of study drug; it will be the analysis set for the safety analyses.

The Efficacy Analysis Set (EAS) includes all enrolled patients who receive neo-adjuvant treatment followed by surgery. This will be the primary analysis set for the efficacy analyses.

Safety Analyses:

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

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 drugs and up to 30 days after study drug discontinuation or initiation of new anticancer therapy, whichever occurs first. Only those AEs that were treatment emergent will be included in summary tables of TEAEs. Immune-mediated AEs will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of tislelizumab and up to 90 days from the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. If an imAE occurs outside of the above-mentioned TEAE window, it will not be classified as a TEAE. All imAEs will be reported separately. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

Laboratory values (eg, hematology, clinical chemistry, and urinalysis), vital signs, electrocardiograms (ECGs), and the results of physical examinations will also be used to assess the safety profile. Descriptive statistics will be used to analyze all safety data in the SAS.

Primary Efficacy Analysis:

MPR rate is the primary endpoint of the study. MPR rate is defined as the proportion of patients in the EAS with ≤ 10% residual viable tumor in the resected primary tumor after completion of neo-adjuvant therapy in an efficacy analysis set. The MPR rate will be summarized descriptively, and the Clopper-Pearson 95% confidence interval (CI) will be calculated to evaluate the precision of MPR estimate. The analysis of MPR rate will occur after all the patients in the efficacy analysis set have been assessed for pathological response

Secondary Efficacy Analysis:

pCR rate is defined as the proportion of patients with absence of residual tumor in the resected primary tumor and all resected lymph nodes after completion of neo-adjuvant therapy followed by surgery assessed by investigator in the efficacy analysis set. The pCR rate will be summarized descriptively and a Clopper-Pearson 95% CI will also be calculated.

EFS is defined as the time from the time of first dose until any of the following events, whichever occurs first: radiographic disease progression according to RECIST v1.1, local or distant recurrence, or death due to any cause in the EAS. The median and other quartiles of EFS will be estimated using the Kaplan-Meier method. The 2-sided 95% CIs will be constructed with the generalized Brookmeyer and Crowley method (Brookmeyer et al, 1982). 2-year/3-year EFS rate is defined as the proportion of patients free from EFS events at 2 years and 3 years after the first dose. EFS rates will be estimated by the Kaplan-Meier method with 95% CI estimated using Greenwood's formula (Greenwood et al, 1926).

Biomarker Analysis:

Potential biomarkers will be analyzed, including immune cell infiltration, programmed cell death protein ligand-1 (PD-L1) expression, tumor mutational burden (TMB) and DNA mutation, gene expression profile (GEP) and the association of biomarkers with disease status, response/resistance to tislelizumab as neo-adjuvant treatment.

Sample Size Considerations:

Sample size is based on clinical considerations. Thirty Evaluable patients will be enrolled to receive neo-adjuvant treatment followed by surgery, and will provide a reasonably robust estimate and precision (95% CI) of the primary endpoint MPR rate. Table 8 (see Section 9.5) summarizes the 95% CI of MPR rate under different assumptions of MPR estimate. With 20% drop out rate, a total of 38 patients will be enrolled in this study.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BGB-A317	tislelizumab
BOR	best overall response
CC	colon cancer
CI	confidence interval
CL	clearance
CR	complete response
CT	computed tomography
CPI	checkpoint inhibitor
CRC	colorectal cancer
DCR	disease control rate
dMMR	mismatch repair deficient
DoR	duration of response
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture (system)
EFS	event-free survival
EOT	end of treatment
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HR	hazard ratio
ICF	informed consent form
ICI	immune checkpoint inhibitor
imAE	immune-mediated adverse event
IRC	Independent Review Committee
MedDRA	Medical Dictionary for Regulatory Activities
MMR	mismatch repair
MPR	major pathological response

Abbreviation	Definition
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability-high
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMPA	National Medical Products Administration
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
pCR	pathological complete response
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)
PR	partial response
R0	complete resection
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
TEF	treatment eligibility form
TMB	tumor mutational burden
TTR	time to response
ULN	upper limit of normal

1. INTRODUCTION AND RATIONALES

1.1. Background Information on Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

Colorectal cancer (CRC) is the fourth most common malignancy and the fifth leading cause of cancer death in China, with an estimation of 376.300 newly diagnosed cases and approximately 191.000 deaths in 2015 (Chen et al, 2016). Overall, the burden of CRC in China is relatively high. Moreover, the incidence of colorectal cancer continued to rise during the past 15 years (Zheng et al, 2018). Since 2004, the cancer screening programs promoted early detection and diagnosis of CRC. One mass screening study demonstrated that the detection ratios of localized CRCs were 17.4%, 23% and 25.9% for Stage I, Stage II and Stage III respectively (Lin et al, 2019). The invasive cancers were found in the majority of new diagnosed CRCs.

Microsatellite instability (MSI) is characterized by alterations in the genome-wide microsatellite repeats, consisting of repeated sequences of 1 to 6 nucleotides (Yamamoto et al, 2020; Li et al, 2020). It is a molecular tumor phenotype resulting from genomic hypermutability. The gain or loss of nucleotides from microsatellite tracts - DNA elements composed of short repeating motifs - is the diagnostic hallmark of MSI (De la Chapelle et al, 2010). These changes can arise from impairments in the mismatch repair (MMR) system (Vilar et al, 2010; Oki et al, 1999).

On the basis of mutation patterns, CRC can be categorized into two discrete groups: tumors that are a mismatch- repair-deficient (dMMR)or have high levels of microsatellite instability (MSI-H) (termed dMMR/MSI- H tumors) signature and high overall mutation burden and tumors that have a mismatch- repair-proficient (pMMR) and are microsatellite- stable (MSS) or have low levels of microsatellite instability (MSI- L) (termed pMMR/MSI-L tumors) signature with a much lower mutation burden(Cancer Genome Atlas Network, 2012). Importantly, MSI-H/dMMR tumors lead to a high tumor mutational burden, with highly immunogenic neoantigens arising from frameshift mutations. As a consequence, tumors of this subgroup are highly infiltrated by cytotoxic T lymphocytes in comparison with other CRCs (Llosa et al, 2015; Marisa et al, 2018; Rosenbaum et al, 2016; Maby et al, 2015).

Approximately 15-20% of all CRCs are MSI-H/dMMR. Germline mutations in MMR genes are found in patients with Lynch syndrome which is responsible for 2%-4% of colon cancer (CC) cases. Somatic defects in MMR gene function were reported occur in approximately 19% of colorectal tumors (NCCN Guidelines, 2021). MSI-H/dMMR is more common in localized cancer (10–15% compared to 5% of metastatic CRC) (Andréet al, 2015 ; Chalabi et al, 2020) and Stage II disease may have higher MSI-H frequency than Stage III disease (22% vs. 12%) (Roth et al, 2010).

The presence of MSI-H/dMMR disease is prognostic, as Stage II MSI-H/dMMR tumors have a lower risk of recurrence than Stage II pMMR/MSI- L tumors (Popat et al, 2005). So MSI-H/dMMR status has been used in the adjuvant setting as a positive prognostic parameter and it is also used for therapeutic management because fluoropyrimidines alone are not indicated in the adjuvant setting for patients with Stage II MSI-H/dMMR CRC, given their favorable survival and the lack of impact of chemotherapy in this situation (Ribic et al, 2003; Sargent et al, 2010). In contrast, patients with MSI-H/dMMR tumors that metastasize have a dismal prognosis (Venderbosch et al, 2014), but expression of programmed cell death protein-1 (PD-1),

programmed cell death protein-1 (PD-L1) and CTLA-4 is substantially upregulated in their cancers (Llosa et al, 2015). These observations suggested that MSI-H/dMMR CRCs might respond well to immune checkpoint blockade.

1.2. Current Treatment of Resectable Stage II and III Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer and Unmet Clinical Needs

Currently, for patients with resectable Stage II-III CC, resection is the recommended modality, which includes laparoscopic and conventional colectomy with en bloc removal of the regional lymph nodes. Post-surgery, adjuvant therapy with a fluoropyrimidine alone is the standard of care for Stage II CC harboring high-risk features. High-risk assessment should consider the potential risks of therapy compared to potential benefit including number of lymph nodes analyzed (less than 12), poor prognostic features (poor differentiation [exclusive of those that are MSI-H], lymphatic or venous invasion, perineural invasion, obstruction and perforation, positive margins) and other comorbidities and anticipated life expectancy. For Stage III diseases, combination therapy with fluoropyrimidine and oxaliplatin for 3–6 months is recommended as adjuvant therapy (Sobrero et al, 2020; Grothey et al, 2018; Iveson et al, 2019; NCCN Guidelines, 2021). For patients with resectable Stage II-III rectal cancer, preoperative chemoradiation followed by radical surgery is recommended by International treatment guidelines (NCCN Guidelines, 2021).

Data on neo-adjuvant chemotherapy in CCs are limited. The phase 3 FOxTROT study (NCT00647530) provided useful data about such strategies for CC patients (Seymour et al, 2019). In this randomized trial, 1052 patients with localized CC were randomized to a perioperative sequence (6 weeks of FOLFOX, then surgery, then 18 weeks of FOLFOX) or the standard strategy (surgery then 24 weeks of FOLFOX). Neo-adjuvant treatment was well tolerated and associated with evidence of histological regression in 59% of patients (4% of pathological complete response [pCR]), histological downstaging and reduced rate of incomplete resections (5% vs. 10%). In this study a trend toward improved survival was found in patients receiving neo-adjuvant chemotherapy. Importantly, FOXTROT was the first study to show that pathological response to neo-adjuvant treatment in CCs is closely related to recurrence risk, with 0% and 8% recurrences in patients with a pCR and marked regression, respectively, compared with 26% for patients with no regression. Based on these study results, the option for neo-adjuvant therapy with FOLFOX and CAPEOX was added to the NCCN guidelines for the treatment of CC. Furthermore, important data from the FOxTROT study relating to the MMR status was reported: 95% of patients with dMMR tumors who received neo-adjuvant chemotherapy (n = 106) showed little or no response, and only 8.1% of patients with pMMR tumors (n = 592) had major pathological responses (MPRs) to neo-adjuvant chemotherapy.

With the knowledge of the immunogenic microenvironment in MSI-H/dMMR tumor, several clinical trials have demonstrated improved outcomes for patients with MSI-H/dMMR in metastatic CRC treated with inhibitors of PD-1(Le et al, 2016; Overman et al, 2017; Overman et al, 2018; Andre et al, 2018; Lenz et al, 2018). With these results, FDA granted approval for the PD-1 blocking antibodies, pembrolizumab and nivolumab for the indication of MSI-H/dMMR metastatic CRC, respectively.

After these initial successes with MSI-H/dMMR CRC in metastatic setting, the development of immune checkpoint inhibitors (ICI) for early-stage colorectal cancer specially as neo-adjuvant treatment also has demonstrated impressive tumor response. In the NICHE study, patients with early-stage CC received a neo-adjuvant treatment with ipilimumab plus nivolumab before surgery(Chalabi et al, 2020). Strikingly, total all 21 dMMR CC patients had a pathological response, with 95% of MPRs (≤10% of residual viable tumor in the surgical specimen), including 12 (60%) of pCRs. With a median follow-up of 8.1 months, all dMMR CC patients from the NICHE study were alive and disease free. The treatment was well tolerated, and only 5 patients (13%) who experienced Grade 3 or 4 treatment-related toxicity.

Although MSI-H/dMMR is a favorable prognostic feature in localized (Stage I–III) CCs, T4 stage and N2 stage are currently the best-known prognosticators for the MSI-H/dMMR population (Sinicrope et al, 2019; Sinicrope et al, 2013). In this population, the 3 -year disease-free survival rates are approximately 60–65% for T4 and/or N2 Stage III tumors, compared to 90% for low-risk MSI-H/dMMR Stage III CC patients. There is an urgent need for therapeutic improvements for patients with high-risk Stage III MSI-H/dMMR CC. Furthermore, pathological response (pCR and marked regression) to neo-adjuvant treatment in CCs is closely related to recurrence risk. The neo-adjuvant treatment may improve disease-free survival by reducing primary tumor burden before surgery. However, the clinical research of immune checkpoint inhibitors (ICI) for early-stage colorectal cancer was scarce in China.

In summary, for early-stage MSI-H/dMMR CRCs, identifying patients who are at risk of disease recurrence, providing appropriate neo-adjuvant treatment with immune checkpoint inhibitors (ICI) and refining therapeutic strategies, are urgently unmet needs to improve the prognostication of MSI-H/dMMR CRC patients.

1.3. Background Information on Tislelizumab

1.3.1. Pharmacology

Tislelizumab is a humanized, immunoglobulin G4 (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 as well as high affinity ([K_D] = 0.15 nM). It competitively blocks binding efforts by both PD-L1 and programmed cell death protein ligand-2 (PD-L2), thus inhibiting PD-1-mediated negative signaling in T cells. In in vitro cell-based assays, tislelizumab was observed to consistently and dose-dependently enhance the functional activity of human T cells and to preactivated, primary peripheral blood mononuclear cells (PBMCs). In addition, tislelizumab has demonstrated antitumor activity in several allogeneic xenograft models, in which peripheral blood mononuclear cells were coinjected 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 ADCC, antibody-dependent cellular phagocytosis (ADCP) or complement-dependent cytotoxicity (CDC) effects in humans (Labrijn et al, 2009; Zhang et al, 2018). Tislelizumab was specifically engineered to abrogate these potential mechanisms of T-cell CL and potential resistance to anti-PD-1 therapy.

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

1.3.2. 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. The tissue cross-reactivity was evaluated in the normal frozen tissues from both humans and monkeys. The cytokine release assays were also evaluated using fresh human peripheral blood mononuclear cells. The pivotal toxicology studies were conducted following GLP regulations. The single dosing regimens spanned from the intended human doses to 10-fold higher than the maximum of the intended human doses, and the repeat dosing regimens spanned to 3-fold higher than the maximum of the intended human doses. The cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

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 no-observed-adverse-effect-level (NOAEL) of tislelizumab in the 13-week monkey toxicity study was considered to be 30 mg/kg. The safety profile of tislelizumab is considered adequate to support the current study, BGB-A317-214.

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

1.3.3. Clinical Pharmacology

Based on pooled data from 2596 patients across 12 clinical studies, the pharmacokinetic (PK) of tislelizumab was best characterized using a 3-compartmental linear population PK model with linear clearance mechanisms. No time-varying clearance was observed in tislelizumab PK. The C_{max} and AUC increased in a nearly dose-proportional manner from 0.5 to 10 mg/kg. The terminal $t_{1/2}$ was estimated to be approximately 23.8 days, and the steady state is expected to be reached in 12 weeks. Tislelizumab PK was generally similar between Chinese patients and patients of other ethnic groups and across tumor types. Please refer to the Tislelizumab Investigator's Brochure for more detailed information on the clinical pharmacology of tislelizumab.

1.3.4. Prior Clinical Experience of Tislelizumab

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

1.3.4.1. Pooled Safety Assessment of Monotherapy Studies

As of 20 May 2021, there were 2150 patients in the pooled monotherapy studies: 1992 patients treated in 7 solid tumor studies and 158 patients treated in 3 hematologic malignancy studies.

Solid tumor studies included the following: BGB-A317_Study_001 (Phase 1a/1b advanced solid tumors), BGB-A317-102 (Phase 1/2 advanced solid tumors), BGB-A317-204 (Phase 2 locally advanced or metastatic urothelial bladder cancer), BGB-A317-208 (Phase 2 previously-treated unresectable hepatocellular carcinoma [HCC]), BGB-A317-209 (Phase 2 previously-treated locally advanced unresectable or metastatic MSI-H or mismatch repair deficient [dMMR] solid tumors), BGB-A317-302 (Phase 3 advanced unresectable/metastatic esophageal squamous cell carcinoma), and BGB-A317-303 (Phase 3 non-small cell lung cancer [NSCLC]).

A pooled monotherapy analysis in solid tumor was conducted to provide a comprehensive review of the tislelizumab safety profile. Patients included in this analysis (N = 1992) had a median age of 60.0 years with 72.1% of them being male. Median treatment exposure duration was 4.1 months (range: 0.1 to 41.5), and median study follow-up duration was 11.5 months (range: 0.1 to 58.9).

1.3.4.1.1. Pooled Demographics and Baseline Characteristics

Table 1 shows the demographics and baseline characteristics for the patients with solid tumors treated in the pooled monotherapy studies.

Table 1: Demographics, Baseline Characteristics, Treatment Exposure Duration, and Study Follow-up Duration in Pooled Monotherapy Studies

	Solid Tumor Studies[a] (N = 1992)
Age (Years)	
Median	60.0
Min, Max	18, 90
Sex, n(%)	
Male	1437 (72.1)
Female	555 (27.9)
Race, n(%)	
White	532 (26.7)
Asian	1383 (69.4)
Other	55 (2.8)
Missing	22 (1.1)
Time Since Diagnosis (Years)	
Median	1.255
Min, Max	0.02, 40.96
Baseline ECOG Performance Status, n(%)	
0	654 (32.8)
1	1338 (67.2)
2	0 (0.0)
Missing	0 (0.0)
Prior Systemic Anticancer Therapy Regimens[b]	
Median	1.0
Min, Max	0, 12
Prior Systemic Anticancer Therapy Regimens[b] (Grouped), n(%)	
0	318 (16.0)
1	1055 (53.0)
2	393 (19.7)

	Solid Tumor Studies[a] (N = 1992)
>=3	226 (11.3)
Treatment Exposure Duration for Tislelizumab (Months)	
Median	4.070
Min, Max	0.10, 41.46
Study Follow-up Duration (Months)	
Median	11.530
Min, Max	0.07, 58.91

Source: Tislelizumab Investigator's Brochure.
Abbreviations: Max, maximum; Min, minimum; N, total number of patients treated; n, number of patients within each category.
[a] Solid Tumor Studies include: BGB-A317_Study_001, BGB-A317-102, BGB-A317-204, BGB-A317-208, BGB-A317-209, BGB-A317-302, and BGB-A317-303.
[b] Only systemic therapies were selected.
Patients from the chemotherapy control arm were not included in studies BGB-A317-302 and BGB-A317-303.

The patients in the solid tumor group of pooled monotherapy studies had a median treatment exposure duration of 4.07 months (range: 0.10 to 41.46) and median study follow-up duration of 11.53 months (range: 0.07 to 58.91). The median age of the patients was 60 years and 72.1% were male. These patients had a median of 1.0 prior systemic anticancer therapy regimens (range: 0 to 12), and their most common tumor types were NSCLC (639 of 1992 patients, 32.1%), esophageal squamous cell carcinoma (15.9%), HCC (15.9%), urothelial bladder cancer (5.7%), and colorectal cancer (5.2%).

1.3.4.1.2. Treatment-Related Treatment-Emergent Adverse Events

Of the 1992 patients with solid tumors treated with tislelizumab monotherapy, 1391 (69.8%) experienced ≥ 1 treatment-related TEAE. The most commonly occurring TEAEs (≥ 5% of patients) assessed as related to tislelizumab irrespective of grade were aspartate aminotransferase (AST) increased (250 patients, 12.6%), alanine aminotransferase (ALT) increased (242 patients, 12.1%), hypothyroidism (197 patients, 9.9%), anaemia (186 patients, 9.3%), rash (159 patients, 8.0%), pruritus (142 patients, 7.1%), fatigue (138 patients, 6.9%), decreased appetite (115 patients, 5.8%), blood bilirubin increased (111 patients, 5.6%), and diarrhoea (103 patients, 5.2%).

Two hundred sixty-nine patients (13.5%) experienced at least 1 ≥ Grade 3 TEAE assessed as related to tislelizumab. The most frequent ≥ Grade 3 TEAEs that occurred in ≥ 1% of the patients were AST increased (25 patients, 1.3%) and ALT increased and anaemia (20 patients each, 1.0%).

1.3.4.1.3. Treatment-Emergent Serious Adverse Events

Of the 1992 patients with solid tumors treated with tislelizumab monotherapy, 706 patients (35.4%) experienced ≥ 1 treatment-emergent SAE. The most commonly occurring treatment-emergent SAEs (irrespective of relationship to study drug) were pneumonia (95 patients, 4.8%), pneumonitis (33 patients, 1.7%), dysphagia (23 patients, 1.2%), and pleural effusion and pyrexia (20 patients each, 1.0%).

Two hundred and nine patients (10.5%) experienced ≥ 1 tislelizumab-related treatment-emergent SAE. The most common treatment-emergent SAEs deemed related to tislelizumab were

pneumonitis (31 patients, 1.6%). All other tislelizumab-related treatment-emergent SAEs occurred in less than 1% of patients.

1.3.4.1.4. Immune-Mediated Adverse Events

Anti-PD1 therapies are known to cause imAEs in some patients, and therefore imAEs have been defined as AEs of special interest (AESI) in tislelizumab clinical studies and as such are being reported expeditiously and they are being closely monitored.

ImAEs are consistent with an immune-mediated mechanism or immune-mediated component for which noninflammatory etiologies (eg, infection or tumor progression) have been ruled out. ImAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. There is a potential temporal relationship between the initiation of treatment with tislelizumab and onset of an imAE that spans several days to several months.

All imAEs presented here are assessed as related to study drug by the investigator and categorized by the Safety/Pharmacovigilance team of the sponsor. Certain imAEs have multiple Medical Dictionary for Regulatory Activities (MedDRA) terms associated with the same category. Special categories have been created to group patients experiencing these events.

All imAEs that occurred in ≥ 2 patients with solid tumor in the total pooled monotherapy studies are shown in Table 2.

Table 2: Adjudicated Immune-Mediated Adverse Events of Any Grade Occurring in ≥ 2 Patients in Pooled Monotherapy Studies

	Solid Tumor Studies[a] (N = 1912)	
Categories **Preferred Term**	**Any Grade** **n (%)**	**≥ Grade 3** **n (%)**
Patients with at Least One Immune-Mediated Adverse Event	286 (15.0)	73 (3.8)
Immune-Mediated Hypothyroidism	118 (6.2)	1 (0.1)
Hypothyroidism	115 (6.0)	1 (0.1)
Tri-iodothyronine free decreased	2 (0.1)	0 (0.0)
Primary hypothyroidism	1 (0.1)	0 (0.0)
Thyroxine free decreased	1 (0.1)	0 (0.0)
Tri-iodothyronine decreased	1 (0.1)	0 (0.0)
Immune-Mediated Pneumonitis	70 (3.7)	28 (1.5)
Pneumonitis	41 (2.1)	15 (0.8)
Immune-mediated lung disease	14 (0.7)	4 (0.2)
Interstitial lung disease	10 (0.5)	7 (0.4)
Pneumonia	5 (0.3)	1 (0.1)
Organising pneumonia	1 (0.1)	1 (0.1)
Immune-Mediated Hepatitis	34 (1.8)	19 (1.0)
Alanine aminotransferase increased	12 (0.6)	5 (0.3)
Aspartate aminotransferase increased	9 (0.5)	5 (0.3)
Hepatitis	8 (0.4)	5 (0.3)
Immune-mediated hepatitis	6 (0.3)	2 (0.1)
Liver injury	3 (0.2)	1 (0.1)
Hepatic cytolysis	2 (0.1)	2 (0.1)
Autoimmune hepatitis	1 (0.1)	0 (0.0)

	Solid Tumor Studies[a] (N = 1912)	
Categories **Preferred Term**	**Any Grade** **n (%)**	**≥ Grade 3** **n (%)**
Blood bilirubin increased	1 (0.1)	0 (0.0)
Gamma-glutamyltransferase increased	1 (0.1)	1 (0.1)
Hepatic failure	1 (0.1)	1 (0.1)
Transaminases increased	1 (0.1)	1 (0.1)
Immune-Mediated Skin Adverse Reaction	24 (1.3)	9 (0.5)
Rash	13 (0.7)	4 (0.2)
Drug eruption	4 (0.2)	2 (0.1)
Rash maculo-papular	2 (0.1)	2 (0.1)
Acute febrile neutrophilic dermatosis	1 (0.1)	0 (0.0)
Dermatitis	1 (0.1)	1 (0.1)
Erythema multiforme	1 (0.1)	0 (0.0)
Pruritus	1 (0.1)	0 (0.0)
Rash macular	1 (0.1)	1 (0.1)
Rash papular	1 (0.1)	1 (0.1)
Rash pruritic	1 (0.1)	0 (0.0)
Immune-Mediated Colitis	17 (0.9)	6 (0.3)
Colitis	8 (0.4)	3 (0.2)
Diarrhoea	8 (0.4)	3 (0.2)
Immune-mediated enterocolitis	2 (0.1)	1 (0.1)
Rectal haemorrhage	1 (0.1)	0 (0.0)
Immune-Mediated Myositis/Rhabdomyolysis	14 (0.7)	5 (0.3)
Blood creatine phosphokinase increased	7 (0.4)	2 (0.1)
Myositis	5 (0.3)	2 (0.1)
Immune-mediated myositis	3 (0.2)	2 (0.1)
Immune-Mediated Hyperthyroidism	12 (0.6)	1 (0.1)
Hyperthyroidism	12 (0.6)	1 (0.1)
Immune-Mediated Thyroiditis	7 (0.4)	0 (0.0)
Autoimmune thyroiditis	4 (0.2)	0 (0.0)
Thyroiditis	2 (0.1)	0 (0.0)
Thyroiditis subacute	1 (0.1)	0 (0.0)
Immune-Mediated Adrenal Insufficiency	6 (0.3)	1 (0.1)
Adrenal insufficiency	5 (0.3)	1 (0.1)
Glucocorticoid deficiency	1 (0.1)	0 (0.0)
Immune-Mediated Myocarditis	6 (0.3)	3 (0.2)
Immune-mediated myocarditis	3 (0.2)	3 (0.2)
Myocarditis	2 (0.1)	0 (0.0)
Autoimmune myocarditis	1 (0.1)	0 (0.0)
Immune-Mediated Nephritis And Renal Dysfunction	6 (0.3)	2 (0.1)
Renal failure	2 (0.1)	1 (0.1)
Blood creatinine increased	1 (0.1)	0 (0.0)
Immune-mediated nephritis	1 (0.1)	0 (0.0)
Nephritis	1 (0.1)	0 (0.0)
Renal impairment	1 (0.1)	1 (0.1)
Focal segmental glomerulosclerosis	0 (0.0)	0 (0.0)
Other Immune-Mediated Reactions	6 (0.3)	0 (0.0)

	Solid Tumor Studies[a] (N = 1912)	
Categories **Preferred Term**	**Any Grade** **n (%)**	**≥ Grade 3** **n (%)**
Arthritis	3 (0.2)	0 (0.0)
Immune-mediated arthritis	1 (0.1)	0 (0.0)
Pericarditis	1 (0.1)	0 (0.0)
Polymyalgia rheumatica	1 (0.1)	0 (0.0)

Source: Tislelizumab Investigator's Brochure.
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
A patient with multiple occurrences of an AE is counted only once. The number (percentage) for System Organ Class represents all counts of patients with relevant Preferred Terms in that class. All AEs are coded using MedDRA v24.0.
AEs with incidence ≥ 2 patients at category level in 'Any Grade' column of 'Solid Tumor Studies' are included in this table.
Sorted in descending order of the number of patients in System Organ Class then Preferred Terms in 'Solid Tumor Studies' column.
[a] Solid Tumor Studies include: BGB-A317_Study_001, BGB-A317-102, BGB-A317-204, BGB-A317-208, BGB-A317-302, and BGB-A317-303.
Patients from the chemotherapy control arm were not included in studies BGB-A317-302 and BGB-A317-303.

Of the 1912 patients with solid tumors included in the pooled analysis of imAEs, 286 patients (15.0%) experienced ≥ 1 imAE of any grade. The most commonly occurring imAEs of any grade were hypothyroidism (115 patients, 6.0%), pneumonitis (41 patients, 2.1%), immune-mediated lung disease (14 patients, 0.7%), rash (13 patients, 0.7%), and ALT increased and hyperthyroidism (12 patients each, 0.6%). Analysis of the patients with ≥ 1 imAE that was also ≥ Grade 3 in severity showed that 73 patients (3.8%) experienced such events. The most commonly occurring imAEs that were ≥ Grade 3 in severity were pneumonitis (15 patients, 0.8%) and interstitial lung disease (7 patients, 0.4%).

1.3.4.1.5. Infusion-Related Reactions

Infusion-related reactions, including high-grade hypersensitivity reactions, following administration of tislelizumab are uncommon. Of the 1992 patients treated with tislelizumab monotherapy, 58 patients (2.9%) experienced ≥ 1 infusion-related reaction of any grade. The most commonly occurring infusion-related reactions of any grade were infusion-related reactions (28 patients, 1.4%); pyrexia (17 patients, 0.9%); rash (5 patients, 0.3%); and hypotension, nausea (4 patients, 0.2%), and pruritus (3 patients, 0.2%). There were 5 patients (0.3%) with ≥ Grade 3 infusion-related reactions. The most common ≥ Grade 3 IRRs was infusion-related reaction (2 patients, 0.1%). All other ≥ Grade 3 IRRs occurred in single patients.

1.3.4.1.6. Fatal Adverse Events

A summary of the treatment-emergent fatal AEs that occurred in the pooled monotherapy studies in solid tumor are shown in Table 3.

Table 3: Treatment-Emergent Fatal Adverse Events Regardless of Causality in Pooled Monotherapy Studies

	Solid Tumor Studies[a] (N = 1992) n (%)
Patients with at Least One TEAE Leading to Death	141 (7.1)
General disorders and administration site conditions	38 (1.9)
Death	16 (0.8)
Multiple organ dysfunction syndrome	11 (0.6)
General physical health deterioration	10 (0.5)
Sudden death	1 (0.1)
Respiratory, thoracic and mediastinal disorders	32 (1.6)
Respiratory failure	10 (0.5)
Acute respiratory failure	3 (0.2)
Haemoptysis	2 (0.1)
Pleural effusion	2 (0.1)
Pneumonitis	2 (0.1)
Pulmonary embolism	2 (0.1)
Pulmonary haemorrhage	2 (0.1)
Bronchiectasis	1 (0.1)
Dyspnoea	1 (0.1)
Haemothorax	1 (0.1)
Lung disorder	1 (0.1)
Oesophagobronchial fistula	1 (0.1)
Pulmonary arterial hypertension	1 (0.1)
Pulmonary thrombosis	1 (0.1)
Respiratory arrest	1 (0.1)
Tracheal stenosis	1 (0.1)
Infections and infestations	20 (1.0)
Pneumonia	14 (0.7)
Sepsis	2 (0.1)
Abdominal infection	1 (0.1)
Bronchitis	1 (0.1)
Mediastinitis	1 (0.1)
Septic shock	1 (0.1)
Staphylococcal sepsis	0 (0.0)
Hepatobiliary disorders	15 (0.8)
Hepatic failure	10 (0.5)
Acute hepatic failure	2 (0.1)
Hepatic function abnormal	1 (0.1)
Hepatitis	1 (0.1)
Hepatorenal syndrome	1 (0.1)
Gastrointestinal disorders	14 (0.7)
Upper gastrointestinal haemorrhage	7 (0.4)
Ascites	2 (0.1)
Dysphagia	1 (0.1)
Ileus	1 (0.1)
Large intestinal obstruction	1 (0.1)

	Solid Tumor Studies[a] (N = 1992) n (%)
Oesophageal obstruction	1 (0.1)
Vomiting	1 (0.1)
Nervous system disorders	10 (0.5)
Cerebral infarction	2 (0.1)
Hepatic encephalopathy	2 (0.1)
Brain oedema	1 (0.1)
Cerebral artery embolism	1 (0.1)
Cerebral artery occlusion	1 (0.1)
Cerebral haemorrhage	1 (0.1)
Depressed level of consciousness	1 (0.1)
Headache	1 (0.1)
Cardiac disorders	8 (0.4)
Acute myocardial infarction	2 (0.1)
Cardiac failure	1 (0.1)
Cardiac tamponade	1 (0.1)
Cardio-respiratory arrest	1 (0.1)
Cardiopulmonary failure	1 (0.1)
Myocardial ischaemia	1 (0.1)
Pericardial effusion	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.2)
Metastases to liver	1 (0.1)
Tumour fistulisation	1 (0.1)
Tumour haemorrhage	1 (0.1)
Tumour compression	0 (0.0)
Metabolism and nutrition disorders	2 (0.1)
Cachexia	1 (0.1)
Decreased appetite	1 (0.1)
Renal and urinary disorders	2 (0.1)
Renal failure	1 (0.1)
Renal impairment	1 (0.1)
Investigations	1 (0.1)
Platelet count decreased	1 (0.1)
Musculoskeletal and connective tissue disorders	1 (0.1)
Muscular weakness	1 (0.1)
Psychiatric disorders	1 (0.1)
Depression	1 (0.1)
Vascular disorders	1 (0.1)
Shock haemorrhagic	1 (0.1)
Arterial haemorrhage	0 (0.0)

Source: Tislelizumab Investigator's Brochure.
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
A patient with multiple occurrences of an AE is counted only once. The number (percentage) for System Organ Class represents all counts of patients with relevant Preferred Terms in that class. All AEs are coded using MedDRA v24.0.
Sorted in descending order of the number of patients in System Organ Class then Preferred Terms in 'Solid Tumor Studies' column.

[a] Solid Tumor Studies include: BGB-A317_Study_001, BGB-A317-102, BGB-A317-204, BGB-A317-208, BGB-A317-209, BGB-A317-302, and BGB-A317-303.

Of 1992 patients in the solid tumor group of pooled monotherapy studies, 163 (8.2%) died ≤ 30 days after their last dose of tislelizumab. The causes of death for these patients were adverse events (54 patients, 2.7%), disease under study (52 patients, 2.6%), disease progression (50 patients, 2.5%), and other (7 patients, 0.4%).

1.3.4.2. Efficacy Assessment of Tislelizumab

On 11 March 2022, tislelizumab monotherapy in MSI-H/dMMR metastatic solid tumor was approved under conditional approval by the China National Medical Products Administration (NMPA) based on the result of Study BGB-A317-209.

BGB-A317-209 is a single-arm, multi-center, open-label, Phase 2 study to evaluate the efficacy and safety of tislelizumab (BGB-A317), an anti-PD-1 monoclonal antibody, as monotherapy in patients with previously-treated locally advanced unresectable or metastatic MSI-H or dMMR solid tumors. The primary efficacy endpoint of the study is objective response rate (ORR) as assessed by the Independent Review Committee (IRC) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

As of 08 July 2021, 80 patients were enrolled (median age 53 years; range: 19-81 years) and received at least one dose of tislelizumab. Most patients had metastatic disease (98.8%), and the majority of patients had CRC (61.3%). Of the 75 patients in the Efficacy Analysis Set, ORR_{IRC} was 46.7% (n = 35; 95% confidence interval [CI] 35.1 to 58.6) in all tumor types (1-sided $p < 0.0001$), including 5 complete responses (CR) and 30 partial responses (PR). ORR_{IRC} was 39.1% (n = 18; 95% CI 25.1 to 54.6) in colorectal cancer (CRC) patients (N = 46), 55.6% (n = 5; 95% CI 21.2 to 86.3) in gastric or gastroesophageal junction cancer patients (N = 9), and 60.0% (n = 12; 95% CI 36.1 to 80.9) in other patients (N =20). Median duration of response (DoR) was not reached, median time to response $(TTR)_{IRC}$ was 11.9 weeks (range: 8.4-98.9 weeks) and disease control rate (DCR) was 72.0% (95% CI 60.4 to 81.8). Median PFS_{IRC} was not reached (95% CI 7.5 months to not estimable [NE]). Median overall survival (OS) in safety analysis set was not reached (95% CI 28.7 months to NE)(Li et al, 2022).

1.4. Study Rationales

1.4.1. Rationale for Tislelizumab as Neo-adjuvant Treatment of Resectable Microsatellite Instability-High or Mismatch Repair Deficient CRC

The promising antitumor activity of anti-PD-1 antibodies reported for metastatic and localized MSI-H/dMMR CRC (see section 1.2).These outcomes have been attributed to the higher mutational burden of dMMR tumors, particularly the accumulation of insertions–deletions (indels), giving rise to more neoantigens (Overman et al, 2018; Overman et al, 2017; Diaz et al, 2015; Germano et al, 2017; Mandal et al, 2019). Possibly as a result of their higher neoantigen burden, dMMR tumors are also characterized by an increased density of intratumoral T cells (Fabrizio et al, 2018; Maby et al, 2015).

With mass screening, more CRCs were diagnosed at their early-stage and MSI-H is more common (10–15%) in early stage CRCs compared to metastatic CRC (see Section 1.1). Treating

with immune checkpoint inhibitors (ICI) have showed higher response rates in early-stage disease compared with metastatic disease. That may be attributed to a difference in T cell infiltration (TCI), a lower degree of systemic immune suppression, the absence of visceral metastases and a lower tumor burden (Blank et al, 2018; Forde et al, 2018). These biological features suggested that early stage MSI-H/dMMR CRCs might respond well to immune checkpoint blockade.

Furthermore neoadjuvant therapeutic strategies have been successful in many gastro-intestinal cancer locations and the pathological response (pCR and marked regression) to neoadjuvant treatment in CCs is closely related to recurrence risk (see Section 1.2) and may improve long-term benefit. However according to FOxTROT study, the presence of MSI-H/dMMR disease demonstrated the lack of impact of chemotherapy (see Section 1.2).

Preliminary data from the ongoing Phase 1 and Phase 2 studies show that tislelizumab has been well tolerated in patients with advanced tumors in multiple solid and hematological malignancies. The safety profile for single-agent tislelizumab is similar to those observed in other PD-1 inhibitors (Tislelizumab Investigator's Brochure).

Tislelizumab has been approved in China for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma, for the treatment of patients with pretreated locally advanced or metastatic urothelial carcinoma with PD-L1 high expression and in combination with Paclitaxel and Carboplatin as first-line treatment in patients with locally advanced or metastatic squamous NSCLC. Tislelizumab is also being investigated for the treatment of patients with advanced cancers, including, but not limited to, NSCLC, esophageal carcinoma, gastric cancer, HCC, and MSI-H/dMMR metastatic solid tumor (Tislelizumab Investigator's Brochure).

This study is a window of opportunity design, in which patients receive Tislelizumab as neo-adjuvant therapy between their cancer diagnosis and standard treatment (surgery). Patients are CRC treatment naïve. Tumor biopsies before and after the investigational treatment are collected for translational research. This study design can enable detailed characteristics of the pharmacodynamic effects of Tislelizumab and the tumor biology. It offers a unique opportunity to study pharmacodynamic response in the setting of a tumor unperturbed by prior therapy and may improve the understanding of pharmacodynamic parameters and help to identify biomarkers for better patient selection.

Given the promising antitumor activity of anti-PD-1 antibodies reported for metastatic and localized MSI-H/dMMR CRC and the biological features of localized MSI-H/dMMR CRC, Tislelizumab, an efficient PD-1 inhibitor as neo-adjuvant treatment for resectable MSI-H/dMMR CRC may bring clinical benefit and warrants further clinical development.

1.4.2. Rationale for Selection of Tislelizumab Dose and Treatment Duration

The clinical fixed dose of 200 mg intravenously once every 3 weeks was selected based on comparable safety and efficacy profiles between 2 and 5 mg/kg in BGB-A317_Study_001:

- 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. Additionally, PK data also shows no relationship between exposure and treatment-emergent imAEs (Wu et al, 2019a; Wu et al, 2019b).

- Confirmed response rates in patients treated with tislelizumab on a once every 3 weeks schedule were favorable compared to those treated on a once every 2 weeks schedule. While there are differences in response rates between dose levels, this is more likely a reflection of small sample size and patient heterogeneity than dose response.
- Clearance of tislelizumab was not dependent on body weight, and the observed serum exposure of a 200 mg dose fell between serum exposure observed after 2 mg/kg and 5 mg/kg doses. Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg once every 3 weeks.
- Exposure-response analysis indicated that there was a lack of clinically significant exposure-response relationships for ORR and safety endpoints across a variety of advanced solid tumors and classical Hodgkin lymphoma for tislelizumab. These findings support 200 mg once every 3 weeks dose regimen for pivotal studies.

In conclusion, the observed clinical activity in patients with advanced tumors, coupled with a manageable safety profile and supportive data, support the proposed tislelizumab dose of 200 mg intravenously once every 3 weeks as the recommended dose for pivotal studies, please refer to the Tislelizumab Investigator's Brochure.

Three-cycle neo-adjuvant treatment (9 weeks) with tislelizumab is selected as planned treatment duration. That is considering the minimum time to have treatment response with ICI therapy and to avoid potential surgery delay.

1.4.3. Biomarker Strategy Rationale

Biomarker analyses will be performed to explore the association of biomarkers with patient prognosis, response, and potential resistance to tislelizumab as neo-adjuvant treatment.

A number of biomarkers have been identified that correspond with response to immunotherapy for patients with dMMR CRC in the neo-adjuvant setting by the Niche study (Chalabi et al, 2020).

The NICHE study reports potentially predictive biomarkers as well as pharmacodynamic biomarkers (post-treatment versus pre-treatment) for response monitoring.

For potentially predictive biomarkers: Tumor infiltrated immune cell analysis using multiplex immunofluorescence have demonstrated the capability of immune cell infiltration in predicting response or resistance to anti-PD-1 therapies. PD-L1 expression, TMB and GEP (various signatures) have been reported to be correlated to the response to anti-PD-1 therapies(Miller et al, 2019; Keung et al, 2020; Cristescu R et al, 2019; Marabelle A et al, 2020). No clear conclusions could be derived from these biomarkers in NICHE study due to the limited number of patients Considering the limited number of patients, the role of these biomarkers in predicting response to tislelizumab as neo-adjuvant therapy warrants further exploration. Apart from their potential predictive value, GEP and TMB panels can be designed to explore underlying resistance mechanism to guide potential combination strategies. In summary, the role of immune cell infiltration, PD-L1 expression, TMB/DNA mutation and GEP in predicting response/resistance to tislelizumab as neo-adjuvant treatment will be investigated.

For pharmacodynamic biomarkers (post-treatment versus pre-treatment) for response monitoring: In NICHE study, enhanced $CD8^+$ T cell infiltration and IFNγ score (pooled from the GEP panel) were observed post treatment in dMMR CRC patients, indicating the potential role of immune cell infiltration and GEP in identifying pharmacodynamic biomarkers for response monitoring. The pharmacodynamic change of PD-L1 expression and TMB/DNA mutation were not reported by the Niche study, and their role as pharmacodynamic biomarkers can be further explored.

Consequently, immune cell infiltration, PD-L1, TMB/DNA mutation and GEP can be explored in paired tumor samples (pre-treatment and post-treatment) to identify their potential predictive value, their potential role in response monitoring, as well as resistance mechanisms in patients who receive tislelizumab as neo-adjuvant therapy in MSI-H/dMMR CRC patients.

1.5. Benefit-Risk Assessment

The promising antitumor activity of anti-PD-1 antibodies in treating MSI-H/dMMR CRC was reported (see Section 1.2). These outcomes have been attributed to the higher mutational burden and more neoantigens of dMMR tumors (see Section 1.4.1). Possibly as a result of their higher neo-antigen burden, dMMR tumors are also characterized by an increased density of intratumoral T cells. MSI-H/dMMR is more common in localized cancer (10–15% compared to 5% of metastatic CRC) (see Section 1.1). Treatment with ICIs has shown higher response rates in early-stage disease compared with metastatic disease. This has been attributed to a difference in TCI, a lower degree of systemic immune suppression, the absence of visceral metastases and a lower tumor burden (see Section 1.4.1)

MSI-H/dMMR CRC has a favorable prognostic feature in localized (Stage I–III) disease. However, there is still an unmet need for therapeutic improvements for patients with high-risk early-stage MSI-H/dMMR CRC (see Section 1.2).

Furthermore, neo-adjuvant therapeutic strategies have been successful in many gastro-intestinal cancer locations and the pathological response (pCR and marked regression) to neo-adjuvant treatment in CCs is closely related to recurrence risk (Seymour et al, 2019). This treatment strategy for early-stage MSI-H/dMMR CRCs may improve long-term benefit. In China, the clinical research of ICI for early-stage CRC was scarce.

Preliminary data from the ongoing Phase 1 and Phase 2 studies show that tislelizumab has been well tolerated in patients with advanced tumors in multiple solid and hematological malignancies. The safety profile for single-agent tislelizumab is similar to that observed in other PD-1 inhibitors. Two pivotal Phase 2 studies demonstrated clinical meaningful benefit. The initial data collected in other studies suggest that tislelizumab can result in antitumor activity across a variety of tumor types. Antitumor activity has been observed across the dose ranges evaluated in patients. Therefore, the benefit-risk profile for tislelizumab monotherapy appears to be favorable in oncology population based on preliminary efficacy and safety data Tislelizumab Investigator's Brochure.

In summary, for early-stage MSI-H/dMMR CRCs, identifying patients who are at risk of disease recurrence, providing neo-adjuvant treatment with ICIs and refine therapeutic strategies for early-stage MSI-H/dMMR CRCs, is an urgent unmet need. Given the promising antitumor activity of anti-PD-1 antibodies reported for metastatic and localized MSI-H/dMMR CRC, the biological features of localized MSI-H/dMMR CRC, introducing tislelizumab, an PD-1 inhibitor as neo-adjuvant treatment for resectable MSI-H/dMMR CRC may bring clinical benefit and warrants further research.

1.6. Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and in accordance with Good Clinical Practice (GCP) standards.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- To evaluate major pathological response (MPR) rate in patients receiving tislelizumab as neo-adjuvant treatment.

2.1.2. Secondary Objectives

- To evaluate pathological complete response (pCR) rate in patients receiving tislelizumab as neo-adjuvant treatment.
- To evaluate event-free survival (EFS) in patients receiving tislelizumab as neo-adjuvant treatment
- To explore potential biomarkers that may correlate with clinical responses/resistance to tislelizumab as neo-adjuvant treatment.
- To evaluate the safety and tolerability of neo-adjuvant treatment with tislelizumab in patients with early-stage (Stage II-III) Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) colorectal cancer

2.1.3. Exploratory Objectives

- To evaluate R0 resection rate in patients receiving tislelizumab as neo-adjuvant treatment
- To evaluate perioperative events (including but not limited to treatment related surgery delay, postoperative complication) in patients receiving tislelizumab as neo-adjuvant treatment.

2.2. Study Endpoints

2.2.1. Primary Endpoint

- MPR rate is defined as the proportion of patients in the EAS with ≤ 10% residual viable tumor in the resected primary tumor after completion of neo-adjuvant therapy.

2.2.2. Secondary Endpoints

- The pCR rate is defined as the proportion of patients in the EAS with absence of residual tumor in the resected primary tumor and all resected lymph nodes after completion of neo-adjuvant therapy.
- EFS is defined as the time from first dose until any of the following events, whichever occurs first: radiographic disease progression according to RECIST v1.1, local or distant recurrence, or death due to any cause in the EAS. The 2-year/3-year EFS rate is defined as the proportion of patients free from EFS events at 2 years and 3 years as estimated using the Kaplan-Meier method.

- Potential biomarkers including immune cell infiltration, PD-L1 expression, tumor mutational burden (TMB) and DNA mutation, gene expression profile (GEP) and the association of biomarkers with disease status, response/resistance to tislelizumab as neo-adjuvant treatment.
- Incidence and severity of TEAEs, including serious adverse events and imAEs, with severity determined according to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) in the safety analysis set (SAS).

2.2.3. Exploratory Endpoints

- Complete resection (R0) rate – defined as the proportion of patients with R0 resection.
- To evaluate perioperative events (including but not limited to treatment-related surgery delay, postoperative complication) in patients receiving tislelizumab as neo-adjuvant treatment.

3. STUDY DESIGN

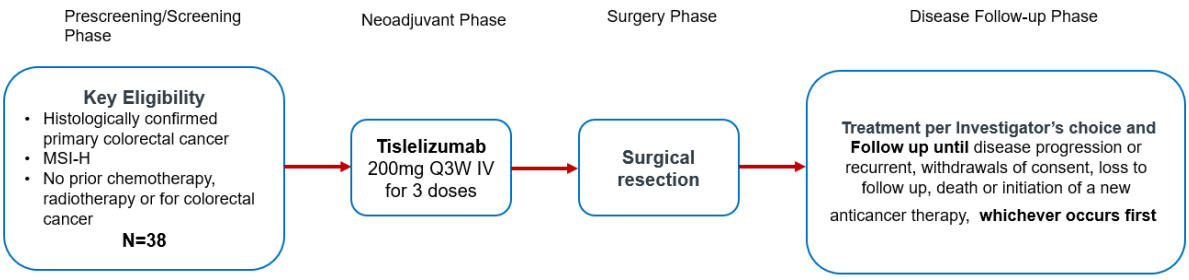
3.1. Summary of Study Design

This is an open-label, multicenter Phase 2 study designed to investigate the preliminary efficacy and safety of tislelizumab monotherapy as neo-adjuvant treatment in approximately 38 patients with early-stage (Stage II-III) MSI-H or dMMR CRC.

The study consists of a screening phase (and/or prescreening phase), a treatment phase that includes a neo-adjuvant phase, surgery, and a disease follow-up phase.

The study schema is presented in Figure 1.

Figure 1: Study Schema



Abbreviations: MSI-H, microsatellite instability-high; IV, intravenously; N, number of patients; Q3W, once every 3 weeks.

For all study procedures see Section 7 and Appendix 1.

3.2. Prescreening Period

Patients with unknown MSI and MMR status are required to provide blood and tumor tissues for central laboratory confirmation of MSI status during the prescreening period (defined as within 56 days prior to the first dose of the study drug). A separate prescreening informed consent must be obtained. Refer to Section 7.1 and Section 7.7 for details.

3.3. Screening Period

Screening evaluations will be performed within 28 days before first dose. Patients who agree to participate in this study will sign the informed consent form (ICF) before undergoing any screening procedure. Patients who are suspected to have a serious respiratory concurrent illness or who exhibit significant respiratory symptoms unrelated to the underlying cancer will also take a pulmonary function test (refer to Section 7.2.4 and Appendix 1 for details). Screening evaluations may be repeated as needed within the screening period; the investigator will assess preliminary patient eligibility according to the latest screening assessment results.

Archival tumor tissue must be collected for the purpose of biomarker analysis. In the absence of archival tumor tissues, a fresh tumor biopsy at baseline is mandatory (Section 7.7).

3.4. Treatment Period

Neo-adjuvant Phase:

After completing all screening activities, patients confirmed to be eligible by the investigator will receive tislelizumab 200 mg intravenously once every 3 weeks for 3 cycles.

During the neo-adjuvant phase, patients who are found to have disease progression at scheduled tumor assessments (before Cycle 3 and surgery) or at any time during neo-adjuvant treatment, and whose tumors are still deemed resectable and non-metastatic, will proceed to receive surgery if amenable and will remain eligible for all on-study evaluations based on investigator's judgement.

Patients who discontinue neo-adjuvant treatment early because of urgent surgery (eg., because of intestinal obstruction, intestinal perforation, or intestinal bleeding), disease progression or intolerable AEs and who do not proceed to have a complete resection will proceed to receive other treatment as determined by the investigator. Further in-clinic study procedures for these patients should be discussed with the medical monitor.

Surgery:

Upon completion of neo-adjuvant therapy, patients will undergo surgical resection of their tumor. Surgical specimens will be assessed for pathological response (MPR and pCR). In addition, exploratory biomarker analysis of surgical specimens (primary tumor tissue and dissected lymph nodes) will be performed.
Before surgery, tumor imaging and assessment will be performed within 9 weeks ±7 days after first dose, and the investigator will reassess the patient to reconfirm disease resectability. The surgical procedure should be performed within 10 weeks from the first administered dose of study treatment. If surgery cannot be performed within this time window (eg, because of a prolonged AE), the medical monitor should be consulted. The investigator and the medical monitor will determine the acceptable length of this time window. Complete resection (R0) should be performed.

Disease Follow-up Phase:

Patients will continue adjuvant treatment and perform follow-up which will be determined by the investigator according to the stage of disease and benefit-risk assessment in accordance with the relevant clinical practice (eg. Cancer NCCN guidelines, CSCO guideline). Patients will continue to undergo tumor assessments based on RECIST v1.1, which will be performed every 12 weeks (±14 days) for the first 3 years, and then every 24 weeks (±28 days) for a total of 5 years, and then once each year (± 28 days) thereafter. Patients will continue with the scheduled tumor assessments until the patient experiences disease progression or recurrence according to RECIST v 1.1, withdraws consent, is lost to follow up, death, begins a new anticancer therapy (excluding adjuvant therapy), or until the study terminates, whichever occurs first.

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per NCI-CTCAE v5.0) and laboratory results. Vital signs, physical examinations, ECOG PS change, electrocardiogram (ECG) results, and other examinations will also be used for safety assessment. Safety assessments are further detailed in Section 7.5 and in the Schedule of Assessments (Appendix 1).

3.5. End-of-Treatment/Safety Follow-up

The End-of-Treatment Visit (EOT)/Safety Follow-up will be conducted as follows:

EOT/ Safety Follow-up 1: Patients who received surgery will be asked to return to the clinic for the EOT/Safety Follow up Visit (to occur within 30 days [±7 days] after the surgery, or before the initiation of a new anticancer treatment, whichever occurs first).

EOT/ Safety Follow-up 2: Patients who discontinued pre-operative treatment for any reason and for whom surgery will not be conducted will be asked to return to the clinic for the EOT/Safety Follow-up Visit (to occur within 30 days [± 7 days] after the last dose of study treatment, or before the initiation of a new anticancer treatment, whichever occurs first).

If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT/Safety Follow-up visit, these tests need not be repeated. Tumor assessment is not required at the EOT/Safety Follow-up, and should follow the regular schedule of assessments as outlined in Section 7.6.

In addition, telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 days and 90 days (± 14 days) after the last dose of study drug, regardless of whether the patient starts a new anticancer therapy. If patients report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

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

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

3.6. Discontinuation From the Study Treatment or From the Study

3.6.1. Patient Discontinuation From Study Treatment

Patients have the right to withdraw from the study or to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue the study treatment for reasons other than disease progression should be followed for assessments of antitumor activity (Section 7.6) and safety (Section 7.5), if possible.

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

- Treatment Completed
- Disease progression
- AEs
- Patient decision
- Pregnancy

- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety, if he or she was to continue the study treatment.
- Use of any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other country) herbal medicine and Chinese (or other country) patent medicines] for the treatment of cancer) (Section 6.3).
- Patient noncompliance. Investigative site staff should first counsel patients who are significantly noncompliant (eg, missing 2 treatment cycles) on the importance of study drug compliance and drug accountability. The investigator may, in consultation with the medical monitor, discontinue patients from treatment if they are consistently noncompliant.

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

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

- Patient withdrawal of consent
- Death
- Lost to follow-up
- Patients have completed all study assessments

3.7. End of Study

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

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

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

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for an EOT 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 terminate study participation of an individual clinical study site at any time. The site will be informed of the decision in advance. Reasons for terminating a site's study participation may include but are not limited to the following:

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

4. STUDY POPULATION

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

4.1. Inclusion Criteria

Each patient eligible to participate in this study must 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 schedule of assessments.
2. Age ≥ 18 years on the day of signing the ICF.
3. ECOG PS of 0 or 1.
4. Pathologically (histologically) confirmed diagnosis of potentially resectable Stage II or Stage III (per the Eighth American Joint Committee on Cancer staging system for Colon/Rectal Cancer) CRC with MSI-H confirmed by sponsor-designated central laboratory or known MSI-H status by local laboratory. Patients should be eligible for an R0 resection with curative intent.
5. Evaluable or measurable disease as assessed by the investigator per RECIST v1.1.
6. With unknown MSI status by local laboratory, patients must provide blood (approximately 2 mL peripheral whole blood) and tumor tissues (archival formalin-fixed paraffin-embedded [FFPE] blocks or at least 10 freshly cut unstained slides) for central MSI confirmation. Patients must be able to provide paired tumor tissues (pretreatment and post-treatment tumor tissues as FFPE blocks or approximately 14 [≥ 10] freshly cut unstained slides) for retrospective analysis of other exploratory biomarkers related to response/resistance. A fresh biopsy is mandatory in the absence of pre-treatment archival tumor tissues.
7. Adequate organ function as indicated by the following clinical laboratory values (obtained within 7 days before first dose):
    a. Patients must not have required a blood transfusion or growth factor support ≤ 14 days before blood sample collection at screening for any of the following:
        i. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
        ii. Platelets ≥ 75 x 10^9/L
        iii. Hemoglobin ≥ 90 g/L or ≥ 5.6 mmol /L (Note: For patient with cancer-induced anemia, hemoglobin ≥ 80 g/L or 4.9 mmol/L is eligible with appropriate supportive care.)
        iv. International normalized ratio or prothrombin time ≤ 1.5 x upper limit of normal (ULN)
        v. Activated partial thromboplastin time ≤ 1.5 x ULN
    b. Serum creatinine ≤ 1.5 x ULN or estimated Glomerular Filtration Rate ≥ 60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation (Appendix 9).

c. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilbert's syndrome).

d. AST and ALT ≤ 2.5 x ULN.

8. Women of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study (see Appendix 8) and for ≥ 120 days after the last dose of study drugs, and have a negative urine or serum pregnancy test ≤ 7 days before first dose.

9. Nonsterile men must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of study drugs (see Appendix 8):

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

4.2. Exclusion Criteria

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

1. Any prior therapy for current CRC, including chemotherapy or radiotherapy or immunotherapy (including but not limited to interferons, interleukin-2, tumor necrosis factor interleukin, and thymosin).

2. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways.

3. History of severe hypersensitivity reactions to other humanized monoclonal antibodies.

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

5. 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.

6. Any condition that requires systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before first dose.

   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 non-autoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen).

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

8. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence within 14 days after intervention).

9. With history of interstitial lung disease, noninfectious pneumonitis or uncontrolled diseases including pulmonary fibrosis, acute lung diseases, hypertension, etc. Patients with significantly impaired pulmonary function or who require supplemental oxygen at baseline must undergo an assessment of pulmonary function at screening.

10. Infections (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal or antiviral therapy within 14 days before first dose.

    Note: Antiviral therapy is permitted for patients with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.

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

    Note: Inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Patients with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at screening should have been treated for > 14 days before first dose.

12. Patients with active hepatitis C.

    Note: Patients with a negative HCV antibody test at screening or positive HCV antibody test followed by a negative HCV RNA test at screening are eligible. The HCV RNA test will be performed only for patients testing positive for HCV antibody. Patients receiving antivirals at screening should have been treated for > 14 days before first dose.

13. A known history of HIV infection.

14. Any major surgical procedure requiring general anesthesia ≤ 28 days before first dose. Patients must have recovered adequately from the toxicity and/or complications from the intervention before first dose.

15. Prior allogeneic stem-cell transplantation or organ transplantation.
16. 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 first dose.
    b. Pulmonary embolism ≤ 28 days before first dose.
    c. Any history of acute myocardial infarction ≤ 6 months before first dose.
    d. Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 6) ≤ 6 months before first dose.
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before first dose.
    f. Any history of cerebrovascular accident ≤ 6 months before first dose.
    g. Uncontrolled hypertension that cannot be managed by standard antihypertension medications ≤ 28 days before first dose.
    h. Any episode of syncope or seizure ≤ 28 days before first dose.
17. Has received a live vaccine ≤ 4 weeks before first dose.

    Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
18. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug, or affect the explanation of drug toxicity or AEs, or result in insufficient or impaired compliance with study conduct.
19. Women who are pregnant or are breastfeeding.
20. 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.

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

Tislelizumab is a monoclonal antibody formulated for intravenous injection in a single-use vial (20R glass, United States Pharmacopeia [USP] Type I), containing a total of 100 mg of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in 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. Please also refer to the Tislelizumab Investigator's Brochure for other details regarding tislelizumab.

5.2. Dosage, Administration, and Compliance

Tislelizumab 200 mg will be administered on Day 1 of each 21-day cycle (once every 3 weeks) for 3 cycles before surgery.

Tislelizumab will be administered by intravenous infusion through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 60 minutes afterward in an area with resuscitation equipment and emergency agents. For Cycle 3, a ≥ 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

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

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of imAEs and infusion-related reactions are provided in detail in Section 8.7 and Appendix 7.

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

5.3. Surgery

A surgeon with experience in locally advanced resectable CRC should evaluate patients at screening to determine eligibility for surgical resection. Patients should be eligible for an R0 resection with curative intent at time of screening. Before surgery, the investigator will reassess the patient to reconfirm disease. The presurgical visit and associated assessments should occur

within 14 days of surgery and in accordance with local institutional practice. Pre-operative evaluation should be performed per local standard of care (including, but not limited to, blood tests, organ function tests [as indicated], and other evaluation procedures).

The surgical procedure should be performed in accordance with the relevant local guidance and/or clinical practice within 10 weeks after the first dose of neo-adjuvant study treatment as best as possible. If surgery cannot be performed within this time window (eg, because of a prolonged AE), the investigator and the medical monitor will determine the acceptable length of this time window.

The performed surgical procedure should be documented and reported in the eCRF. If, after neo-adjuvant treatment or during the operation, the surgeon determines that the patient should not proceed with the planned surgery, the reason should be documented and reported in the eCRF as well.

5.4. Incorrect Administration or Overdose

Any overdose of tislelizumab (defined as ≥ 600 mg in a 24-hour period) should be recorded in the patient's chart and on the appropriate eCRF. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration are required to be reported within 24 hours of awareness via the SAE reporting process as described Section 8.6. Supportive care measures should be administered as appropriate.

5.5. Investigational Medicinal Product Accountability

The investigational medicinal product required for completion of this study (tislelizumab) will be provided by the sponsor. The investigational site will acknowledge the receipt of the investigational medicinal product. Any damaged shipments will be replaced.

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

5.6. Dose Delay or Modification

Every effort should be made to administer the study drugs on the same day according to the planned dose and schedule. In the event of significant toxicities, dosing 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.

For AEs that are assessed as related to tislelizumab, the following general guidance should be followed unless otherwise specified:

- ≤ Grade 2: Maintain dose level.
- Grade 3: Omit dose until resolved to ≤ Grade 1 or baseline except for alopecia or AEs that, in the opinion of the investigator, are not considered a safety risk for the patient.

- Grade 4: Permanent discontinuation from study. Exceptions may be considered after consultation with the medical monitor.

5.6.1. Dose Interruptions or Delay for Study Drugs

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

Every effort should be made to administer the study drug according to the planned dose and schedule. In the event of significant toxicities, dosing may be delayed and/or interrupted based on the guidelines 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.

Tislelizumab treatment may be temporarily suspended if the patient experiences a toxicity that is considered related to tislelizumab and requires a dose to be withheld. Tislelizumab treatment should resume as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe). If the administration of study drug can resume within ≤ 10 days, it should be administered in the current cycle. If the study drug needs to be withheld for > 10 days, it should be omitted from the current cycle and administration should continue at the start of the next cycle.

Management guidelines for imAEs and infusion-related reactions in patients treated with tislelizumab are presented Section 8.7 and Appendix 7, respectively.

5.6.2. Dose Reductions for Study Drugs

There will be no dose reductions allowed for tislelizumab.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

The exclusion criteria (Section 4.2) specify that patients must not have received prior therapy for current cancer, including chemotherapy and radiotherapy, and prior treatment with anti-PD-1, anti-PD-L1, PD-L2 or anti-CTLA-4 (Section 4.2), or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways. All prior and concomitant medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) given to patients within 30 days before the first dose and 30 days after the last dose of study treatment (as of the safety follow-up visit) should be recorded on the CRF.

6.2. Permitted Concomitant Medications/Procedures

Unless noted otherwise, most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care at the discretion of the investigator for supportive care (eg, antiemetics, antidiarrheals, hematopoietic growth factors, red blood cell/platelet transfusions) and in a patient's interest are allowed. Anemia is frequently observed in colorectal cancer patients (Wilson et al, 2017). For patients with cancer-induced anemia at baseline or with worsened cancer-induced anemia during the study period, appropriate management of cancer-induced anemia is recommended per the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines 2022) for cancer- and chemotherapy-induced anemia or local clinical practice guidance. Opiates and other medication required for palliative management of patients are allowed. Patients must notify the investigator of all concurrent medications used during the study.

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

6.2.1. Systemic Corticosteroids

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

6.2.2. Hepatitis B Treatment

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

6.2.3. Hepatitis C Treatment

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 following the international or local guidelines as appropriate. However, interferon-based therapy for HCV is not permitted on study. Patients who are given antiviral therapy must initiate treatment > 2 weeks before enrollment and continue treatment during the study and for 6 months after study drug treatment discontinuation.

6.3. Prohibited Concomitant Medications/Procedures

The following medications are prohibited:

- Other than the adjuvant therapy, any concurrent anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents including Chinese [or other country] herbal medicine and Chinese [or other country] patent medicines for the treatment of cancer [regardless of cancer type]) ≤ 14 days (or ≤ 5 half-lives, if applicable, whichever is shorter) before first dose and during the study.
- Live vaccines within 28 days before first dose and up to 60 days after the last dose of study drugs.
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or which are known to potentially interfere with liver or other major organ functions (eg, hypericin) ≤ 14 days (or ≤ 5 half-lives, if applicable, whichever is longer) before first dose and during the study. Patients must notify the investigator of all herbal remedies used during the study.

6.4. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

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

6.5. Potential Interactions Between the Study Drugs and Concomitant Medications

The potential for drug-drug interaction between tislelizumab and small-molecule drug products is very low, given that tislelizumab is a therapeutic monoclonal antibody. Tislelizumab is unlikely to have an effect on drug-metabolizing enzymes or transporters because it is expected to be degraded into amino acids and recycled into other proteins.

7. STUDY ASSESSMENTS AND PROCEDURES

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

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

7.1. Prescreening

Patients with unknown MMR and MSI status must undergo examination or confirmation of MSI status by a central laboratory within 56 days prior to the first dose of study drug. The details for collection, storage, shipment, and analysis of tissue block are detailed in the laboratory manual.

At prescreening period, the following criteria are a prerequisite for the confirmation of MSI status by central laboratory:

- Pathologically (histologically) confirmed diagnosis of potentially resectable Stage II or Stage III (per the Eighth American Joint Committee on Cancer staging system for Colon/Rectal Cancer) CRC without any prior therapy for current CRC, including chemotherapy or radiotherapy or immunotherapy
- Mandatory availability for shipment of blood and tumor tissue to qualified central laboratory for analysis. Approximately 2 mL peripheral whole blood together with tumor tissues (archival FFPE blocks or at least 10 freshly cut unstained slides) are required. Information on previous histopathology reports and previous molecular analysis (if applicable) is required to accompany the tissue samples. In the absence of sufficient archival tumor tissues, a fresh biopsy of a tumor lesion at baseline is mandatory.
- Written informed consent for collection, storage and analysis of tissue block must be obtained from the patient according to International Council for Harmonisation (ICH)/GCP, and national/local regulations.

7.2. Screening

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

For patients who have been confirmed to have MSI-H by central laboratory during the prescreening period, the central confirmation of MSI status is not required during the screening period.

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

Procedures conducted during the Screening Visit only 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 sections about safety assessments (Section 7.5), tumor and response evaluations (Section 7.6), and biomarkers (Section 7.7).

Rescreening under limited conditions may be allowed after consultation with the sponsor: Eg, when a patient's laboratory results narrowly miss a laboratory criterion, and are correctable and not due to rapidly deteriorating condition or disease progression. Rescreening is allowed only once.

7.2.1. Informed Consent and Screening Log

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

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

7.2.2. Demographic Data and Medical History

Demographic data will include age or date of birth, gender, and self-reported race/ethnicity.

Medical history includes any history of clinically significant disease, surgery, or cancer history; reproductive status (ie, of childbearing potential or no childbearing potential); history of alcohol consumption and tobacco (ie, former or current or never); and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days before first dose.

7.2.3. Women of Childbearing Potential and Contraception

Childbearing potential is defined as being physiologically capable of becoming pregnant. Refer to Appendix 8 for contraception guidelines and definitions of "Women of Childbearing Potential" and "No Childbearing Potential."

7.2.4. Pulmonary Function Tests

Patients who are suspected of having or known to have serious/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 which may include, but is not limited to, spirometry and assessment of diffusion capacity done during the screening period to assist the determination of suitability for the study.

Tests may be repeated as clinically indicated while on study (refer to Appendix 1 for details).

7.3. Enrollment

7.3.1. Confirmation of Eligibility

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

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

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

7.3.2. Patient Numbering

Each patient enrolled in this study will receive a unique identification number after signing the ICF. Patient numbers will be assigned in chronological order starting with the lowest number. Once an identification number has been assigned to a patient, it cannot be re-assigned to any other patient. Rescreened patients will sign a new ICF and receive a new identification number.

7.4. Study Drug Dispensation

Tislelizumab will be dispensed and administered as described in Section 5.2.

7.5. Safety Assessments

7.5.1. Vital Signs

Vital signs will include measurements of body temperature (˚C), pulse rate and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be collected while the patient is in a seated position after resting for 10 minutes. If coinciding with study drugs administration, the patient's vital signs are required to be recorded within 60 minutes before, during, and approximately 30 minutes after the first 2 cycles of study drug administration. For subsequent cycles, vital signs will be collected within 60 minutes before the infusion of study drug, and if clinically indicated, during and approximately 30 minutes after the infusion of study drug. Height should only be measured and recorded during screening. Weight will be measured before study drug administration in every cycle.

7.5.2. Physical Examinations

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

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

recorded as AEs on the eCRF. Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

7.5.3. Eastern Cooperative Oncology Group Performance Status

ECOG PS(Appendix 3) will be assessed during the study per timepoints as indicated in Appendix 1.

7.5.4. Laboratory Safety Tests

Local and/or central laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in in Appendix 2, per the timepoints shown in Appendix 1.

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

Thyroid assessments will be performed as specified in Appendix 1.

Details about sample collection and shipment will be provided in a separate instruction manual. Investigators should use results from the same local laboratories for assessing eligibility, safety monitoring, and dosing decision for each patient.

7.5.4.1. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune CPIs, serum creatinine kinase (CK) and CK cardiac isoenzyme (CK-MB) is monitored in all tislelizumab studies to protect the study patients and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 7 for guidelines for management of suspected immune-mediated myocarditis).

If CK-MB fractionation is not available, serum troponin (troponin I and/or T) measurements will be performed instead per local guidelines, and used consistently throughout the study.

7.5.5. Electrocardiograms

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

7.5.6. Adverse Events

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

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

7.5.7. Hepatitis B and C Testing

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

and HCV antibody). If HBsAg or HBcAb is positive, then an HBV DNA test will be triggered. If HCV antibody is positive, an HCV RNA test will be triggered.

7.6. Tumor and Response Evaluations

Tumor imaging will be performed within 28 days before first dose of study drug. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to the first dose of study drug may be used for the purposes of screening rather than repeating the standard-of-care tests.

Before surgery, patients will undergo computed tomography (CT) scans (with oral/intravenous contrast, unless contraindicated) or magnetic resonance imaging (MRI) of the neck, chest, pelvis, and abdomen within 9 weeks ±7 days after first dose to reconfirm resectability. Other known or suspected sites of disease must be included in the imaging assessments (bone, brain, etc).

After surgery, disease follow-up tumor assessment will be performed by CT or MRI (including neck, chest, pelvis, and abdomen) every 12 weeks (±14 d ays) for the first 3 years, then every 24 weeks (±28 days) for a total of 5 years, and then once each year (±28 days) thereafter based on RECIST v1.1. Patients will continue with the scheduled tumor assessments until the patient experiences disease progression or recurrence according to RECIST v 1.1, withdraws consent, is lost to follow up, death, begins a new anticancer therapy (excluding adjuvant therapy), or until the study terminates, whichever occurs first.

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

- Screening evaluations will be performed within 28 days before first dose.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a noncontrast CT scan of the chest plus a contrast-enhanced MRI (if possible) of the abdomen 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.

Response will be assessed by the investigator using RECIST v1.1 (see Appendix 4).

7.7. Biomarkers

Shipping, storage, and handling of blood, archival tumor, fresh tumor, and leftover tumor tissue for the assessment of biomarkers will be managed through a central laboratory. Refer to the laboratory manual for details of sample handling and the Schedule of Assessments (Appendix 1) for timepoints.

During the prescreening period, patients with unknown MSI and MMR status are required to provide blood and tumor tissues for central laboratory confirmation of MSI status. Approximately 2 mL peripheral whole blood together with tumor tissues (archival FFPE blocks or at least 10 freshly cut unstained slides) are required for central laboratory confirmation of MSI status.

Patients with known MSI-H status by local laboratory must undergo central laboratory assessment of MSI-H during or after the screening period if tumor samples are obtainable. For patients with known dMMR status determined by local laboratory, central laboratory confirmation of MSI-H status will be performed during screening period for enrollment. Approximately 2 mL peripheral whole blood together with tumor tissues (archival FFPE blocks or at least 10 freshly cut unstained slides) are required for central laboratory assessment/confirmation of MSI-H. Available paired tumor tissues (pretreatment and post-treatment tumor tissues as FFPE blocks or approximately 14 [≥ 10] freshly cut unstained slides) need to be sent for retrospective analysis of other exploratory biomarkers related to response and resistance for all patients in a BeiGene-designated central or test laboratory. These exploratory biomarkers include immune cell infiltration, PD-L1, TMB/DNA mutation, and GEP for all enrolled patients.

A fresh tumor biopsy at a tumor lesion is mandatory if there are no available pre-treatment archival tumor samples. Written patient consent is required for fresh 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. Approximately 2 mL of peripheral whole blood will be required for collection to work as the MSI test control.

7.8. Visit Windows

All visits must occur within ±3 days from the scheduled date, unless otherwise noted (Appendix 1). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed before any study treatment infusion/dose unless otherwise noted. Laboratory results are required to 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 on the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule every 3 weeks from Day 1 of Cycle 1 during pre-operative treatment phase.

7.9. Unscheduled Visits

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

If an unscheduled visit is necessary to assess toxicity or evaluate suspected disease progression, 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. SAFETY MONITORING AND REPORTING

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

8.1. Risks Associated With Study Drugs

8.1.1. Risks Associated With Tislelizumab

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

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of imAEs, specifically the induction or exacerbation of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Section 8.7.3.

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 evaluation and management guidelines for suspected imAEs are provided in Appendix 7.

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies and clinical data with tislelizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were considered. Specifically, patients at risk for study-emergent active autoimmune diseases, with a history of autoimmune diseases that may relapse, who have undergone allogenic stem-cell or organ transplantation or who have received a live viral vaccine ≤ 28 days before first dose are excluded from the study. Refer to Section 4.2 for the full list of exclusion criteria.

8.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE v5.0.

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 5), physical examinations, laboratory measurements (hematology, clinical chemistry, etc), and other assessments including those listed in Appendix 1. In addition, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions or infection.

At the start of each cycle, the study drug will be administered only after clinical laboratory results have been reviewed. Administration of study drug will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (for additional information, see Section 5.2).

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

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

8.3. Adverse Events

8.3.1. Definitions and Reporting

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

Examples of AEs include:

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

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

8.3.2. Assessment of Severity

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

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

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- 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 (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.6.2.

8.3.3. Assessment of Causality

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

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always 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 his/her 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 drugs (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drugs
- Biological plausibility

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

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely

- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug), however, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs)

8.3.4. Follow-up of Adverse Events

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

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

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

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

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

8.3.5. Laboratory Test Abnormalities

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 ×ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the Adverse Event 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 should be recorded as "hyperkalemia."

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

8.4. Definition of a Serious Adverse Event

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

- Results in death
- Is life-threatening

  Note: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE, which hypothetically might have caused death, if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization

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

- Results in disability/incapacity

  Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered SAEs:

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

8.5. Suspected Unexpected Serious Adverse Reaction

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

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

8.6.1. Adverse Event Reporting Period

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

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

AEs and SAEs should be recorded according to the details in Table 4. For the follow-up period for AEs, see Section 8.3.4. For the definition of TEAEs, see Section 9.4.2.

Table 4: Guidance for Duration of Recording New or Worsening Adverse Events

Event Type	Record New or Worsening Events That Occur During This Period	
	Begin	**End**
SAEs [a]	Signing of informed consent	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Nonserious AEs due to progressive disease	Do not record (see Section 8.6.4)	
All nonserious AEs, except those due to progressive disease	First dose of study drug	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Immune-mediated AEs (serious or nonserious)	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; SAE, serious adverse event.
[a] All SAEs considered related to the study drug that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

8.6.2. Reporting Serious Adverse Events

8.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 5.

Table 5: Time Frames and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

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

Abbreviations: SAE, serious adverse event.

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

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

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

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

The sponsor will provide contact information for receipt of SAE reports.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

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

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

All SUSARs (as defined in Section 8.5), will be submitted to all applicable regulatory authorities and investigators for tislelizumab studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated responsible

person is required to promptly notify his/her IRB or IEC. The investigator should place copies of safety reports from the sponsor in the investigator site file.

8.6.3. Eliciting Adverse Events

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

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

8.6.4. Disease Progression

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

8.6.5. Deaths

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

8.6.6. Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving study drugs or within 120 days after the last dose of study drugs, a pregnancy report form is required to be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

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

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

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

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following reference safety information document:

- Tislelizumab Investigator's Brochure

8.6.8. Assessing and Recording Immune-Mediated Adverse Events

Since treatment with anti-PD-1 can cause autoimmune disorders, AEs considered by the investigator to be immune-mediated (Section 8.7.3) should be classified as imAEs and identified as such in the eCRF AE page until Day 90 after the last dose of the study drug.

Investigators should consult the guidance on diagnostic evaluation and management of imAEs which are commonly seen with immune CPIs in Appendix 7.

An extensive list of potential imAEs is presented in Section 8.7.3, Table 7. All conditions similar to 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 7.

8.6.9. Recording Infusion-Related Reactions

The symptoms of infusion-related reactions may include but are not limited to fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Each individual sign and symptom of an infusion-related reaction should be recorded as a separate AE in the eCRF and identified as an infusion-related reaction. Refer to the eCRF completion guidelines for details.

8.7. Management of Adverse Events of Special Interest

As a routine precaution, patients must be monitored for ≥ 60 minutes after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2 in an area with resuscitation equipment and emergency agents. For Cycle 3, a minimum of a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The management of infusion-related reactions, severe hypersensitivity reactions, and imAEs according to the NCI-CTCAE criteria are outlined in the following subsections.

8.7.1. Infusion-Related Reactions

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.

Treatment modifications for symptoms of infusion-related reactions due to the study drug are provided in Table 6.

Table 6: Treatment Modifications for Symptoms of Infusion-Related Reactions Due to Study Drugs

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

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

Once the tislelizumab infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions. 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 study drug.

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

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

8.7.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

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

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

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

8.7.3. Immune-Mediated Adverse Events

Immune-mediated AEs are of special interest in this study. If the events listed below or similar events occur, the investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic, toxin, disease progression or other neoplastic causes) with appropriate diagnostic tests, which may include but 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 in the eCRF AE page should be checked.

A list of potential imAEs is shown below in Table 7. All conditions similar to those listed should be evaluated in patients receiving tislelizumab to determine whether they are immune-mediated.

Recommendation for diagnostic evaluation and management of imAEs is based on European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines (Haanen et al, 2017; Brahmer et al, 2018), and common immune-mediated toxicities are detailed in Appendix 7. For any AEs not included in Appendix 7, please refer to the ASCO Clinical Practice Guideline (Brahmer et al, 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Table 7: Immune-Mediated Adverse Events

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

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

Recommendations for managing imAEs are detailed in Appendix 7.

If a toxicity does not resolve to ≤ Grade 1 within 12 weeks, the study drug 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.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

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

9.1. Statistical Analysis

No hypothesis testing or p-value will be provided for the below statistical analyses since the study is of exploratory purpose.

9.1.1. Analysis Sets

The Safety Analysis Set (SAS) includes all enrolled patients who received ≥ 1 dose of study drug; it will be the analysis set for the safety analyses.

The Efficacy Analysis Set (EAS) includes all enrolled patients who receive neo-adjuvant treatment followed by surgery. This will be the primary analysis set for the efficacy analyses.

9.1.2. Patient Disposition

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

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

9.1.3. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of the safety analysis set will be summarized using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, and time since current cancer diagnosis. Categorical variables include histology, stage of disease, gender, age, race.

9.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the clinical study report (CSR) for this protocol. Prior medications will be defined as medications that stopped before the day of the first dose of the study drug. Concomitant medications will be defined as medications that 1) started before the first dose of the study drug and were continuing at the time of the first dose of the study drug or 2) started on or after the date of the first dose of the study drug and up to 30 days after the patient's last dose (as of the Safety Follow-up Visit). In addition, telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 days, and 90 days (±14 days) after the last dose of study treatment, regardless of whether the patient starts a new anticancer therapy.

If patients report a suspected immune-mediated AE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

9.2. Efficacy Analyses

9.2.1. Primary Efficacy Analysis

The primary efficacy endpoint is MPR rate defined as the proportion of patients in the EAS with ≤ 10% residual viable tumor in the resected primary tumor after completion of neo-adjuvant therapy. The MPR rate will be summarized descriptively, and Clopper-Pearson 95% CI will be calculated to evaluate the precision of MPR estimate. The analysis of MPR rate will occur after all the patients in the efficacy analysis set have been assessed for pathological response.

9.2.2. Secondary Efficacy Analyses

The pCR rate is defined as the proportion of patients in the EAS with absence of residual tumor in the resected primary tumor and all resected lymph nodes after completion of neo-adjuvant therapy followed by surgery assessed by investigator. The pCR rate will be summarized descriptively, and a Clopper-Pearson 95% CI will also be calculated.

EFS is defined as the time from the time of first dose until any of the following events in the EAS, whichever occurs first: radiographic disease progression according to RECIST v1.1, local or distant recurrence, or death due to any cause. The median and other quartiles of EFS will be estimated using the Kaplan-Meier method. The 2-sided 95% CIs will be constructed with the generalized Brookmeyer and Crowley method (Brookmeyer et al, 1982). The 2-year/3-year EFS rate is defined as the proportion of patients free from EFS events at 2 years and 3 years after the first dose. EFS rates will be estimated by the Kaplan-Meier method with 95% CI estimated using Greenwood's formula (Greenwood et al, 1926). Patients who die without a progression/disease recurrence will be considered to have experienced an event on the date of their death. Patients who did not report progression/recurrence of disease or who die will be censored on the date of their last evaluable tumor assessment. Patients who started any subsequent anticancer therapy (excluding adjuvant therapy) without a prior reported progression/recurrence will be censored at the last evaluable tumor assessment before initiation of the subsequent anticancer therapy.

9.3. Biomarker Analysis

Potential biomarkers including immune cell infiltration, PD-L1 expression, tumor mutational burden (TMB) and DNA mutation, gene expression profile (GEP) and the association of biomarkers with disease status and response/resistance to tislelizumab as neo-adjuvant treatment will be analyzed.

9.4. Safety Analyses

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v5.0. Laboratory values (eg, hematology, clinical chemistry, urinalysis), vital signs, ECGs, and physical examinations will also be used to assess the safety profile. Descriptive statistics will be used to analyze all safety data in the SAS.

9.4.1. Extent of Exposure

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

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

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

9.4.2. Adverse Events

The AE verbatim descriptions (the investigator's description from the eCRF) will be classified into standardized medical terminology using the MedDRA. AEs will be coded to MedDRA (Version 20.0 or higher) by lowest level term, preferred term (PT), and primary system organ class (SOC).

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 the study drug and up to 30 days after study drug discontinuation (Safety Follow-up Visit) or initiation of new anticancer therapy, whichever occurs first. Only those AEs that were treatment emergent will be included in summary tables of TEAEs. Immune-mediated AEs will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of tislelizumab and up to 90 days from the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. If an imAE occurs outside of the above-mentioned TEAE window, it will not be classified as a TEAE. All imAEs will be reported separately. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

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.

The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. SAEs, deaths, TEAEs of ≥ Grade 3 severity, imAEs, treatment-related TEAEs and TEAEs that led to treatment discontinuation, dose interruption, or dose delay will be summarized.

9.4.3. Laboratory Analyses

Clinical laboratory (eg, hematology, serum chemistry, coagulation, and urinalysis) values will be evaluated for each laboratory parameter as appropriate. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this protocol. Descriptive summary statistics for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline change.

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

9.4.4. Vital Signs

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

9.5. Sample Size Consideration

Sample size is based on clinical considerations. Thirty evaluable patients (who received neo-adjuvant treatment followed by surgery) will be enrolled and will provide a reasonably robust estimate and precision (95% CI) of the primary endpoint MPR rate. Table 8 summarizes the 95% CI of MPR rate under different assumptions of MPR estimate. With a 20% drop out rate, a total of 38 patients will be enrolled in this study.

Table 8: 95% CI of MPR rate under different assumptions of MPR estimate

MPR estimate	95% CI
MPR=30%	（14.7%，49.4%）
MPR=40%	（22.7%，59.4%）
MPR=50%	（31.3%，68.7%）
MPR=60%	（40.6%，77.3%）

9.6. Interim Analyses

No interim analysis is planned.

10. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The investigator must maintain adequate and accurate records to ensure that the conduction of the study will 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.

10.1. 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.

10.2. Access to Information for Auditing or Inspections

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

11. QUALITY ASSURANCE AND QUALITY CONTROL

11.1. Regulatory Authority Approval

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

11.2. Quality Assurance

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

11.3. Study Site Inspections

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

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

11.4. Drug Accountability

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

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

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

12. ETHICS/PROTECTION OF HUMAN PATIENTS

12.1. Ethical Standard

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.

12.2. 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.

12.2.1. Protocol Amendments

Any protocol amendments will be prepared by the sponsor. All protocol modifications must be submitted to health authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF, in accordance with local requirements. Written documentation from 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.

12.3. Informed Consent

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

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

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

Patients must 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.

12.4. Patient and Data Confidentiality

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

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

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

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

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

In limited circumstances, such as in connection with insurance purposes or patient support services ancillary to certain study sites (eg, for patient travel or reimbursement), the 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, the electronic data capture [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 United States Food and Drug Administration (US FDA), the China National Medical Products Administration (China NMPA), and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

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

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

12.5. Financial Disclosure

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

13. DATA HANDLING AND RECORD KEEPING

13.1. Data Collection and Management Responsibilities

13.1.1. Data Entry in the Electronic Case Report Form

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

13.1.2. Data Collection

Data required by the protocol will be entered into an electronic data capture (EDC) system.

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

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

13.1.3. Data Management/Coding

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

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

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

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

The AE verbatim descriptions (the investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA by lowest level term, PT, and primary SOC. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

13.2. Data Integrity and In-house Blinding

Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias or to share such outputs from the EDC system with other functions/persons who do not have access to the EDC.

13.3. Study Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into ≥ 1 of the following 2 categories: 1) the investigator's study file and 2) 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 the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG tracings, electroencephalograms, X-ray images, pathology and special assessment reports, consultant letters, screening and enrollment logs, etc.

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

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements 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 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 BeiGene to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

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.

13.4. Protocol Deviations

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

The investigator is to document and explain any deviations from the approved protocol. 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, in accordance with established IRB/IEC policies and procedures.

13.5. Study Report and Publications

A CSR 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 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, 2020).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor for review before submission or presentation in accordance with the clinical study agreement. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. 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 in advance of the publication/presentation.

13.6. Completion of the Study and Study Center Closure

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

- Return/provide all study data to the sponsor
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drugs

- Review of study records for completeness
- Collection of all study documents for the study master file filing according to GCP and local regulation
- Shipment of samples (including but not limited to those for biomarkers) to the assay laboratory for central laboratory analysis according to protocol and laboratory manual requirements

In addition, the sponsor reserves the right to suspend the enrollment or prematurely discontinue this study either at a single study center or at all study centers at any time for any 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 IEC/IRB 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 drug in accordance with the applicable sponsor procedures for the study.

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

13.7. Information Disclosure and Inventions

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

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

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

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

These restrictions do not apply to:

- 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 IEC/IRB 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 13.5.

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

14. REFERENCES

Andre, T. L. et al. Nivolumab+ipilimumab combination in patients with DNA mismatch repair-deficient/ microsatellite instability- high (dMMR/MSI- H) metastatic colorectal cancer (mCRC): first report of the full cohort from CheckMate-142. J. Clin. Oncol. 36 (Suppl.), 553 (2018).

André T.; de Gramont, A.; Vernerey, D.; et al. Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to BRAF Mutation and Mismatch Repair Status of the MOSAIC Study. J. Clin. Oncol. 2015, 33, 4176–4187.

BeiGene Investigator's Brochure, Tislelizumab (BGB-A317). Edition 9.0, October 2021

Blank, C. U. et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat. Med. 24, 1655–1661 (2018).

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

Brookmeyer R and Crowley J. A confidence interval for the median survival time, Biometrics 1982; 38(1): 29-41.

Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature 487, 330–337 (2012).

Chalabi, M.; Fanchi, L.F.; Dijkstra, K.K.; et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. Nat. Med. 2020, 26, 566–576

Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115-32.

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

De la Chapelle, A. & Hampel, H. Clinical relevance of microsatellite instability in colorectal cancer. J. Clin. Oncol. 28, 3380–3387 (2010).

Diaz, L. A. Jr. & Le, D. T. PD-1 blockade in tumors with mismatch-repair deficiency. NEJM 373, 1979 (2015).

Dolgin M, Association NYH, Fox AC, Gorlin R, et al. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.

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

Fabrizio, D. A. et al. Beyond microsatellite testing: assessment of tumor mutational burden identifies subsets of colorectal cancer who may respond to immune checkpoint inhibition. J. Gastrointest. Oncol. 9, 610–617 (2018).

Forde, P. M., Chaft, J. E. & Pardoll, D. M. Neoadjuvant PD-1 blockade in resectable lung cancer. NEJM 379, e14 (2018).

Germano, G. et al. Inactivation of DNA repair triggers neoantigen generation and impairs tumour growth. Nature 552, 116–120 (2017).

Greenwood M. The natural duration of cancer. Reports on public health and medical subjects. HMSO, London. 1926;33:1-26.

Grothey, A.; Sobrero, A.F.; Shields, A.F.; et al. Duration of Adjuvant Chemotherapy for Stage III Colon Cancer. N. Engl. J. Med. 2018, 378, 1177–1188.

Haanen JB, 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.

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

Iveson, T.; Sobrero, A.F.; Yoshino, T.; et al. Prospective pooled analysis of four randomized trials investigating duration of adjuvant (adj) oxaliplatin-based therapy (3 vs 6 months {m}) for patients (pts) with high-risk stage II colorectal cancer (CC). J. Clin. Oncol. 2019, 37 (Suppl. 15), 3501.

Keung E, Burgess M, Salazar R, et al. Correlative analyses of the SARC028 trial reveal an association between sarcoma-associated immune infiltrate and response to pembrolizumab. Clin Cancer Res. 2020 Mar 15;26(6):1258-1266.

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

Le, D. T. et al. Programmed death-1 blockade in mismatch repair deficient colorectal cancer. J. Clin. Oncol. 34, 103 (2016).

Lenz, H.-J. J. et al. Durable clinical benefit with nivolumab (NIVO) plus low- dose ipilimumab (IPI) as first- line therapy in microsatellite instability- high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC). Ann. Oncol. 29 (Suppl.),LBA18_PR (2018)

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

Li J, Xu Y, Zang A, et al. Updated analysis from a phase 2 study of tislelizumab (TIS) monotherapy in patients (pts) with previously treated, locally advanced, unresectable/metastatic microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) solid tumors. Journal of Clinical Oncology 40, no. 4_suppl (February 01, 2022) 1-1.

Li K, Luo HQ, Huang LF et al. Microsatellite instability: a review of what the oncologist should know. Cancer Cell Int. 2020 Jan 13;20:16.

Lin GZ, Feng ZQ, Liu HZ, et al. Mass screening for colorectal cancer in a population of two million older adults in Guangzhou, China. Sci Rep. 2019 Jul 18;9(1):10424.

Llosa N, Cruise M, Tam A, et al. The vigorous immune microenvironment of microsatellite instable colon. Cancer Discov. 2015 Jan;5(1):43-51.

Maby, P.; Tougeron, D.; Hamieh, M.; et al. Correlation between Density of CD8+ T-cell Infiltrate in Microsatellite Unstable Colorectal Cancers and Frameshift Mutations: A Rationale for Personalized Immunotherapy. Cancer Res. 2015, 75, 3446–3455.

Mandal, R. et al. Genetic diversity of tumors with mismatch repair deficiency influences anti-PD-1 immunotherapy response. Science 364, 485–491 (2019).

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.

Marisa, L.; Svrcek, M.; Collura, A.; et al. The Balance Between Cytotoxic T-cell Lymphocytes and Immune Checkpoint Expression in the Prognosis of Colon Tumors. J. Natl Cancer Inst. 2018, 110, 68–77.

Miller BC, Sen DR, Al Abosy R, et al. Subsets of exhausted $CD8^+$ T cells differentially mediate tumor control and respond to checkpoint blockade. Nat Immunol. 2019;20(3):326-336.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Cancer Therapy Evaluation Program. 27 November 2017.

National Comprehensive Cancer Network (NCCN). NCCN Treatment Practice Guidelines in Oncology: Rectal Cancer version 1, 2021 Accessed 18 Feb. 2021.

National Comprehensive Cancer Network (NCCN). NCCN Treatment Practice Guidelines in Oncology: Colon Cancer version 1, 2021 Accessed 18 Feb. 2021.

National Comprehensive Cancer Network (NCCN). NCCN Treatment Practice Guidelines in Oncology: Hematopoietic Growth Factors version 1, 2022. Accessed 19 May 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(6):649-55.

Oki, E., Oda, S., Maehara, Y. and Sugimachi, K. Mutated gene-specific phenotypes of dinucleotide repeat instability in human colorectal carcinoma cell lines deficient in DNA mismatch repair. Oncogene 18, 2143–2147 (1999).

Overman, M. J. et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repairdeficient/ microsatellite instability- high metastatic colorectal cancer. J. Clin. Oncol. 36, 773–779 (2018).

Overman, M. J. et al. Nivolumab in patients with metastatic DNA mismatch repair- deficient or microsatellite instability- high colorectal cancer (CheckMate 142): an open- label, multicentre, phase 2 study. Lancet Oncol. 18, 1182–1191 (2017).

Popat, S., Hubner, R. & Houlston, R. S. Systematic review of microsatellite instability and colorectal cancer prognosis. J. Clin. Oncol. 23, 609–618 (2005).

Ribic, C.M.; Sargent, D.J.; Moore, M.J.; et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N. Engl. J. Med. 2003, 349, 247–257.

Rosenbaum, M.W.; Bledsoe, J.R.; Morales-Oyarvide, V.; et al. PD-L1 expression in colorectal cancer is associated with microsatellite instability, BRAF mutation, medullary morphology and cytotoxic tumor-infiltrating lymphocytes. Mod. Pathol. 2016, 29, 1104–1112.

Roth AD, Tejpar S, Delorenzi M, et al. Prognostic role of KRAS and BRAF in Stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial J Clin Oncol 2010 Jan 20;28(3):466-74.

Sargent, D.J.; Marsoni, S.; Monges, G.; et al. Defective Mismatch Repair As a Predictive Marker for Lack of Efficacy of Fluorouracil-Based Adjuvant Therapy in Colon Cancer. J. Clin. Oncol. 2010, 28, 3219–3226.

Seymour, M.T.; Morton, D. FOxTROT: An international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant chemotherapy (NAC) for colon cancer. J. Clin. Oncol. 2019, 37, 3504.

Sinicrope, F.A.; Huebner, L.J.; Laurent-Puig, P.; et al. Relative contribution of clinical and molecular features to outcome within low and high risk T and N groups in II colon cancer (CC). J. Clin. Oncol. 2019, 37, 3520

Sinicrope, F.A.; Mahoney, M.R.; Smyrk, T.C.; et al. Prognostic Impact of Deficient DNA Mismatch Repair in Patients With Stage III Colon Cancer From a Randomized Trial of FOLFOX-Based Adjuvant Chemotherapy.J. Clin. Oncol. 2013, 31, 3664–3672.

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

Sobrero, A.F.; Andre, T.; Meyerhardt, J.A.; et al. Overall survival (OS) and long-term disease-free survival (DFS) of three versus six months of adjuvant (adj) oxaliplatin and fluoropyrimidine-based therapy for patients (pts) with stage III colon cancer (CC): Final results from the IDEA (International Duration Evaluation of Adj chemotherapy) collaboration. J. Clin. Oncol. 2020, 38 (Suppl. 15), 4004.

Venderbosch, S, Nagtegaal I, Maughan T, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin. Cancer Res. 20,5322–5330 (2014).

Vilar, E. and Gruber, S.B. Microsatellite instability in colorectal cancer-the stable evidence. Nat. Rev. Clin. Oncol. 7, 153–162 (2010).

Wilson MJ, van Haaren M, Harlaar JJ, et al. Long-term prognostic value of preoperative anemia in patients with colorectal cancer: A systematic review and meta-analysis. Surg Oncol. 2017 Mar;26(1):96-104.

Wu CY, Budha N, Gao Y, et al. Tislelizumab Exposure-Response Analyses of Efficacy and Safety in Patients with Advanced Tumors [ESMO Abstract 482P]. Ann Oncol. 2019a; 30(suppl 5):mdz244.04

Wu CY, Tang Z, Liu L, et al. Population Pharmacokinetics of Tislelizumab in Patients with Advanced Tumors [ESMO Abstract 483P]. Ann Oncol. 2019b;30(suppl 5):mdz244.045.

Yamamoto H, Watanabe Y, Maehata T et al. Microsatellite instability in cancer: a novel landscape for diagnostic and therapeutic approach Arch Toxicol 2020 Oct;94(10):3349-3357.

Zhang T, Song X, Xu L, et al. The binding of an anti-PD-1 antibody to FcγRI has a profound impact on its biological functions. Cancer Immunol Immunother. 2018;67(7):1079-90

Zheng R, Zeng H, Zhang X, et al. The epidemiology of colorectal cancer in China. Global Health Journal Volume 2, Issue 3, September 2018

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Prescreening [a]	Screening [a]	Treatment				EOT Safety Follow-up [c]	Disease follow-up
			Neo-adjuvant treatment Cycles 1 to 3 (every 21 days)			Surgery [b]		
Days (window)	**-56 to ~ -1**	**-28 to ~ -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**		**30 ± 7 days after treatment**	
Informed consent [a]	x	x						
Inclusion/exclusion criteria		x						
Demographics/medical history/prior medications [d]	x	x						
Vital signs/ height and weight [e]		x	x			x	x	
Physical examination [f]		x	x			x	x	
ECOG PS		x	x			x	x	
12-lead ECG [g]		x				x	x	
Adverse events [h]		x	x	x	x	x	x	
Concomitant medications [h]		x	x	x	x	x	x	
Hematology [i]		x	x	x	x	x	x	
Serum chemistry [i]		x	x	x	x	x	x	
CK and CK-MB [i]		x	x	x	x	x	x	
Coagulation parameters [i]		x	x			x	x	
Urinalysis [j]		x	As clinically indicated					
Pregnancy test [j]		x	x			x	x	
Thyroid function [k]		x	x			x	x	

Assessment	Prescreening [a]	Screening [a]	Treatment				EOT Safety Follow-up [c]	Disease follow-up
			Neo-adjuvant treatment Cycles 1 to 3 (every 21 days)			Surgery [b]		
Days (window)	**-56 to ~ -1**	**-28 to ~ -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**		**30 ± 7 days after treatment**	
HBV/HCV tests [l]		x	As clinically indicated					
Pulmonary function tests [m]		x	As clinically indicated					
Tumor tissue sample and whole blood [n]	x	x						
Surgical tumor tissue and lymph node sample [o]						x (after surgery)		
Pathological response assessment [o]						x (after surgery)		
Pre-surgery tumor assessment [p]		x	Within 9 weeks (± 7 days) after first dose					
Tumor assessment [q]								Every 12 weeks (for the first 3 years); every 24 weeks (for a total of 5 years) and then once each year thereafter
Tislelizumab administration [r]			x					

Abbreviations: AE, adverse event; CK, creatine kinase; CK-MB, creatine kinase cardiac muscle isoenzyme; CT, computed tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; EC, ethics committee; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOT, end of treatment; FEV1, forced expiratory volume; FFPE, formalin-fixed paraffin-embedded; FT3, free triiodothyronine; FT4, free thyroxine; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAb, hepatitis B surface antibody; imAE, immune-mediated adverse event; imAE, immune-mediated adverse event; IRB, institutional review board; MRI, magnetic resonance imaging; NCI-CTCAE, National

Cancer Institute Common Terminology Criteria for Adverse Events; OCT, optical coherence tomography; SAE, serious adverse event; TSH, thyroid stimulating hormone; v, version.

a. Patients with unknown MSI and MMR status are required to provide blood and tumor tissues for central confirmation of MSI status during the prescreening period (defined as within 56 days prior to the first dose of the study drug). A separate prescreening informed consent must be obtained for central assessment of microsatellite instability for patients with unknown MMR and MSI status during the prescreening period. Written informed consent is required prior to performing any study-specific tests or procedures during the screening period. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the first dose may be used for screening assessments rather than repeating such tests.
b. The presurgical visit and associated assessments should occur within 14 days of surgery and in accordance with local institutional practices. The surgical procedure should be performed within 10 weeks from the first administered dose of study treatment as best as possible. If surgery cannot be performed within this time window (eg, because of a prolonged AE), the medical monitor should be consulted. (see Section 3.4 .
c. The EOT Visit /Safety Follow-up is conducted when the investigator determines that study treatment will no longer be used, or all the study treatment is completed (Section 3.5). If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the End of Treatment Visit, tests need not be repeated.
d. Includes age or year of birth, gender, and self-reported race/ethnicity; history of clinically significant disease, surgery, or cancer history; reproductive status (ie, of childbearing potential or no childbearing potential); history of alcohol consumption and tobacco (ie, former or current or never), and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used within 30 days before the first dose). Information on radiographic studies performed prior to study entry may be collected for review by the investigator.
e. Vital signs collected on study include temperature, pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. The patient's vital signs are required to be recorded within 60 minutes before, during, and approximately 30 minutes after the first 2 cycles of tislelizumab infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and, if clinically indicated, during and 30 minutes after the infusion. Height should only be measured and recorded during screening. Weight will be measured before study drug administration in every cycle.
f. During the Screening Visit, a complete physical examination will be conducted. At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed.
g. The ECG recordings will be obtained during screening, the Safety Follow-up Visit, and as clinically indicated at other timepoints. Patients should be resting in a semi-recumbent supine position for at least 10 minutes prior to each ECG collection.
h. The AEs and laboratory abnormalities will be graded per NCI-CTCAE v5.0. All AEs will also be evaluated for seriousness. After the informed consent form has been signed, but prior to the first administration of study drug, only SAEs should be recorded. After the first dose of study drugs, all AEs and SAEs, regardless of their assessed relationship to study drug, are to be reported until either 30 days after the last dose of study treatment or the initiation of new anticancer therapy, whichever occurs first. In addition, telephone contacts with patients should be conducted to assess immune-mediated AEs and concomitant medications (if appropriate, ie, associated with an immune-mediated AE or is a new anticancer therapy) at 60 days, and 90 days (± 14 days) after the last dose of study treatment, regardless of whether the patient starts a new anticancer therapy. Immune-mediated AEs (serious or nonserious) will be reported until 90 days after the last dose of study treatment, regardless of whether the patient starts a new anticancer therapy. The investigator should report any SAEs that are assessed as related to tislelizumab treatment, at any time after treatment discontinuation.
i. Local laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2. If laboratory tests at Screening are not performed within 7 days of first dose, these tests should be repeated and reviewed before dosing. Hematology and serum chemistry (including liver function tests) will be performed weekly for the first 3 cycles. After Cycle 1, results are to be reviewed within 48 hours before study drug administration. Urinalysis is to be conducted during the treatment period only if clinically warranted. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

All patients will have CK and CK-MB testing at Screening, repeated at all scheduled visits. If CK-MB fractionation is not available, troponin I and/or troponin T may be tested instead.

j. Urine or serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to the first dose. Urine pregnancy tests will be performed at each visit prior to dosing, and at the EOT/Safety Follow-up Visit. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

k. Analysis of FT3, FT4, and TSH will be performed by a central laboratory or the local study site laboratory. If the tests at Screening are not performed within 7 days of first dose, these tests should be repeated and reviewed before dosing. Thyroid function tests will be performed at Screening, during neo-adjuvant treatment, presurgical visit, and at the Safety Follow-up Visit.

l. Testing will be performed by the local laboratory at Screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody). If HBsAg or HBcAb is positive, then an HBV DNA test will be triggered. If HCV antibody is positive, an HCV RNA test will be triggered.

m. Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer, or with a history of thoracic radiotherapy will undergo pulmonary function testing which may include, but is not limited to, spirometry and assessment of diffusion of oxygenation, at a minimum pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity done during the screening period to assist the determination of suitability on the study. Tests may be repeated as clinically indicated while on study.

n. Patients with unknown MSI and MMR status are required to provide blood and tumor tissues for central laboratory confirmation of MSI status during the prescreening period. Approximately 2 mL peripheral whole blood together with tumor tissues (archival FFPE blocks or at least 10 freshly cut unstained slides) are required for central laboratory confirmation of MSI status. Patients with known MSI-H status by local laboratory must undergo central laboratory assessment of MSI-H during or after the screening period if tumor samples are obtainable. For patients with known dMMR status determined by local laboratory, central laboratory confirmation of MSI-H status will be performed during screening period for enrollment. Approximately 2 mL peripheral whole blood together with tumor tissues (archival FFPE blocks or at least 10 freshly cut unstained slides) are required for central laboratory assessment/confirmation of MSI-H. Available archival pre-treatment FFPE blocks or approximately 14 [≥ 10] freshly cut unstained slides need to be sent for retrospective analysis of other exploratory biomarkers related to response and resistance in sponsor designated central or test laboratory. A fresh tumor biopsy at a tumor lesion is mandatory if there are no available archival tumor samples. Written patient consent is required for fresh 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. Approximately 2 mL of peripheral whole blood will be required for collection to work as the MSI test control.

o. Post-treatment tumor tissue and lymph node tissue obtained from surgical resection is required for pathological response analysis. Assessments on surgical specimen will be done for MPR, pCR, and exploratory biomarker analysis (including mIHC, PD-L1, TMB/DNA mutation, and GEP) (Section 7.7)

p. Tumor imaging will be performed within 28 days before first dose as the baseline data and within 9 weeks ±7 days after first dose to re-confirm the resectability before surgery. See also Section 7.6.

q. After surgery, disease follow-up tumor assessment will be performed by CT or MRI (including neck, chest, pelvis, and abdomen) every 12 weeks (±14 days) for 3 years, and then every 24 weeks (±28 days) for a total of 5 years, and then once each year (±28 days) thereafter based on RECIST v1.1. Patients will continue with the scheduled tumor assessments until the patient experiences disease progression or recurrence according to RECIST v 1.1, withdraws consent, is lost to follow up, death, begins a new anticancer therapy (excluding adjuvant therapy), or until the study terminates, whichever occurs first. See also Section 7.6.

r. Tislelizumab will be given intravenously once every 3 weeks (3 cycles in total). The initial infusion will be delivered over 60 minutes. If well tolerated, subsequent infusions can be administered over 30 minutes. Patients must be monitored for 60 minutes after infusion of tislelizumab on first and second cycle of tislelizumab administration, for third cycle of tislelizumab administration, at least a 30-minute monitoring period is required.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Serum Chemistry	Hematology	Coagulation
Alanine aminotransferase Aspartate aminotransferase Total bilirubin Direct bilirubin Blood urea nitrogen or urea Creatinine Glucose Alkaline phosphatase Lactate dehydrogenase Magnesium Phosphorus Potassium Sodium Chloride Corrected calcium Total protein Albumin Creatine kinase /CK-MB [a]	CBC including RBC Hematocrit Hemoglobin Platelet counts WBC count with differential	Prothrombin time Partial thromboplastin time or activated partial thromboplastin time International normalized ratio
Urinalysis	**Pregnancy Test**	**Thyroid Function**
pH Specific gravity Glucose Protein Ketones Blood 24-hour protein [b]	Urine or serum pregnancy test	TSH Free T3 Free T4

Abbreviations: CBC, complete blood count; CK-MB, creatine kinase cardiac isoenzyme; pH, negative of the logarithm to base 10 of the activity of the (solvated) hydronium ion; RBC, red blood cell; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; WBC, white blood cells.

a. Cardiac enzyme testing has been added to monitor for potential event of immune-mediated myocarditis. In the event that CK-MB fractionation is not available, please 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.

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

APPENDIX 3. ECOG PERFORMANCE STATUS

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

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

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

The text below was obtained from the following reference: 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 (v1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria.

Note: Lesions are either measurable or 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 and MRI (no less than double the slice thickness and a minimum of 10 mm)
- 10 mm caliper measurement by clinical exam (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 scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease

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

Bone lesions:

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

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor 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 loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

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

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

Nontarget Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as 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 nontarget 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 P10 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, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: 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 complete response (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 in order to differentiate between response (or stable disease) and progressive disease.

RESPONSE CRITERIA

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study
- 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, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

- Target lesions that become "too small to measure". While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure".
  When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, 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 Nontarget Lesions

While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points 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 nontarget lesions. (Note: the appearance of one or more new lesions is also considered progression.)
- Non-CR/Non-PD: Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits

- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.
- When the patient has only non-measurable 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 non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) 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 non-measurable 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 disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

While 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 pre-existing 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 taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's BOR assignment will depend on the findings of both target and nontarget 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 non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

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

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
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

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

In trials where confirmation of response is required, repeated "NE" time point 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 time point responses of PR-NE-PR as a confirmed response.

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

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of 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.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (phase 2 or 3) or trials where 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 SD, measurements must have met the SD 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 or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

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

Duration of Stable Disease

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

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

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

APPENDIX 5. PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

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

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

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

APPENDIX 6. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

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

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

APPENDIX 7. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

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

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

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

When alternative explanations to autoimmune toxicity have been excluded, the imAE field associated with the AE in the eCRF should be checked.

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

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

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

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

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

Treatment of Immune-mediated Adverse Events

- Immune-mediated AEs can escalate quickly; study treatment interruption, close monitoring, timely diagnostic work-up and treatment intervention, as appropriate, with patients is required.

- Immune-mediated AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice and contact the study medical monitor.
- For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study medical monitor.
- Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory imAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil [MMF]).
- Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy.

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse 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 at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological Toxicity	**1** Mild symptoms	–	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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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.
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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: 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 judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST 5-20X 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 ALT or AST > 20X ULN	Initiate IV methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: • If on oral prednisolone, change to pulsed IV methylprednisolone • If on IV, add mycophenolate mofetil (MMF) 500-1000 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 drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3X baseline or > 3X-6X ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6X ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended	Continue study treatment.
	2 Fasting glucose value 160-250 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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
			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.
	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	Management as per local guideline. Consider referring patient to a	Continue treatment or, if symptoms continue

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	inflammation, swelling, limited instrumental (fine motor) activities	rheumatologist. If symptoms worsen on treatment manage as a Grade 3 event.	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 3X 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
Myocarditis	**< 2** Asymptomatic but significantly increased	Initiate cardiac evaluation under close monitoring with repeat serum testing; consider referral to a	

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	CK-MB or increased troponin OR clinically significant intraventricular conduction delay	cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2	Hold study treatment. If a diagnosis of myocarditis is confirmed, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1g/day and add MMF, infliximab or anti-thymocyte globulin	
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; 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 8. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials 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, or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- 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).
  - 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, postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be combined with a highly effective form of birth control, 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 postmenopausal follicle-stimulating hormone (FSH) concentration > 30 IU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

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

Adapted from Recommendations related to contraception and pregnancy testing in clinical trials. 15 September 2014. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

APPENDIX 9. 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) Levey et al, 2009) equation and the Modification of Diet in Renal Disease Study equation. National Kidney Disease Education Program calculators rely on creatinine determinations which are isotope dilution mass spectrometry traceable. All laboratories should be using creatinine methods calibrated to be isotope dilution mass spectrometry traceable.

The CKD-EPI equation calculator should be used when serum creatinine (S_{cr}) reported in mg/dL. This equation is recommended when estimated GFR values above 60 mL/min/1.73 m^2 are desired.

$$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

where:

S_{cr} is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

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, which is an accepted average adult surface area.

The online calculator for CKD-EPI can be found here:
https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators