CLINICAL STUDY PROTOCOL

Protocol Title:	Phase 2 Study Investigating Efficacy and Safety of Anti-PD-1 Monoclonal Antibody Tislelizumab (BGB-A317) Combined With or Without Anti-TIGIT Monoclonal Antibody BGB-A1217 in Patients With Previously Treated Recurrent or Metastatic Cervical Cancer
Protocol Number:	BGB-A317-A1217-202 (AdvanTIG-202)
Phase:	2
Investigational Products:	BGB-A1217 and Tislelizumab (BGB-A317)
Proposed Indication(s):	Cervical Cancer
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive, 3rd Floor San Mateo, California 94404, USA
Sponsor Medical Monitor:	[redacted] Telephone: [redacted] [redacted]
Original Protocol	04 September 2020
Protocol Amendment 0.1 (Russia):	04 May 2023

FINAL PROTOCOL APPROVAL SHEET

Phase 2 Study Investigating Efficacy and Safety of Anti-PD-1 Monoclonal Antibody Tislelizumab (BGB-A317) Combined With or Without Anti-TIGIT Monoclonal Antibody BGB-A1217 in Patients With Previously Treated Recurrent or Metastatic Cervical Cancer

BeiGene, Ltd. Approval:

See electronic signature approval

INVESTIGATOR SIGNATURE PAGE

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Protocol Identifier: BGB-A317-A1217-202

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.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. PRINT your name, title, and the name and address of the center in which the study will be conducted.

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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SYNOPSIS

Name of Sponsor/Company:	BeiGene, Ltd.
Investigational Product(s):	BGB-A1217 and tislelizumab (BGB-A317)
Title of Study:	Phase 2 Study Investigating Efficacy and Safety of Anti-PD-1 Monoclonal Antibody Tislelizumab (BGB-A317) Combined With or Without Anti-TIGIT Monoclonal Antibody BGB-A1217 in Patients With Previously Treated Recurrent or Metastatic Cervical Cancer
Protocol Identifier:	BGB-A317-A1217-202
Phase of Development	2
Number of Patients:	Approximately 167 patients in total
Study Centers:	Approximately 100 centers globally

Study Objectives:

Primary:

- To evaluate the efficacy of BGB-A1217 combined with tislelizumab as measured by objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (RECIST v1.1), by Independent Review Committee (IRC) in patients who had previously treated recurrent or metastatic cervical cancer with PD-L1 visually-estimated Combined Positive Score (vCPS) ≥ 5% or regardless of PD-L1 expression

Secondary:

- To evaluate the efficacy of BGB-A1217 combined with tislelizumab as assessed by ORR by investigator review
- To evaluate the efficacy of tislelizumab monotherapy as assessed by ORR by both IRC and investigator review
- To evaluate the efficacy of BGB-A1217 combined with tislelizumab and tislelizumab monotherapy as measured by duration of response (DOR), progression-free survival (PFS), time to response (TTR), disease control rate (DCR), and clinical benefit rate (CBR) by both IRC and investigator review
- To evaluate the efficacy of BGB-A1217 combined with tislelizumab and tislelizumab monotherapy as measured by overall survival (OS)
- To evaluate Health Related Quality of Life (HRQoL) via cancer-specific patient-reported outcomes (PROs) in patients treated with BGB-A1217 combined with tislelizumab and tislelizumab monotherapy
- To evaluate the safety and tolerability of BGB-A1217 combined with tislelizumab and tislelizumab monotherapy
- To characterize the pharmacokinetics (PK) of BGB-A1217 and tislelizumab

- To assess host immunogenicity to BGB-A1217 and tislelizumab

Exploratory:

- To evaluate quality of life (QoL) via a generic PRO in patients treated with BGB-A1217 combined with tislelizumab and tislelizumab monotherapy
- To evaluate potential association of biomarkers with patient prognosis, response, or resistance to BGB-A1217 in combination with tislelizumab or tislelizumab alone

Study Endpoints:

Primary:

- ORR, defined as the proportion of patients who had complete response (CR) or partial response (PR) assessed by IRC per RECIST v1.1 for Cohort 1

Secondary:

- ORR, defined as above assessed by investigator's review per RECIST v1.1 for Cohort 1
- ORR, defined as above assessed by both IRC and investigator's review per RECIST v1.1 for Cohort 2
- DOR, defined as the time from the first confirmed objective response until the first documentation of progression or death, whichever comes first, assessed by both IRC and investigator's review according to RECIST v1.1 for Cohorts 1 and 2
- Other efficacy endpoints (PFS, TTR, DCR, and CBR) that need tumor assessments by both IRC and investigator's review per RECIST v1.1 for Cohorts 1 and 2
  - PFS, defined as the time from the date of first dose of study drug to the date of first documentation of disease progression or death, whichever occurs first
  - TTR, defined as the time from the date of first dose of study drug to first documentation of response
  - DCR, defined as the proportion of patients who achieve CR, PR, or stable disease (SD)
  - CBR, defined as the proportion of patients who achieve CR, PR, or durable SD (SD ≥ 24 weeks)
- OS, defined as the time from the date of first dose of study drug until the date of death from any cause for Cohorts 1 and 2
- HRQoL, defined as assessment of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cervical Cancer Module (EORTC QLQ-CX24) for Cohorts 1 and 2
- Adverse events (AEs) and serious adverse events (SAEs) as characterized by type, frequency, severity (as graded by National Cancer Institute – Common Terminology Criteria for Adverse Events [NCI-CTCAE] v5.0), timing, seriousness, and relationship to study drugs, physical examinations, electrocardiograms (ECGs), and laboratory assessments for Cohorts 1 and 2
- Serum BGB-A1217 and tislelizumab concentrations at specified timepoints

- Immunogenic responses to BGB-A1217 and tislelizumab, evaluated through the detection of antidrug antibodies (ADAs)

Exploratory:

- Evaluate status of exploratory biomarkers including but not limited to expression of TIGIT, CD226, CD155, CD112 and PD-L1; gene expression profiling; tumor mutation burden; tumor-infiltrating immune cells in archival and/or fresh tumor tissue and blood before study treatment, during study treatment, or at disease progression/reoccurrence; and the association between these biomarkers with clinical efficacy, disease status, and resistance
- QoL is measured by assessment of the European Quality of Life 5-Dimensional-5-Level Questionnaire (EQ-5D-5L)

Study Design:

This is an open-label, 2-cohort, multicenter, Phase 2 study to evaluate the efficacy and safety of tislelizumab combined with or without BGB-A1217 in patients with previously treated recurrent or metastatic cervical cancer. The study is composed of two stages:

- **Stage 1 (randomization)**: Approximately 80 patients whose tumor regardless of PD-L1 expression will be randomized at 1:1 ratio to receive either tislelizumab (200 mg intravenously [IV] once every 3 weeks [Q3W]) combined with BGB-A1217 (900 mg IV Q3W) or tislelizumab (200 mg IV Q3W) monotherapy.
- **Stage 2 (expansion)**: After the enrollment is completed in Stage 1, the sample size of the combination therapy cohort will continue to be expanded in Stage 2 with approximately 87 additional patients who will receive tislelizumab (200 mg IV Q3W) combined with BGB-A1217 (900 mg IV Q3W).

The total sample size of the combination therapy cohort (Cohort 1) will be approximately 127 patients. The total sample size of the tislelizumab monotherapy cohort (Cohort 2) will be approximately 40 patients.

In Stage 1, the PD-L1 expression will be retrospectively tested centrally. In Stage 2, PD-L1 expression will be prospectively tested centrally, and only patients whose tumors are evaluable for PD-L1 expression will be enrolled. For Cohort 1 (including patients enrolled in Stage 1 and Stage 2), the percentage of patients whose tumors have PD-L1 vCPS < 5% or whose tumors are not evaluable for PD-L1 expression would be capped to be no more than 40%, to reflect the natural distribution of PD-L1 expression in cervical cancer. vCPS is the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining and tumor-associated immune cells with PD-L1 staining at any intensity.

Study drugs will be administered until disease progression per RECIST v1.1 by IRC, unacceptable toxicity, or withdrawal for other reasons, whichever occurs first. End-of-Treatment (EOT), safety follow-up and survival follow-up visits will be conducted following study drug discontinuation.

The study design schema is shown in Figure 1.

Study Assessments:

Tumor Assessment:

Tumor imaging will be performed ≤ 28 days before the first dose of study drugs. During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) for the first 54 weeks, then every 12 weeks (± 7 days) thereafter.

Response and progressive disease (PD) will be assessed using RECIST v1.1. When PD is assessed by the

investigator, IRC is required to complete central image review and convey the results to the investigator as soon as possible. If PD is NOT confirmed by IRC, it is recommended to continue the study treatment until PD is confirmed by IRC, if this is in the best interest of the patient as discussed with the medical monitor. In the situation where the investigator believes the patient must urgently discontinue study treatment without waiting for IRC confirmation, the investigator must contact the medical monitor to inform the decision of treatment discontinuation.

A patient who discontinues study drugs early for reasons other than disease progression by IRC (eg, toxicity, PD by the investigator) will continue to undergo tumor assessments following the original plan until the patient experiences PD per RECIST v1.1 by IRC, withdraws consent, is lost to follow-up, death, or until the study terminates, whichever occurs first.

If at the investigator's discretion a patient could continue to benefit from tislelizumab and BGB-A1217 combination treatment or tislelizumab monotherapy (patients' assigned treatment) after PD per RECIST v1.1 by IRC, the patient may continue their assigned treatment. The following criteria must be met in order to treat patients who may continue to benefit from study treatment after PD:

- Absence of clinical symptoms and signs of PD (including clinically significantly worsening of laboratory values)
- Stable Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic PD and inform patients that this practice is not considered standard in the treatment of cancer.

The decision to continue study drugs beyond initial progression must be agreed by the medical monitor and documented in the study records. Patients who receive study treatment beyond progression will have tumor assessments performed according to the original schedule until study treatment discontinuation.

Safety Assessment:

Patients will be evaluated for any AEs and SAEs occurring up to 30 days after the last dose of study drugs (all severity grades, per NCI-CTCAE v5.0) or initiation of a new anticancer therapy, whichever occurs first, and immune-mediated AEs (imAEs) occurring up to 90 days after the last dose of study drugs, regardless of initiation of a subsequent anticancer therapy. All drug-related SAEs will be recorded by the investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow-up, whichever occurs first. All study drug-related SAEs will be followed until they resolve to baseline or ≤ Grade 1, the investigator assesses the AE as stable and unlikely to improve, or the patient is lost to follow-up, whichever occurs first.

Duration of Patient Participation:

Duration of patient participation will vary by patient. Each patient's visit course will include: screening (up to 28 days), treatment (until disease progression, intolerable toxicity, or withdrawal for other reasons, and EOT Visit), safety follow-up (30 [±7], 60 [± 14], and 90 [± 14] days after the last dose of study drugs), and survival follow-up (approximately every 3 months ± 14 days after the last Safety Follow-up Visit).

Study Population:

The study will enroll approximately 167 patients who meet the following inclusion/exclusion criteria,

with approximately 127 patients in Cohort 1(tislelizumab combined with BGB-A1217) and 40 patients in Cohort 2 (tislelizumab monotherapy).

Key Eligibility Criteria:

Adult patients (≥ 18 years of age or the legal age of consent, at the time of voluntarily signing of informed consent) with histologically or cytologically confirmed squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix and who had progression on or after one or more lines of chemotherapy for management of recurrent or metastatic disease and are not amenable to curative treatment are eligible. Patients must submit qualified archival tumor tissue with an associated pathology report or agree to a tumor biopsy for determination of PD-L1 expression and other biomarker analyses. Patients must have an ECOG PS of ≤ 1 and life expectancy ≥ 12 weeks with adequate organ functions. Patients must have ≥ 1 measurable lesion as defined per RECIST v1.1. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, TIGIT or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways are excluded. Patients with disease or condition treatment within limited period as mentioned in Section 4.2 are excluded.

Investigational Product, Dose, and Mode of Administration:

Tislelizumab, 200 mg Q3W administered by IV infusion

BGB-A1217, 900 mg Q3W administered by IV infusion

Statistical Methods:

Analysis Sets:

- The Safety Analysis Set (SAS) includes all patients of each cohort who received ≥ 1 dose of study drugs. This will be the primary analysis set for efficacy analysis, and the analysis set for safety analysis.
- The Efficacy Evaluable Analysis Set (EAS) includes all treated patients (SAS) without critical protocol deviation of each cohort who had measurable disease at baseline per RECIST v1.1 by IRC and who had ≥ 1 evaluable post-baseline tumor assessment unless discontinued due to clinical PD or death within 7 weeks after the first dose. It will be used for the sensitivity analysis of the primary efficacy endpoint ORR.
- The PK Analysis Set includes all patients who received ≥ 1 dose of any component of study drug per the protocol, for whom any postdose PK data are available.
- The Immunogenicity Analysis Set includes all patients who received at least 1 dose of any component of study drug for whom both baseline antidrug antibody results and at least 1 post-baseline antidrug antibody result are available.

Efficacy Analysis:

Primary Efficacy Analysis

The primary efficacy endpoint is confirmed ORR as determined by IRC using the RECIST v1.1 in Cohort 1. ORR is defined as the proportion of patients achieving best overall responses of CR or PR.

The binomial exact test will be performed among the patients whose tumor with PD-L1 vCPS ≥ 5% and patients whose tumor regardless of PD-L1 expression in Safety Analysis Set in a sequential way.

Patients whose tumor with PD-L1 vCPS ≥ 5%

The ORR in this population is assumed as 30%, which is deemed a clinically meaningful improvement

based on a historical control of 15%. Hence, the null and alternative hypotheses are set as the following:

H_0: ORR ≤ 15%

H_a: ORR > 15%

Patients whose tumor regardless of PD-L1 expression

The ORR in this population is assumed as 25%, which is deemed a clinically meaningful improvement based on a historical control of 15%. Hence, the null and alternative hypotheses are set as the following:

H_0: ORR ≤ 15%

H_a: ORR > 15%

If the obtained one-sided p-value is ≤ 0.025, it will be concluded that BGB-A1217 combined with tislelizumab statistically significantly increases ORR compared with the historical control in patients whose tumor with PD-L1 vCPS ≥ 5% or regardless of PD-L1 expression population. Therefore, the superiority of BGB-A1217 combined with tislelizumab will be demonstrated. A Clopper-Pearson 95% confidence interval (CI) of ORR will be constructed to assess the precision of the rate estimate.

The primary efficacy analysis will be conducted when ORR data are mature, which is 6 months (approximately 4 tumor assessments) after the last patient receives the first dose of study drug in Stage 2 and will be based on the Safety Analysis Set.

Approximately 4 months after the enrollment is completed in Stage 1, there will be a preliminary analysis of ORR and safety (using descriptive statistics) for the first 40 patients in Cohort 1 and for all 40 patients in Cohort 2. Enrollment of Stage 2 will continue in parallel. At the time of preliminary analysis, if no more than 5 responders are observed in Cohort 1 at Stage 1, which corresponds to a Bayesian predictive probability of success less than 0.1 (Chen et al 2019; Lee and Liu 2008), the study will be terminated.

Sensitivity analysis of ORR will be carried out in the Efficacy Evaluable Analysis Set.

Secondary Efficacy Analysis

ORR as assessed by investigator's review will be summarized for secondary efficacy analysis in the Safety Analysis Set in Cohort 1, and ORR assessed by both IRC and investigator will be summarized in Cohort 2.

Other efficacy endpoints with necessary tumor assessments, as well as OS, will also be summarized for secondary efficacy analysis. The secondary efficacy analysis will be conducted in the Safety Analysis Set assessed by both IRC and investigator (if applicable) in Cohort 1 and Cohort 2.

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

PFS and OS will be analyzed in the Safety Analysis Set using methods similar to those described for DOR. The PFS censoring rule will follow the same as DOR. For OS, patients will be censored either at the date that the patient was last known to be alive or the date of data cutoff, whichever comes earlier, in

the absence of death.

PFS and OS rates at 3 months, 6 months, 9 months, and 12 months will be calculated based on Kaplan-Meier method.

TTR will be analyzed in the Safety Analysis Set using sample statistics such as mean, median, and standard deviation for patients who have achieved an objective response.

DCR and CBR will be summarized similarly as ORR in the Safety Analysis Set and as well as in the Efficacy Evaluable Analysis Set for sensitivity analysis.

HRQoL is an assessment of a patient's health state using the scores of EORTC QLQ-C30 and the EORTC QLQ-CX24 scales. The postbaseline scores will be analyzed in Safety Analysis Set.

Safety Analyses:

Extent of exposure to each study drug will be summarized by duration, dosage, and dose intensity for each arm.

Verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA®) terms and graded per NCI-CTCAE v5.0. All treatment-emergent AEs (TEAEs) will be summarized. A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days of last dose of study drugs or initiation of a new anticancer therapy. The TEAE classification also applies to imAEs that are recorded up to 90 days after the last dose of study drugs, regardless of whether the patient starts a new anticancer therapy.

Clinical laboratory data with values outside of the normal ranges will be identified. Selected laboratory data will be summarized by grade. Changes in vital signs will also be summarized by visit.

Pharmacokinetic Analyses:

Tislelizumab and BGB-A1217 serum concentration data will be tabulated and summarized by visit/cycle at which these concentrations are collected. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Additional PK analyses may be conducted as appropriate.

Sample Size Consideration:

The sample size calculation of Cohort 1 was based on the power of the comparison between the estimated ORR in the study and the historical rate in a sequential way as patients whose tumor with PD-L1 vCPS ≥ 5% followed by regardless of PD-L1 expression. An assumed ORR of 30% in the patients whose tumor with PD-L1 vCPS ≥ 5% compared to the historical rate of 15%; an assumed ORR of 25% in patients whose tumor regardless of PD-L1 expression compared to the historical rate of 15%.

- With 76 patients (60% whose tumor with PD-L1 vCPS ≥ 5%), the power is 0.860 to demonstrate that the ORR in patients whose tumor with PD-L1 vCPS ≥ 5% is statistically higher than the historical rate of 15% using a binomial exact test; the 95% CI of an observed 30% ORR is 20.2% to 41.9%.
- With 89 patients (70% whose tumor with PD-L1 vCPS ≥ 5%), the power is 0.927 to demonstrate that the ORR in patients whose tumor with PD-L1 vCPS ≥ 5% is statistically higher than the historical rate of 15% using a binomial exact test; the 95% CI of an observed 30% ORR is 21.0% to

40.0%.

- With 102 patients (80% whose tumor with PD-L1 vCPS ≥ 5%), the power is 0.940 to demonstrate that the ORR in patients whose tumor with PD-L1 vCPS ≥ 5% is statistically higher than the historical rate of 15% using a binomial exact test; the 95% CI of an observed 30% ORR is 21.7% to 40.3%.
- With 127 patients, the power is 0.807 to demonstrate that the ORR in the patient population whose tumor regardless of PD-L1 expression is statistically higher than the historical rate of 15% using a binomial exact test; the 95% CI of an observed 25% ORR is 17.9% to 33.7%.

The PD-L1 expression will be closely monitored for Cohort 1, and enrollment of patients whose tumors are PD-L1 vCPS < 5% or not evaluable will be stopped as necessary when reaching approximately 40%. This is to ensure that the percentage of patients with tumor PD-L1 vCPS ≥ 5% is no less than 60% of the Safety Analysis Set.

In addition, 40 patients will be enrolled in Cohort 2 to investigate the safety and efficacy of tislelizumab monotherapy in patients with previously treated recurrent or metastatic cervical cancer.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADAs	antidrug antibodies
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BOR	best overall response
CBR	clinical benefit rate
CD	cluster of differentiation
CK-MB	creatine kinase-muscle/brain
CPS	Combined Positive Score
CR	complete response
CT	computed tomography
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture (system)
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End-of-Treatment (Visit)
FDG	fluorine-18 [F-18] fluorodeoxyglucose
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HPV	Human papilloma virus
HRQoL	Health related quality of life
ICF	informed consent form
IEC	Independent Ethics Committee
IgG	immunoglobulin G
imAE	immune-mediated adverse event
IRB	Institutional Review Board
IRC	Independent Review Committee
ITIM	immunoreceptor tyrosine-based inhibitory motif
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NK	natural killer
ORR	objective response rate

Abbreviation	Definition
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed death-ligand 1
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	Patient reported outcomes
PVR	Poliovirus receptor
Q3W	every 3 weeks
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TTR	time to response
TIL	tumor-infiltrating lymphocyte
ULN	upper limit of normal
vCPS	visually-estimated Combined Positive Score

1. INTRODUCTION AND RATIONALES

1.1. Background Information on Cervical Cancer

Cervical cancer is the fourth most common cancer and the fourth leading cause of cancer death in women with approximately 570,000 new diagnoses and 311,000 deaths worldwide in 2018. The estimated age-standardized incidence of cervical cancer was 13.1 per 100,000 women globally and varied widely among countries, with rates ranging from less than 2 to 75 per 100,000 women. China and India together contributed more than one-third of the global cervical cancer burden, with 106,000 cases and 48,000 deaths in China and 97,000 cases and 60,000 deaths in India (Arbyn et al 2020).

Squamous, glandular, and other epithelial tumors including adenosquamous carcinoma, neuroendocrine tumors, and undifferentiated carcinoma are the 3 categories of epithelial tumors of the cervix recognized by the World Health Organization (WHO). Squamous cell carcinomas account for 70% to 80% of cervical cancers and adenocarcinomas account for 20% to 25%.

The most significant cause of cervical cancer is persistent papillomavirus infection. Human papilloma virus (HPV) is detected in 99% of cervical tumors, particularly the oncogenic subtypes, such as HPV 16 and 18. Post-licensure reports from countries with established HPV vaccination programs indicated that HPV vaccination has a beneficial effect at the population level as early as 3 years after the introduction of an HPV vaccination program, including decreases in the incidence of high-grade cervical abnormalities and the incidence of genital warts (Markowitz et al 2016; Ali et al 2013).

HPV has been recognized as the most important etiological factor in cervical cancer. HPV 16/18 account for at least two-thirds of cervical carcinomas. Squamous cell carcinomas and their precursor, intraepithelial squamous lesions, are related to HPV infection in almost all cases, and the presence of HPV 16 DNA is associated with poor prognosis. Adenocarcinomas encompass a heterogeneous group of tumors. Endocervical adenocarcinoma of usual type and its precursor, the adenocarcinoma in situ, have been shown to be positive for HPV in nearly 90% and 100% of cases, respectively. HPV 18 is more common in adenocarcinomas and adenosquamous carcinomas than in squamous cell carcinomas (Marth et al 2017).

1.2. Current Treatment of Recurrent or Metastatic Cervical Cancer

The primary treatment of advanced cervical cancer includes surgery, chemoradiotherapy, or combination of surgery and chemoradiation. In some cases, the tumor might be eradicated, and the treatment response can be durable. Patients who develop metastatic disease (ie, stage IVB) account for less than 5% of new cases and are rarely curable, with the primary treatment often as platinum-containing chemotherapy. It is estimated that recurrent or metastatic disease develops in 15% to 61% of women, usually within the first 2 years after completing primary treatment (Pfaendler and Tewari 2016). For recurrent or metastatic disease, highly selected patients (ie, locoregional recurrence and isolated distance metastasis) may be candidates for radical retreatment (ie, surgery, radiotherapy, and/or chemotherapy), but the treatment options are limited, and the prognosis is poor for the majority of women who are not amenable to therapy

with curative intent. Palliative systemic therapy with the aim of relieving symptoms and improving quality of life is usually indicated.

For first-line treatment of recurrent or metastatic disease, the standard of care has been cisplatin-based doublets with or without bevacizumab. There were 2 Phase 3 trials demonstrating the superiority of combination treatment of cisplatin with topotecan or paclitaxel to cisplatin monotherapy in terms of response rate and progression-free survival (PFS) (Moore et al 2004; Long et al 2005). There were no statistically significant differences in terms of overall survival (OS) from a large randomized Phase 3 study, which consisted of four different cisplatin-based doublets with paclitaxel, topotecan, gemcitabine or vinorelbine as the first-line treatment setting. Nevertheless, the paclitaxel-cisplatin combination treatment showed the highest response rate (29%), median PFS (5.8 months), and median OS (12.8 months) and was considered the preferred regimen (Monk et al 2009). The combination of paclitaxel and carboplatin could be considered an alternative for patients who are not candidates for cisplatin. Recently, a Phase 3, randomized trial (GOG 240) enrolled patients with primary stage IVB or recurrent/persistent disease who had not been treated with chemotherapy for recurrence and were not amenable to curative therapy. Patients were randomized to paclitaxel-cisplatin or paclitaxel-topotecan doublet, both with or without bevacizumab. The results showed that the addition of bevacizumab to chemotherapy was associated with increased OS (17.0 months versus 13.3 months; hazard ratio (HR), 0.71; 95% CI, 0.54 to 0.95; p = 0.004) and higher response rates (48% versus 36%, p = 0.008). Bevacizumab, as compared with chemotherapy alone, was associated with an increased incidence of ≥ Grade 2 hypertension (25% versus 2%), ≥ Grade 3 thromboembolic events (8% versus 1%), and ≥ Grade 3 gastrointestinal fistulas (3% versus 0%) (Tewari et al 2014).

For patients who have progressed after first-line platinum-based therapy, the treatment options are even more limited, and no standard of care has been established. Single cytostatic agents, including vinorelbine, topotecan, gemcitabine, or nanoparticle albumin-bound paclitaxel, have been evaluated as second-line treatment. However, response rates are low, and duration of response (DOR) is short. Summary of reported second-line single agents for recurrent/advanced cervical cancer is shown in Table 1 (Boussios et al 2016).

Table 1: Summary of Reported Second-Line Single Agents for Recurrent or Metastatic Cervical Cancer

Study	Agent	N	ORR (%)	PFS (months)	OS (months)
Thigpen T 2003	Cisplatin	190	23	NS	NS
	Ifosfamide	35	14–40	NS	NS
Takeuchi S 1991	Irinotecan	55	24	NS	NS
Verschraegen CF 1997	Irinotecan	42	21	NS	NS
Garcia AA 2007	Capecitabine	26	15.4	2.9	5.9
Look KY 2008	Capecitabine	21	0	NS	NS
Lorvidhaya V 2010	Capecitabine	45	2	4.1	9.3
Katsumata N 2011	S-1	36	31.8	5.2	15.4

Bookman MA 2000	Topotecan	45	12.5	2.1	6.6
Noda K 1996	Topotecan	22	18	NS	NS
Abu-Rustum NR 2000	Topotecan	12	17	NS	NS
Nascimento de Oliveira 2013	Topotecan	21	10	2.93	4.66
Coronel J 2009	Topotecan	18	NS	3.5	7.0
Fiorica JV 2009	Topotecan	25	NS	2.4	6.2
Muggia FM 2004	Vinorelbine	44	13.7	NS	NS
Muggia FM 2005	Vinorelbine	28	7.1	NS	NS
Miller DS 2008	Pemetrexed	29	15	3.1	7.4
Lorusso D 2010	Pemetrexed	43	13.9	2.5	8.8
Garcia AA 2007	Docetaxel	27	8.7	3.8	7.0
Schilder RJ 2005	Gemcitabine	22	4.5	2.1	6.5
Schilder RJ 2000	Gemcitabine	24	8	1.9	4.9
Thigpen T 1981	Cisplatin	12	17	NS	NS
Rose PG 2006	Pegylated liposomal doxorubicin	26	11	NS	NS
Rose PG 1996	Altretamine	29	0	NS	4.6
Rose PG 1998	Etoposide	24	8	NS	3.7
Curtin JP 2001	Paclitaxel	41	32	NS	7.3
Sutton GP 1993	Ifosfamide	39	15	NS	4.2
Sutton GP 1989	Ifosfamide	27	11	NS	NS
Vermorken JB 1991	DAC	15	0	NS	NS
van der Burg ME 1992	4∗-epidoxorubicin	24	4.2	3.2	NS

Abbreviations: DAC, 5-aza-2∗-deoxycytidine; N, number; NS, not stated; OS, overall survival; ORR, objective response rate; PFS, progression free survival

Virus-induced cancers are attractive targets for immunotherapy because viral proteins are strong immune stimulants. In June 2018, pembrolizumab received accelerated approval by the US FDA for the treatment of patients with recurrent or metastatic cervical cancers with disease progression on or after chemotherapy whose tumors express programmed death-ligand 1 (PD-L1) (Keytruda prescribing information 2020). The efficacy of pembrolizumab was investigated in a single cohort (Cohort E) in KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. The cohort enrolled 98 patients in total, and 77 patients had tumors that expressed PD-L1 with a Combined Positive Score (CPS) ≥ 1 and received at least 1 line of chemotherapy in the metastatic setting. For those 77 patients, 95% had M1 disease and 5% had recurrent disease; 35% had 1 prior line of therapy while 65% had ≥ 2 prior lines of therapy in the recurrent or metastatic setting. The objective response rate (ORR) was 14.3% (95% CI 7.4%, 24.1%). At the time of data cutoff, the median DOR was not reached, with 91% of responders having a response duration ≥ 6 months. Meanwhile, no responses were

observed in patients whose tumors did not have PD-L1 expression (CPS < 1) (Chung et al 2019). In CheckMate 358, a Phase I/II study evaluating nivolumab-based therapy in virus-associated tumors, 19 patients who had recurrent or metastatic cervical cancer with ≤ 2 prior systemic therapies were treated with nivolumab monotherapy 240 mg every 2 weeks. The ORR was 26.3% (95% CI, 9.1% to 51.2%), and DOR was not reached at data cutoff (range, 23.3 to 29.5+ months) (Naumann et al 2019). With those reports of moderate efficacy combined with durable response, immunotherapy remains an active compound of investigation in late line treatment of cervical cancer.

1.3. BGB-A1217 as a TIGIT Inhibitor

BGB-A1217 is a humanized immunoglobulin G (IgG) 1 monoclonal antibody binding to T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT) under clinical development for the treatment of human malignancies.

TIGIT (also known as VSIG9, VSTM3, or WUCAM) is a 26 kDa type I transmembrane glycoprotein and an immune checkpoint receptor, a member of the poliovirus receptor (PVR)/nectin family that plays an important role in promoting T-cell exhaustion in both chronic viral infections and tumor escape from immune surveillance (Yu et al 2009; Boles et al 2009; Stanietsky et al 2009; Levin et al 2011; Johnston et al 2014). TIGIT was initially discovered in a genomic search for genes specifically expressed in T cells that had a protein domain that consisted of inhibitory signaling motifs. The genes and cDNAs coding for TIGIT were cloned and characterized in mouse and human (Yu et al 2009). Mature human TIGIT contains 223 amino acid residues (National Center for Biotechnology Information 2018). Its extracellular domain consists of amino acid residues 1 through 120, and the transmembrane domain and cytoplasmic C-terminal tail comprises residues 121 through 223.

TIGIT-deficient mice ($TIGIT^{-/-}$) showed increased susceptibility to an experimental autoimmune model (Joller et al 2014). TIGIT overexpressing natural killer (NK) cells produced less interferon-gamma (IFN-γ) upon TIGIT/PVR ligation. In contrast, NK cells from TIGIT-deficient mice produced more IFN-γ in the presence of PVR-expressing target cells (Li et al 2014). Agonistic anti-TIGIT antibody could reduce the production of proinflammatory cytokines, including IFN-γ and IL-17, by antigen-restimulated splenocytes and antigen-specific proliferation. Consistent with these observations, blockade of TIGIT pathway in vivo by TIGIT blocking antibody alone or in combination with an anti-programmed cell death protein-1(PD-1) antibody reduced tumor growth in syngeneic mouse models (College of American Pathologist (CAP) Guidelines 2018; Argast et al 2018; Dixon et al 2018). All these findings strongly suggest that TIGIT is a critical immune checkpoint receptor in the maintenance of immune tolerance.

TIGIT is primarily expressed on immune cells, such as T cells, and NK cells (Manieri et al 2017). When expressed on effector T cells (cluster of differentiation [CD] 4^+ [CD4+] and $CD8^+$), activation of TIGIT has been shown to reduce cytokine production and T-cell proliferation, all of which could be rescued by TIGIT blocking antibodies or TIGIT expression knockdown (Joller et al 2014; Lozano et al 2012; Chauvin et al 2015). A similar phenomenon was also observed for NK cells (Stanietsky et al 2009; Zheng et al 2017).

TIGIT is also expressed on $FoxP3^+$ regulatory T (Treg) cells, especially in tumor tissues (Joller et al 2014; Kurtulus et al 2015). TIGIT-positive Treg cells demonstrated greater suppressive

functions when compared to TIGIT-negative Tregs, with higher expression of effector molecules, such as IL-10, granzymes, and Fgl2 (Joller et al 2014). A high TIGIT/CD226 ratio in Tregs is associated with increased Treg frequencies in tumors and poor clinical outcome upon immune checkpoint blockade (Fourcade et al 2018). Some studies have also shown that TIGIT suppresses immune responses mediated by dendritic cells by binding with PVR, especially in enhancement of IL-10 production and inhibition of IL-12 production (Yu et al 2009).

As an immune "checkpoint" molecule, TIGIT initiates inhibitory signaling in immune cells when engaged by its ligands, PVR (CD155) and poliovirus receptor-related 2 (PVR-L2) (CD112 or nectin-2). These ligands are primarily expressed on antigen-presenting cells and tumor cells (Casado et al 2009; Stanietsky et al 2009; Yu et al 2009; Levin et al 2011). The binding affinity of TIGIT to PVR (equilibrium dissociation constant [K_D]: ~1 nM) is much higher than to PVR-L2, and whether the TIGIT:PVR-L2 interaction is functionally relevant in mediating inhibitory signals remains to be determined. The co-stimulatory receptor, CD226, binds to the same ligands with lower affinity (K_D: ~100nM) but delivers a positive signal and enhances the cytotoxicity of T cells and NK cells (Bottino et al 2003; Stanietsky et al 2009). High affinity binding of TIGIT to PVR could compete off CD226-PVR interaction, thereby reducing the activation of T cells or NK cells (Stanietsky et al 2009).

The cytoplasmic tail of TIGIT has an inhibitory immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tail tyrosine-like motif. In NK cells, TIGIT engagement induces the phosphorylation of tyrosine residues in its ITIM and immunoreceptor tail tyrosine-like motifs through the Src kinases Fyn and Lck. Then, the phosphorylations of TIGIT lead to binding of Grb2 and β-arrestin 2 and subsequent recruitment of SHIP-1 and SHP-2 to terminate PI3K and NK-κB signaling in the NK cells (Liu et al 2013; Stanietsky et al 2009). Engagement of agonistic TIGIT antibody induces T-cell receptor complex disruption (Stanietsky et al 2009). Additionally, interaction between TIGIT and PVR on dendritic cells could lead to phosphorylation of PVR and modulation of ERK activation in dendritic cells (Yu et al 2009).

Up-regulation of TIGIT expression in tumor-infiltrating lymphocytes (TILs) has been reported in many types of cancers, such as lung (Tassi et al 2017), stomach (He et al 2017), breast (Gandara et al 2018; Gil Del Alcazar et al 2017), esophageal (Xie et al 2016), brain (Hung et al 2018), acute myeloid leukemia (Kong et al 2016), and melanoma (Mahnke and Enk et al 2016). Interestingly, TIGIT expression appears to be minimally expressed by peripheral effector cells while being significantly up-regulated by tumor localized effector cells, which strongly suggests that the tumor microenvironment utilizes TIGIT signaling to further suppress/evade immune-mediated tumor cytotoxicity (Johnston et al 2014). Further, up-regulation of TIGIT signaling plays an important role in immune tolerance to cancer, similar to its function in the presence of chronic viral infections (Yin et al 2018; Chauvin et al 2015. Blockade of TIGIT receptor alone or in combination with PD-1/PD-L1 blockade has been shown both in vitro and in vivo to rescue functionally "exhausted" T cells (Johnston et al 2014; Chauvin et al 2015). In mouse models, TIGIT blockade in combination with anti–PD-1/PD-L1 antibodies demonstrated significantly better antitumor efficacy than either monotherapy (Johnston et al 2014; Dixon et al 2018).

In mouse models, Fc with effector functions is critical for TIGIT antibody-mediated antitumor activity (College of American Pathologist (CAP) Guidelines 2018; Argast et al 2018; Leroy et al 2018). In CT26.WT mouse colon cancer model, anti-mouse TIGIT antibody of mIgG2a isotype (antibody-dependent cellular cytotoxicity enabling) demonstrated potent antitumor activity either

in monotherapy or in combination with anti-PD-1 antibody. In contrast, anti-TIGIT antibody with Fc devoid of effector functions did not show any of the antitumor efficacies in the same model, indicating that Fc-mediated effector functions are required for TIGIT antibody-mediated antitumor effects. Additionally, the observed efficacy was associated with an increased activity of effector T cells ($CD8^+$ and $CD4^+$) and also with Treg depletion within the tumor microenvironment. Argast and colleagues (College of American Pathologist (CAP) Guidelines 2018; Argast et al 2018) also observed that effector functions were critical for TIGIT antibody-induced in vivo efficacy. Waight and colleagues (Waight et al 2018), reported the interaction of anti-TIGIT with FcγR on antigen-presenting cells enhanced antigen-specific T cell responses and antitumor activity.

Taken as a whole, targeting TIGIT provides a potential mechanism to rescue immune cells (eg, T cells, NK cells, and dendritic cells) from the immunosuppressive tumor microenvironment, thereby inducing an efficient antitumor immune response. Blocking antibodies targeting the PD-1/PD-L1 pathway have achieved remarkable results in the treatment of many different tumor types. However, based upon the rate of primary and secondary resistance to PD-1 blockade, it is apparent that additional immuno-regulatory mechanism(s) underlie tumor immune escape. Indeed, research shows that the TIGIT pathway cooperates with PD-1 to maximize the suppression of effector TILs as well as to promote resistance to anti-PD-1 therapy. Therefore, TIGIT represents an ideal target with the potential to significantly improve and/or extend the therapeutic benefit of anti-PD-1 therapy to a greater number of patients.

1.3.1. Nonclinical

1.3.1.1. Pharmacology

BGB-A1217 binds to the extracellular domain of human TIGIT with high specificity and affinity (K_D = 0.135 nM), as demonstrated by target-binding assays and surface plasmon resonance characterization. It competitively blocks TIGIT binding to PVR. In in vitro cell-based assays, BGB-A1217 “in a dose dependent manner”: “consistently and dose-dependently enhances the functional activities of activated human peripheral blood mononuclear cells (PBMCs)”. Additionally, BGB-A1217 has shown antitumor activities in both the GL261 mouse glioma tumor model and the CT26.WT mouse colon cancer model in humanized TIGIT knock-in mice. In the MC-38 mouse colon cancer model in humanized TIGIT knock-in mice, BGB-A1217 in combination with anti-mouse PD-1 significantly inhibited tumor growth compared with either therapy alone.

BGB-A1217 has the constant region of a wild-type human IgG1 to enable the Fc-mediated effector functions. BGB-A1217 has demonstrated competent binding to complement 1q (C1q) and all FcγRs, including FcγRI, FcγRIIA, FcγRIIB, and FcγRIIIA, in in vitro binding assays, and induces antibody-dependent cellular cytotoxicity against TIGIT overexpressing cell line, but no antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity against primary T cells in cell-based assays.

Refer to the BGB-A1217 Investigator’s Brochure for detailed information regarding pharmacology studies.

1.3.1.2. Toxicology

Humanized TIGIT knock-in mice containing human TIGIT gene and cynomolgus monkeys were selected for nonclinical safety evaluation of BGB-A1217 based on the homology of TIGIT amino acid sequence, binding affinity, and efficacy studies. Cynomolgus monkeys were the most relevant species based on the homology sequence of TIGIT, though it demonstrates a relatively lower BGB-A1217 binding affinity compared to human TIGIT (with EC50 756-fold weaker). BGB-A1217 does not bind to mouse TIGIT due to the significant sequence divergence between human and mouse TIGIT; however, BGB-A1217 demonstrates a comparable binding affinity in TIGIT receptor occupancy assays with CD3+ splenocytes from humanized TIGIT knock-in mice compared to CD3+ human PBMCs (with EC50 of 48.8 ng/mL versus 63.2 ng/mL, respectively). In addition, BGB-A1217 shows significant inhibition of GL261 tumor growth in humanized TIGIT knock-in mice at a dose of 0.4 mg/kg and above via weekly intraperitoneal dosing.

The toxicity and safety profile of BGB-A1217 was characterized in a 4-week repeat dose toxicology study in humanized TIGIT knock-in mice and a 13-week repeat dose toxicology study in cynomolgus monkeys. Furthermore, BGB-A1217 was evaluated in a 4-week repeat dose study in humanized TIGIT knock-in mice with subcutaneous MC-38 tumors. The dose levels spanned from the intended human therapeutic doses to 10-fold higher in the 4-week mouse studies and 20-fold higher in the 13-week monkey study. The cynomolgus monkey was considered the relevant species for toxicity studies based upon the target sequence homology and cross-species TIGIT binding activities of BGB-A1217. The tissue cross reactivity was evaluated in the normal frozen tissues from humans. The cytokine release responses were also evaluated using fresh human PBMCs.

No apparent toxicity was noted in humanized mice after repeated dosing of BGB-A1217 at either 5 or 50 mg/kg weekly for 4 weeks, nor in monkeys following repeated dosing at 10, 30, or 100 mg/kg once every 2 weeks for 13 weeks. The toxicokinetic profile was characterized in both the mouse and monkey studies, and the systemic exposure appeared to be dose-proportional with no gender difference in either study. A trend of accumulation was noted after repeated doses in mice; however, no accumulation was observed over the 13-week dosing period in monkeys. No immunotoxicity was apparent as no changes in clinical pathology or histopathology were observed in these studies. Immunogenicity with positive antidrug antibodies (ADAs) against BGB-A1217 was noted in several mice dosed at 5 and 50 mg/kg over the 4 weeks; however, with the exception of one animal with strong ADA response at 5 mg/kg dose, most of these animals showed weak ADA signal or were proved to be false positives. In monkeys dosed at 10, 30, and 100 mg/kg, positive ADAs against BGB-A1217 were observed in 6 of 10, 3 of 10, and 4 of 10 animals during the dosing period and 3 of 4, 2 of 4, and 2 of 4 animals during the recovery period, respectively. The anti-BGB-A1217 antibodies showed a rapid clearance of BGB-A1217 in serum in a few individual animals but did not appear to have an effect on the overall systemic exposure (area under the concentration-time curve [AUC]) or toxicity assessment.

The tissue cross reactivity of BGB-A1217 was evaluated in frozen normal human tissues using an immunohistochemistry method, with appropriate positive and negative controls. No specific binding of BGB-A1217 was noted with normal human tissues. A variety of factors might contribute to the negative results, including negligible target expression in normal tissues (Yang 2016; Human Protein Atlas 2019) and sensitivity of the immunohistochemistry method.

No significant increase in cytokine release was observed from an in vitro cytokine release assay following treatment of non-activated PBMCs with BGB-A1217 when compared to human IgG. The results suggested that BGB-A1217 had potentially low risks of causing acute cytokine release syndrome.

Overall, no apparent toxicity was noted in the monkey or transgenic mice toxicity studies. No unexpected tissue cross reactivity was found in human or monkey tissues. The toxicokinetic profile was well characterized with dose-proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The no-observed-adverse-effect level (NOAEL) of BGB-A1217 was 50 mg/kg in the 4-week mouse study and 100 mg/kg in the 13-week monkey toxicity study. The safety profile of BGB-A1217 is considered adequate to support first-in-human dosing.

Refer to the BGB-A1217 Investigator's Brochure for detailed information regarding toxicology studies.

1.3.2. Clinical Experience

1.3.2.1. Clinical Experience From Other TIGIT Inhibitors

To date, the first-in-human Phase 1 and 2 clinical studies have been initiated for 6 anti-TIGIT antibodies: MTIG7192A from Genentech/Roche (NCT02794571 and NCT03563716), BMS-986207 from Bristol-Myers Squibb (NCT02913313), MK-7684 from Merck Sharp & Dohme (NCT02964013), OMP-313M32 from OncoMed (NCT03119428), ASP8374 from Astellas/Potenza (NCT03260322), and AB-154 from Arcus (NCT03628677). The goals for these clinical studies are to evaluate the safety and efficacy of anti-TIGIT antibodies alone and/or in combination with anti-PD-1 or anti-PD-L1 antibodies.

To date, clinical data have been released for OncoMed's OMP-313M32 (Sharma et al 2018), Merck's MK-7684 (Golan et al 2018), and Genentech/Roche's tiragolumab (Bendell et al 2020; Rodriguez-Abreu et al 2020).

A total of 68 patients have been treated with MK-7684 alone or MK-7684 in combination with pembrolizumab (an anti-PD-1 antibody) in a Phase 1 study sponsored by Merck Sharp & Dohme, with doses of MK-7684 ranging from 2.1 mg to 700 mg. The preliminary results showed that MK-7684 was well tolerated in the dose escalation phase of the study, with no dose-limiting toxicity (DLT). Adverse events (AEs) that occurred in > 15% of patients were fatigue (n = 5, 15%) for MK-7684 monotherapy and pruritus (n = 10, 21%) for MK-7684 and pembrolizumab combination therapy. Furthermore, only 2 treatment-related AEs ≥ Grade 3 were reported (Grade 3 anemia and Grade 3 diarrhea) for monotherapy and 5 treatment-related AEs ≥ Grade 3 were reported for combination with pembrolizumab (5 Grade 3: alanine aminotransferase [ALT] increased, colitis, γGT increased, hypersensitivity, and rash maculopapular). Of the 34 evaluable patients treated with MK-7684 alone, one partial response (1 of 34 [3.0%]) and a 35% disease control rate were observed. For combination of MK-7684 and pembrolizumab, 6 partial responses (6 of 34 [18%]) and a 48% disease control rate were observed. In addition, pharmacokinetic (PK) findings were linear above 200 mg.

A total of 18 patients have been treated with OMP-313M32 monotherapy in a Phase 1 study sponsored by OncoMed, with doses ranging from 0.3 mg/kg to 20 mg/kg. The preliminary results showed that OMP-313M32 was well tolerated in the dose escalation phase of the study, with no DLT. Treatment-related AEs that occurred in > 15% of patients were rash (n = 5; 27.8%), fatigue (n = 3, 16.7%), nausea (n = 3, 16.7%), and pruritus (n = 3, 16.7%) for OMP-313M32 monotherapy. Grade ≥ 3 treatment-related AEs included rash (n = 3, 16.7%), fatigue (n = 1, 5.6%), hypophosphatemia (n = 1, 5.6%), and autoimmune hepatitis (n = 1, 5.6%). Based upon the safety profile of OMP-313M32 monotherapy, OncoMed has initiated the dose expansion with the combination of OMP-313M32 and nivolumab (an anti-PD-1 antibody) in patients with non-small cell lung, head and neck, esophageal, gastric, cervical, triple negative breast, anal, and hepatocellular cancers or with microsatellite instability-high tumors (NCT03119428).

The Phase 1 data for tiragolumab was released at the 2020 American Association of Cancer Research meeting (Bendell et al 2020). No objective responses occurred in 24 patients treated with tiragolumab monotherapy in Phase 1a. However, in Phase 1b, 5 of 44 patients (11.4%) treated with tiragolumab combined with atezolizumab had achieved partial response (Bendell et al 2020). In the Phase 1a (tiragolumab monotherapy) cohort, there were no Grade 3-5 immune-mediated AEs (imAEs). Grade 1-2 imAEs included infusion-related reaction (n = 2, 8%), rash (n = 2, 8%), hepatitis (n = 1, 4%), and pancreatitis (n = 1, 4%). In the Phase 1b (tiragolumab combined with atezolizumab) cohort, 4% of patients experienced Grade 3-5 imAEs; no Grade 5 imAEs were associated with tiragolumab and/or atezolizumab. These imAEs included infusion-related reaction (n = 4, 8%), rash (n = 14, 29%), hepatitis (n = 10, 20%), pancreatitis (n = 1, 2%), hyperthyroidism (n = 4, 8%), hypothyroidism (n = 3, 6%), and anemia (n = 1, 2%).

A total of 135 patients with previously untreated PD-L1-selected non-small cell lung cancer were treated with tiragolumab 600 mg intravenously (IV) every 3 weeks (Q3W) plus atezolizumab 1200 mg IV Q3W (n = 67) or atezolizumab 1200 mg IV Q3W plus placebo IV Q3W (n = 68) in a Phase 2 study (CITYSCAPE) sponsored by Genentech/Roche. Patients were randomly assigned to 1 of these treatment groups and were stratified by tumor proportion score (1% to 49% or ≥ 50%), histology (squamous versus nonsquamous), and tobacco use (yes or no). Preliminary efficacy results showed a clinically meaningful improvement in ORR and PFS in patients treated with tiragolumab plus atezolizumab (ORR 31%; PFS 5.42 months) compared with those treated with atezolizumab plus placebo (ORR 16%; PFS 3.58 months). This improvement was still observed 6 months later: tiragolumab plus atezolizumab (ORR 37%; PFS 5.55 months) compared with atezolizumab plus placebo (ORR 21%; PFS 3.88 months). In addition, analysis at this 6-month follow-up timepoint showed a greater improvement in ORR in patients in the PD-L1 tumor proportion score ≥ 50% subgroup who received tiragolumab plus atezolizumab (ORR 66%) compared with atezolizumab plus placebo (ORR 24%). Preliminary safety results showed that study treatment with tiragolumab plus atezolizumab was well tolerated; results were generally similar between the 2 treatment groups. More patients in the tiragolumab plus atezolizumab group experienced imAEs compared with those in the atezolizumab plus placebo group (46 [69%] versus 32 [47%]); most imAEs were Grade 1 or Grade 2 events of infusion-related reaction and rash and were manageable. Based on these observed efficacy and safety results, Genentech/Roche is conducting an ongoing Phase 3 study

(SKYSCRAPER-01) in first-line PD-L1 tumor proportion score ≥ 50 non-small cell lung cancer (NCT04294810).

All of these findings support further development of anti-TIGIT antibody in combination with existing therapeutic modalities.

1.3.2.2. Preliminary Safety

The first-in-human study BGB-900-105 evaluating the safety and tolerability of BGB-A1217 in combination with tislelizumab in advanced solid tumors is still ongoing.

As of 16 June 2020, 11 DLT evaluable patients had received at least 1 dose of BGB-A1217 combined with tislelizumab 200 mg Q3W in the dose escalation stage. The dosage of BGB-A1217 ranged from 50 mg to 900 mg Q3W. One patient received a BGB-A1217 dosage of 50 mg Q3W, 3 patients received 150 mg Q3W, 4 patients received 450 mg Q3W, and 3 patients received 900 mg Q3W. The maximum administered dose was BGB-A1217 900 mg combined with tislelizumab 200 mg Q3W. The maximum tolerated dose (MTD) was not reached. BGB-A1217 is safe and well-tolerated up to 900 mg dose level. No DLTs, treatment-related serious adverse events (SAEs), or high-grade AEs occurred during the treatment period for any dose level. Clinical activity documented as stable disease (SD) was observed in 1 patient at each of the following BGB-A1217 doses: 150 mg, 450 mg, and 900 mg. Subsequent to the data cutoff date of 16 June 2020, 6 additional patients have been enrolled and dosed at the maximum administered dose of BGB-A1217 900 mg combined with tislelizumab 200 mg Q3W. BGB-A1217 continues to appear to be safe and well-tolerated up to and including the 900 mg dose level.

In Study BGB-900-105, a treatment-emergent adverse event (TEAE) was 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 up to 30 days following study drug discontinuation or initiation of subsequent anticancer therapy, whichever came first.

As of the data cutoff date of 16 June 2020, 8 (72.7%) of the 11 patients had ≥ 1 TEAE. Most TEAEs were Grade 1 or Grade 2. Three TEAEs (atrial flutter, pericardial effusion malignant, and dyspnea), which occurred in 1 patient each, were Grade 3. Treatment-related TEAEs, and serious TEAEs occurred in 3 (27.3%) patients each.

No patients had Grade 4 or Grade 5 TEAEs, serious treatment-related TEAEs, TEAEs leading to treatment discontinuation, or TEAEs leading to death (Table 2). No TEAE met the criteria of DLT.

The most commonly reported TEAEs were fatigue (3 [27.3%]) and diarrhea and aspartate aminotransferase increased (2 [18.2%] each). All other TEAEs occurred in 1 (1 [9.1%]) patient each (Table 3).

Refer to the BGB-A1217 Investigator's Brochure for detailed safety information.

The Phase 1 study is still ongoing with more dose levels under exploration.

1.3.2.3. Clinical Pharmacology

As of the data cutoff date of 16 June 2020, preliminary PK data of BGB-A1217 are available from a total of 11 patients treated with BGB-A1217 at 50 mg (n=1), 150 mg (n=3), 450 mg

(n=4), and 900 mg (n=3) dose levels in combination with tislelizumab 200 mg in the dose escalation portion of Study BGB-900-105. BGB-A1217 serum concentrations declined in a biexponential manner after IV infusion and the BGB-A1217 exposures (maximum observed plasma concentration [C_{max}] and AUC) increased approximately dose-proportionally from 50 mg to 900 mg.

Peripheral TIGIT receptor occupancy data were available for 11 enrolled patients treated with BGB-A1217 at 50 mg (n=1), 150 mg (n=3), 450 mg (n=4), and 900 mg (n=3) dose levels in Study BGB-900-105. Complete TIGIT receptor occupancy (100%) was observed on CD8, CD4, NK and Treg cells in peripheral blood at all the tested dose levels.

1.3.2.4. Efficacy

The first-in-human study BGB-900-105 evaluating efficacy of BGB-A1217 in combination with tislelizumab in advanced solid tumors is still ongoing. As of 16 June 2020, the clinical activity documented as SD can be observed in 1 patient each at BGB-A1217 doses of 150 mg, 450 mg, and 900 mg.

Table 2: Overview of Treatment-Emergent Adverse Events (Safety Analysis Set)

	BGB-A1217 50 mg + tislelizumab 200 mg (N = 1) n (%)	BGB-A1217 150 mg + tislelizumab 200 mg (N = 3) n (%)	BGB-A1217 450 mg + tislelizumab 200 mg (N = 4) n (%)	BGB-A1217 900 mg + tislelizumab 200 mg (N = 5) n (%)	Total (N = 11) n (%)
Any TEAE	1 (100.0)	3 (100.0)	3 (75.0)	1 (33.3)	8 (72.7)
Any treatment-related TEAE	1 (100.0)	0 (0.0)	2 (50.0)	0 (0.0)	3 (27.3)
Grade ≥ 3 TEAE	1 (100.0)	1 (33.3)	1 (25.0)	0 (0.0)	3 (27.3)
Grade ≥ 3 treatment-related TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious TEAE	1 (100.0)	1 (33.3)	1 (25.0)	0 (0.0)	3 (27.3)
Serious treatment-related TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to treatment discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Related TEAE leading to treatment discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: N = total patients treated; TEAE = treatment-emergent adverse event.
Notes: A patient with multiple occurrences of an AE is counted only once in the AE category. Treatment-related TEAE includes patients who had a BGB-A317- or BGB-A1217-related TEAE.

Table 3: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Analysis Set)

System Organ Class Preferred Term	BGB-A1217 50 mg + tislelizumab 200 mg (N = 1) n (%)	BGB-A1217 150 mg + tislelizumab 200 mg (N = 3) n (%)	BGB-A1217 450 mg + tislelizumab 200 mg (N = 4) n (%)	BGB-A1217 900 mg + tislelizumab 200 mg (N = 3) n (%)	Total (N = 11) n (%)
Patients with ≥ 1 TEAE	**1 (100.0)**	**3 (100.0)**	**3 (75.0)**	**1 (33.3)**	**8 (72.7)**
Gastrointestinal disorders	**1 (100.0)**	**1 (33.3)**	**2 (50.0)**	**0 (0.0)**	**4 (36.4)**
Diarrhoea	0 (0.0)	1 (33.3)	1 (25.0)	0 (0.0)	2 (18.2)
Abdominal pain	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Constipation	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Dry mouth	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
General disorders and administration site conditions	**1 (100.0)**	**0 (0.0)**	**1 (25.0)**	**1 (33.3)**	**3 (27.3)**
Fatigue	1 (100.0)	0 (0.0)	1 (25.0)	1 (33.3)	3 (27.3)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**1 (33.3)**	**1 (25.0)**	**1 (33.3)**	**3 (27.3)**
Back pain	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (9.1)
Flank pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (9.1)
Groin pain	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Infections and infestations	**1 (100.0)**	**0 (0.0)**	**1 (25.0)**	**0 (0.0)**	**2 (18.2)**
Influenza	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
Otitis externa	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Investigations	**1 (100.0)**	**1 (33.3)**	**0 (0.0)**	**0 (0.0)**	**2 (18.2)**
Aspartate aminotransferase increased	1 (100.0)	1 (33.3)	0 (0.0)	0 (0.0)	2 (18.2)
Nervous system disorders	**1 (100.0)**	**0 (0.0)**	**1 (25.0)**	**0 (0.0)**	**2 (18.2)**
Neuralgia	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)

System Organ Class Preferred Term	BGB-A1217 50 mg + tislelizumab 200 mg (N = 1) n (%)	BGB-A1217 150 mg + tislelizumab 200 mg (N = 3) n (%)	BGB-A1217 450 mg + tislelizumab 200 mg (N = 4) n (%)	BGB-A1217 900 mg + tislelizumab 200 mg (N = 3) n (%)	Total (N = 11) n (%)
Somnolence	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**1 (33.3)**	**1 (25.0)**	**0 (0.0)**	**2 (18.2)**
Cough	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Dyspnoea	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (9.1)
Skin and subcutaneous tissue disorders	**1 (100.0)**	**0 (0.0)**	**0 (0.0)**	**1 (33.3)**	**2 (18.2)**
Drug eruption	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (9.1)
Dry skin	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
Blood and lymphatic system disorders	**0 (0.0)**	**0 (0.0)**	**1 (25.0)**	**0 (0.0)**	**1 (9.1)**
Anaemia	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Cardiac disorders	**1 (100.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (9.1)**
Atrial flutter	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
Ear and labyrinth disorders	**0 (0.0)**	**1 (33.3)**	**0 (0.0)**	**0 (0.0)**	**1 (9.1)**
Ear discomfort	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (9.1)
Eye disorders	**0 (0.0)**	**0 (0.0)**	**1 (25.0)**	**0 (0.0)**	**1 (9.1)**
Dry eye	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 (0.0)**	**0 (0.0)**	**1 (25.0)**	**0 (0.0)**	**1 (9.1)**
Cancer pain	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Pericardial effusion malignant	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Psychiatric disorders	**0 (0.0)**	**1 (33.3)**	**0 (0.0)**	**0 (0.0)**	**1 (9.1)**
Confusional state	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (9.1)

N = total patients treated; TEAE = treatment-emergent adverse event.
Notes: A patient with multiple occurrences of an AE is counted only once in the AE category. MedDRA version 22.0 was used to code adverse events. Adverse events were graded using CTCAE version 5.0 per protocol. Events are sorted in descending order of the number of patients for SOC and PT in the Total column.

1.4. Tislelizumab as a PD-1 Inhibitor

1.4.1. Pharmacology

Tislelizumab (also known as BGB-A317) 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 (KD = 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 pre-activated, primary PBMCs. Tislelizumab has demonstrated in-vivo antitumor activity in several allogeneic xenograft models, in which PBMCs were co-injected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

Tislelizumab is an IgG4-variant antibody to gamma fragment crystallizable region (Fc) receptors (FcγR) such as FcγRI and FcγRIIIA, and it has very low binding affinity to C1q, a subunit of complement 1. In vitro assays with tislelizumab suggest either low or no antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, or complement-dependent cytotoxicity effects in humans (Labrijn et al 2009). Tislelizumab was specifically engineered to abrogate these potential mechanisms of T-cell clearance and potential resistance to anti-PD-1 therapy.

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

1.4.2. 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, repeat-dose toxicology study in cynomolgus monkeys. Tissue cross-reactivity was evaluated in normal frozen tissues from both humans and monkeys. The cytokine release assays were conducted using fresh human whole blood cells. 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. Cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

Overall, no apparent toxicity was noted in mice or monkey toxicity studies. No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in the human whole-blood assay. The toxicokinetic profile was well characterized, with dose-proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The NOAEL of tislelizumab in the 13-week monkey toxicity study was considered to be 30 mg/kg. The safety profile of tislelizumab is considered adequate to support the current study, BGB-900-105.

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

1.4.3. Clinical Pharmacology

Population PK analysis was conducted using data from 798 patients with solid tumors or classical Hodgkin lymphoma who had received doses of 0.5, 2.0, 5.0, and 10 mg/kg once every 2 weeks, 2.0 and 5.0 mg/kg once every 3 weeks, and 200 mg once every 3 weeks. The 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 typical estimates of clearance (CL), central volume (V_c), and peripheral volumes (V_2, V_3) were 0.164 L/day, 2.92 L, 0.928 L, and 1.39 L, respectively, with moderate inter-individual variability in CL (32.2%), V_c (16.7%), V_2 (56.6%), and V_3 (94.2%). The volume of distribution at steady state (Vss) was 5.238 L, which is typical of monoclonal antibodies with limited distribution, which is consistent with a standard IgG monoclonal antibody (Deng et al 2012; Dirks and Meibohm 2010; Keizer et al 2010; Ryman and Meibohm 2017). Based on the population PK analysis, tislelizumab PK was characterized by a terminal half-life of approximately 25.5 days, which is consistent with other therapeutic IgG monoclonal antibodies.

Population PK analysis demonstrated that baseline age, race, alanine aminotransferase, aspartate aminotransferase, bilirubin, lactate dehydrogenase, estimated glomerular filtration rate, Eastern Cooperative Oncology Group (ECOG) Performance Status, immunogenicity, and sum of products of perpendicular diameters in classical Hodgkin lymphoma patients did not show statistically significant impact on the PK of tislelizumab. Although tumor size, albumin, and tumor type were significant covariates on CL, while body weight, sex, and tumor type were significant covariates on V_c, these covariates are not expected to have a clinically relevant impact on tislelizumab exposure. 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. Population PK analysis supports fixed-dosing across different ethnic groups.

1.4.4. Prior Clinical Experience of Tislelizumab

As of 20 May 2019, there are 22 ongoing studies with tislelizumab with over 1705 patients treated. Of these, 13 studies have preliminary data available in the Investigator's Brochure (IB) version 7, 13 September 2019: 7 monotherapy studies, 2 chemotherapy combination therapy studies; and 4 investigational agent combination therapy studies.

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

1.4.4.1. Pooled Safety Assessment of Monotherapy Studies

A pooled analysis of 7 monotherapy studies was conducted to provide a comprehensive safety assessment separately from combination therapy.

Overall, there were 1273 patients in the pooled monotherapy studies: 1137 patients treated in 5 solid tumor studies and 136 patients treated in 2 hematologic malignancies 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 Locally Advanced or Metastatic Urothelial Bladder Cancer), and BGB-A317-209 (Previously-Treated Locally Advanced Unresectable or Metastatic Microsatellite Instability-High [MSI-H] or Mismatch Repair Deficient (dMMR) Solid Tumors). The 2 studies in hematologic malignancies are BGB-A317-203 (Phase 2 Relapsed or Refractory Classical Hodgkin Lymphoma) and BGB-A317-207 (Relapsed or Refractory Mature T- and NK-cell Neoplasms).

Of the 1273 enrolled patients, 544 patients (42.7%) remained on study as of 20 May 2019; and 272 patients (21.4%) were still receiving tislelizumab treatment.

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

1.4.4.1.1. Pooled Demographics and Baseline Characteristics

Table 4 shows the demographics and baseline characteristics for the patients treated in the Pooled Monotherapy studies.

Table 4: Demographics, Baseline Characteristics, Treatment Exposure Duration, and Study Follow-up Duration in Pooled Monotherapy Studies

Measure	Overall[a] N = 1273
Age (years)	
Median	59.0
Min, Max	18, 90
Sex, n (%)	
Male	852 (66.9)
Female	421 (33.1)
Race, n (%)	
Asian	807 (63.4)
Black	11 (0.9)
White	405 (31.8)
Missing	2 (0.2)
Other	48 (3.8)
Prior systemic anti-cancer therapy regimens[b]	
Median	1.0
Min, Max	0, 12
Prior systemic anti-cancer therapy regimens (grouped)[b], n (%)	
0	271 (21.3)
1	413 (32.4)
2	265 (20.8)
≥ 3	324 (25.5)
Study treatment exposure duration (months)	
Median	3.58
Min, Max	0.1, 43.6

Measure	Overall[a] N = 1273
Study follow-up duration (months)	
Median	8.34
Min, Max	0.1, 47.5

Source: Tislelizumab Investigator's Brochure.
Abbreviations: N, total number of patients treated; n, number of patients within each category.
Data cutoff 20 May 2019.
[a] Solid tumor studies include: BGB-A317_Study_001, BGB-A317-102, BGB-A317-204, BGB-A317-208, BGB-A317-209, and hematology studies include: BGB-A317-203, BGB-A317-207.
[b] Only systemic therapies were selected.

Overall, the 1273 patients in the pooled monotherapy analysis had a median treatment exposure duration of 3.58 months (range: 0.1 to 43.6 months) and a median study follow-up duration of 8.34 months (range: 0.1 to 47.5 months). Overall, the total pooled monotherapy population had a median age of 59 years and was 66.9% male.

1.4.4.1.2. Treatment-Related Adverse Events

Of the 1273 total patients treated in the Pooled Monotherapy studies, 846 (66.5%) experienced at least one treatment-related treatment-emergent adverse event (TEAE). The most commonly occurring TEAEs (≥ 5% of patients) assessed as related to tislelizumab were aspartate aminotransferase increased (128 patients, 10.1%), alanine aminotransferase increased (123 patients, 9.7%), hypothyroidism (113 patients, 8.9%), rash (96 patients, 7.5%), and pyrexia (94 patients, 7.4%).

Of the 1273 total patients treated in the Pooled Monotherapy studies, 162 (12.7%) experienced at least one ≥ Grade 3 TEAE assessed as related to tislelizumab. The only ≥ Grade 3 TEAEs that occurred in ≥ 1% (≥ 12 patients) in the total study population were aspartate aminotransferase increased (19 patients, 1.5%) and alanine aminotransferase increased (15 patients, 1.2%).

1.4.4.1.3. Treatment-Emergent Serious Adverse Events

Of the 1273 total patients treated in the Pooled Monotherapy studies, 424 (33.3%) experienced at least 1 treatment-emergent SAE. The most commonly occurring treatment-emergent SAEs were pneumonia (35 patients, 2.7%), pyrexia (22 patients, 1.7%), and ascites (17 patients, 1.3%).

1.4.4.1.4. Immune-Mediated Adverse Events

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

Immune-mediated AEs are consistent with an immune-mediated mechanism or immune-mediated component for which noninflammatory etiologies (eg, infection or tumor progression) have been ruled out. Immune-mediated AEs can include events with an alternate etiology which was exacerbated by the induction of autoimmunity. There is a potential temporal relationship

between the initiation of treatment with tislelizumab and the onset of an imAE that spans a window of days to several months.

All imAEs presented here were assessed as related to study drug by the investigator and categorized by the sponsor Safety/Pharmacovigilance team. 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 ≥ 1% patients in the total Pooled Monotherapy studies are shown in Table 5.

Table 5: Immune-Related Adverse Events of Any Grade Occurring in ≥ 1% in Pooled Monotherapy Studies

Categories Preferred Term	Total (N = 1273)	
	Any Grade n (%)[a]	**Grade ≥ 3 n (%)[a]**
Patients with at least one potential immune-mediated AE[a]	602 (47.3)	121 (9.5)
Immune-related skin adverse reaction	242 (19.0)	11 (0.9)
Rash	97 (7.6)	4 (0.3)
Pruritus	78 (6.1)	0
Pruritus generalized	29 (2.3)	0
Rash maculo-papular	24 (1.9)	1 (0.1)
Immune-related hepatitis	233 (18.3)	51 (4.0)
Aspartate aminotransferase increased	129 (10.1)	21 (1.6)
Alanine aminotransferase increased	124 (9.7)	16 (1.3)
Blood bilirubin increased	74 (5.8)	4 (0.3)
Gamma-glutamyltransferase increased	45 (3.5)	17 (1.3)
Bilirubin conjugated increased	40 (3.1)	3 (0.2)
Immune-related endocrinopathies	187 (14.7)	7 (0.5)
Hypothyroidism	113 (8.9)	0
Hyperthyroidism	47 (3.7)	1 (0.1)
Hyperglycaemia	17 (1.3)	4 (0.3)
Immune-related colitis	75 (5.9)	10 (0.8)
Diarrhoea	66 (5.2)	5 (0.4)
Immune-related pneumonitis	50 (3.9)	30 (2.4)
Pneumonitis	22 (1.7)	9 (0.7)
Lung infection	13 (1.0)	8 (0.6)

Categories Preferred Term	Total (N = 1273)	
	Any Grade n (%)[a]	**Grade ≥ 3 n (%)[a]**
Immune-related myositis/rhabdomyolysis/cardiomyopathy	39 (3.1)	7 (0.5)
Blood creatine phosphokinase increased	30 (2.4)	4 (0.3)
Immune-related nephritis and renal dysfunction	33 (2.6)	6 (0.5)
Blood creatinine increased	25 (2.0)	2 (0.2)

Source: Tislelizumab Investigator's Brochure.
Abbreviations: AE, adverse event; N, total number of patients treated; n, number of patients within each category; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; PT, preferred term; SOC, system organ class.
Note: All AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) and graded according to NCI-CTCAE v4.03. Maximum CTCAE grade was selected per patient under each PT. Potential immune-mediated AE is identified based on a predefined list of AEs and assessed as treatment-related by investigators.
Sorted in descending order of the number of patients in SOC and PT in Any Grade under Total column.
Data cutoff 20 May 2019.
[a] Percentages are based on the total population.

Of the 1273 total patients from the Pooled Monotherapy studies, 602 (47.3%) experienced at least one imAE of any grade. The most commonly occurring imAEs of any grade were aspartate aminotransferase increased (129 patients, 10.1%), alanine aminotransferase increased (124 patients, 9.7%), hypothyroidism (113 patients, 8.9%), rash (97 patients, 7.6%), and pruritus (78 patients, 6.1%). Analysis of the total patients with at least 1 imAE that also was ≥ Grade 3 in severity showed that 121 patients (9.5%) experienced such events. The most commonly occurring imAEs ≥ Grade 3 in severity were aspartate aminotransferase increased (21 patients, 1.6%), gamma-glutamyltransferase increased (17 patients, 1.3%), alanine aminotransferase increased (16 patients, 1.3%), pneumonitis (9 patients, 0.7%), and lung infection (8 patients, 0.6%).

1.4.4.1.5. Infusion-Related Reactions

Infusion-related reactions, including high-grade hypersensitivity reactions, following administration of tislelizumab are common. Of the 1273 total patients in the Pooled Monotherapy studies, 97 (7.6%) experienced at least one infusion-related reaction of any grade. The most commonly occurring infusion-related reactions of any grade that occurred in the total pooled analysis were pyrexia (50 patients, 3.9%), infusion-related reactions (28 patients, 2.2%), and pruritus (11 patients, 0.9%). There were 6 patients who reported a total of 7 ≥ Grade 3 infusion-related reactions in the Pooled Monotherapy studies (reported events included back pain, hypotension, infusion-related reaction, musculoskeletal chest pain, pyrexia, and rash).

1.4.4.1.6. Fatal Adverse Events

A summary of the treatment-emergent fatal AEs that occurred in the Pooled Monotherapy studies is shown in Table 6.

Table 6: Treatment-Emergent Fatal Adverse Events Regardless of Causality in Pooled Monotherapy Studies

Category	Overall (N = 1273) n (%)
All deaths at data cutoff	641 (50.4)
Death ≤ 30 days after last dose	105 (8.2)
Primary cause of death	
Adverse event	21 (1.6)
Disease under study	22 (1.7)
Progressive disease	52 (4.1)
Other	10 (0.8)
Death > 30 days after last dose	536 (42.1)
Primary cause of death	
Adverse event	14 (1.1)
Disease under study	95 (7.5)
Indeterminate	3 (0.2)
Progressive disease	399 (31.3)
Other	24 (1.9)
Missing	1 (0.1)

Source: Tislelizumab Investigator's Brochure.
Abbreviations: N, total number of patients treated; n, number of patients within each category.
Data cutoff 20 May 2019.

Table 6 shows that a total of 105 patients (8.2% of the total population) died ≤ 30 days after the last study drug dose in the Pooled Monotherapy studies as of the data cutoff date of 20 May 2019. Of these 105 patients, there were 21 patients (1.6% of the total population) who had an AE with a fatal outcome ≤ 30 days after the last study drug dose. Of the 536 patients (42.1% of the total population) who died > 30 days after the last study drug dose, 14 patients (1.1% of the total population) died as a result of an AE (refer to the Investigator's Brochure Edition 7, Section 5.2.1.9).

1.4.4.2. Efficacy Assessment of Tislelizumab

Efficacy data are available from 2 of the ongoing monotherapy studies in solid tumors, BGB-A317_Study_001 and BGB-A317-102, both of which are summarized below (data cutoff 20 May 2019).

1.4.4.2.1. Study BGB-A317_Study_001

Study BGB-A317_Study_001 is a 2-stage study consisting of a Phase 1a dose-escalation (0.5 to 10 mg/kg) and dose-finding component with 3 parts (2 and 5 mg/kg given either once every 2 or 3 weeks and a fixed dose of 200 mg given once every 3 weeks) to establish the MTD, if any, and a recommended Phase 2 dose (RP2D), which is followed by a Phase 1b component to investigate efficacy in select tumor types at the RP2D to further evaluate safety and tolerability of tislelizumab. Indication specific cohorts included esophageal, gastric, hepatocellular, and non-small cell lung cancer.

Responses were assessed by the investigator per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria.

There were 451 patients treated in the study and 441 patients were included in the efficacy evaluable set. The Efficacy Evaluable Analysis Set includes all treated patients who had at least 1 measurable baseline target lesion and had at least 1 evaluable postbaseline tumor assessment.

Across all disease cohorts, there were 5 patients (1.1%) with a complete response (CR). A total of 55 patients (12.5%) had a confirmed partial response (PR). The resulting overall clinical response rate was 13.6%. Additionally, there were 142 patients (32.2%) with a best overall response (BOR) of SD. A total of 199 patients (45.1%) had a best response of progressive disease (PD) in this study.

1.4.4.2.2. Study BGB-A317-102

Study BGB-A317-102 is a non-randomized, Phase 1/2 study of tislelizumab monotherapy in Chinese patients with advanced solid tumors. Phase 1 includes a dose verification substudy and a substudy of PK evaluation of the products derived from 2 manufacturing processes and scales. Phase 2 evaluates the activity and safety of tislelizumab at its recommended Phase 2 dose of 200 mg given once every 3 weeks in indication specific expansion cohorts.

Responses were assessed by the investigator per the RECIST v1.1 criteria.

Overall, of the 300 patients treated in Study BGB-A317-102, 249 patients were included in the Efficacy Evaluable Analysis Set. The Efficacy Evaluable Analysis Set includes all treated patients who had at least 1 measurable baseline target lesion and had at least 1 evaluable postbaseline tumor assessment.

The tumor responses in the efficacy evaluable analysis set of Study BGB-A317-102 across all disease cohorts and study phases was 1 patient (0.4%) with a CR and 44 patients (17.7%) with confirmed PR. The resulting overall clinical response rate was 18.1%. Additionally, there were 91 patients (36.5%) with a BOR of SD. A total of 113 patients (45.4%) had a best response of PD in this study.

1.5. Study Rationale

As described earlier, despite the wealth of evidence supporting TIGIT's role in promoting tumor immune tolerance, TIGIT blockade alone (ie, BGB-A1217 monotherapy) is unlikely to result in an effective antitumor response according to existing anti-TIGIT clinical data (see Section 1.3). Therefore, the clinical development of BGB-A1217 focuses on rational combinations, such as with tislelizumab. Taking this into account, the combination use of BGB-A1217 and tislelizumab

as well as tislelizumab monotherapy is designed to evaluate the effect of BGB-A1217 combination with tislelizumab in maximizing the patient's potential therapeutic benefit with simultaneously achieving the clinical objective of characterizing the safety and efficacy.

1.5.1. Rationale for the Dose Selection

1.5.1.1. Rationale for the Selection of BGB-A1217 Dose

BGB-A1217 doses ranging from 50 mg to 900 mg once every 3 weeks (Q3W), in combination with 200 mg of tislelizumab Q3W were explored in the ongoing Ph1/1b Study BGB-900-105. All the tested BGB-A1217 dose levels cleared the DLT window without any significant safety or tolerability events. BGB-A1217 exposures increased in an approximately dose-proportional manner (BGB-A1217 Investigator's Brochure, Sections 5.1.1 , 5.1.2, and 5.2.1). As of 07 August 2020, the maximum administered BGB-A1217 dose of 900 mg, was selected as RP2D.

Complete TIGIT receptor occupancy was observed on circulating T cells and NK cells in peripheral blood at all the tested doses in the Phase 1 study. However, since the correlation between TIGIT receptor occupancy in periphery and receptor occupancy in tumor tissues is unknown, quantitative systems pharmacology (QSP) modeling was performed and preliminary results show near complete TIGIT receptor occupancy in tumor tissues is predicted at doses of 450 mg and above. Due to lack of information on impact of immunogenicity on BGB-A1217 PK, a conservative estimate of 900 mg dose was selected which was deemed to be safe and tolerable in patients. This dose level increases the likelihood of efficacious concentrations and saturation of TIGIT receptors in tumor tissues completely over the entire dosing interval. Absence of any dose-dependent safety events in the ongoing Phase 1 study additionally supports selecting this dose for further evaluation. The preliminary BGB-A1217 PK data from the ongoing BGB-900-105 study indicates lack of significant relationship between the BGB-A1217 exposures and patients body weight supporting the selection of fixed dose for BGB-A1217.

1.5.1.2. Rationale for the Selection of Tislelizumab Dose

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

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

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

Additionally, no unexpected treatment-related AEs occurred in the 200 mg fixed dose cohort (BGB-A317_Study_001, Phase 1a, Part 3) when compared to body weight-based cohorts. Of the

evaluable patients treated (n = 13), 3 patients (23%) had a BOR of PR, 4 patients (31%) had a BOR of SD, and 6 patients (46%) had a BOR of PD. Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg every 3 weeks.

Therefore, the recommended dose for pivotal studies for tislelizumab of 200 mg once every 3 weeks will be utilized for the combination with BGB-A1217; however, alternate doses or dose schedules may be evaluated base on emerging clinical data.

1.5.2. Rationale for Combination of BGB-A1217 and Tislelizumab in the Treatment of Previously Treated Recurrent or Metastatic Cervical Cancer

Cervical cancer is the fourth most common cancer and the fourth leading cause of cancer death in women. It is estimated that recurrent or metastatic disease develops in 15 to 61% of women, usually within the first 2 years after the completing primary treatment. For patients who have progressed after first-line platinum-based therapy, the treatment options are limited, and no standard of care has been established. Single cytostatic agents bring limited response rates and short DOR (Table 1). This indicates significant unmet medical needs in patients with previously treated recurrent or metastatic cervical cancer.

HPV has been recognized as the most important etiological factor in cervical cancers; thus, cervical cancers are attractive targets for immunotherapy because viral proteins are strong immune stimulants. Available data from clinical studies investigating other anti-PD-1 antibodies, pembrolizumab and nivolumab, have shown both a manageable safety profile and promising antitumor activity in patients with previously treated recurrent or metastatic cervical cancer.

As described earlier, targeting TIGIT provides a potential mechanism to rescue immune cells from the immunosuppressive tumor microenvironment, thereby inducing an efficient antitumor immune response. Research showed that the TIGIT pathway cooperates with PD-1 to maximize the suppression of effector TILs and promotes resistance to anti-PD-1 therapy. Blocking antibodies targeting the PD-1/PD-L1 pathway have achieved remarkable results in the treatment of cervical cancer. Therefore, TIGIT represents an ideal target with the potential to significantly improve and/or extend the therapeutic benefit of anti-PD-1 therapy in cervical cancer.

Given the promising anti-tumor activity of anti-PD-1 antibodies reported in this indication and given the scientific rationale that TIGIT may improve the therapeutic benefit of anti-PD-1 therapy, the combination of BGB-A1217 and tislelizumab may bring significant clinical benefit in this indication and support further clinical development.

1.5.3. Biomarker Strategy Rationale

Biomarker analyses including but not limited to PD-L1 expression, TIGIT pathway molecules, gene expression profiling, tumor mutations, and TIL will be performed to explore the association with patient prognosis, response, and potential resistance mechanisms to tislelizumab in combination with BGB-A1217 and tislelizumab monotherapy.

PD-L1 was expressed in tumor and tumor infiltrating inflammatory cells in cervical carcinoma, and its enhanced expression was correlated with HPV-positivity (Yang et al 2017). A meta-analysis based on 7 studies with 783 patients showed that PD-L1 was trend to be a prognostic factor of poor OS in Asian patients (HR = 4.77, 95% CI = 3.02–7.54, $p < 0.001$) and of poor PFS

in Asian patients (HR = 4.78, 95% CI = 1.77–12.91, p = 0.002), which suggest PD-L1 is a poor prognostic indicator for cervical cancer (Gu et al 2019). The potential predictive role of PD-L1 underlying checkpoint blockade was first reported in KEYNOTE-158 study, in which at a median follow-up of 11.7 months (range, 0.6-22.7 months), the ORR was 14.3% (95% CI, 7.4-24.1) in 77 PD-L1 positive patients (CPS ≥1) previously treated with ≥1 line of chemotherapy in the metastatic setting, whereas no responses in patients with PD-L1 expression of CPS < 1. Given those results, PD-L1 IHC 22C3 pharmDx was identified as an aid in identifying cervical cancer patients for treatment with pembrolizumab. However, the predictive role of PD-L1 in combination treatment of immunotherapies with cervical cancer is still not clear. In this study, another PD-L1 score algorithm named visually-estimated Combined Positive Score (vCPS) will be assessed centrally. vCPS is the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining and tumor associated immune cells with PD-L1 staining at any intensity. Based on tumor bank derived cervical cancer tissues, the prevalence of vCPS ≥ 5% was approximal 60%. The predictive role of vCPS will be assessed in BGB-A1217 in combination of tislelizumab therapies and tislelizumab alone.

In addition to PD-L1, clinical data from various studies suggested tumor PD-L1 expression, tumor mutational burden, abundance and location of TILs, and tumor- and immune-related gene expression profile are a few factors associated with response to immunotherapies including anti-PD-1 antibodies in different cancers (Vilain et al 2017; Goodman et al 2017; Gandara et al 2018; Jiang et al 2018). In melanoma patients, a high TIGIT/CD226 ratio on Treg cells correlated with poor clinical outcome upon anti-PD1 or anti-PD-L1 antibody treatment, which suggest signaling through TIGIT pathway in tumor tissues might contribute to resistance to current immune checkpoint inhibitors targeting PD-1 or PD-L1 (Fourcade et al 2018). Therefore, expression of TIGIT pathway molecules including TIGIT, CD226, CD155, CD112, as well as tumor mutations, TILs, and gene expression profile will be studied, and its relationship with clinical response to study treatment will be further assessed.

Furthermore, mechanisms of resistance to immunotherapeutics are also not well understood and need more exploration. Identification of somatic mutations or gene expression profiles that associated with disease progression or acquired resistance to study treatment may increase understanding of disease pathobiology and collecting biological evidence for combination strategy.

1.6. Benefit-Risk Assessment

Currently, no standard of care has been established as second-line and later treatment of recurrent or metastatic cervical cancer. Single cytostatic agents have been used for decades with limited response rates and the DOR is short (Table 1). Pembrolizumab received accelerated approval by the FDA in PD-L1 positive population based on moderate and durable response. The ORR was 14.3% (95% CI 7.4%, 24.1%), and 91% of responders had a duration ≥ 6 months.

The safety profile of tislelizumab monotherapy is considered as acceptable based on previous nonclinical and clinical data. Safety data from OncoMed's OMP-313M32, Merck's MK-7684, and Genentech/Roche's tiragolumab indicated a tolerated safety profile for TIGIT monotherapy as well as its combination with anti-PD-(L)1 (Section 1.3.2). Similarly, BGB-A1217 combined with tislelizumab 200 mg Q3W is safe and well-tolerated, with no DLTs, no treatment-related

SAEs, or high-grade AEs occurred during the treatment period for each dose level in the ongoing 900-105 Phase 1/1b study as of 16 June 2020.

Given the unmet medical need and limited treatment options in this indication, the benefit/risk assessment, based on the available safety data of anti-TIGIT monoclonal antibodies in combination of anti-PD-1/L1 antibodies and the available efficacy data from the PD-1 antibodies in this indication, the combination of BGB-A1217 and tislelizumab is considered favorable. This Phase 2 study will be conducted in order to assess the potential benefit and safety of tislelizumab combined with BGB-A1217.

1.7. Study Conduct

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

- To evaluate the efficacy of BGB-A1217 combined with tislelizumab as measured by ORR according to RECIST v1.1, by Independent Review Committee (IRC) in patients who had previously treated recurrent or metastatic cervical cancer with PD-L1 visually-estimated Combined Positive Score (vCPS) ≥ 5% or regardless of PD-L1 expression

2.1.2. Secondary Objectives

- To evaluate the efficacy of BGB-A1217 combined with tislelizumab as assessed by ORR by investigator review
- To evaluate the efficacy of tislelizumab monotherapy as assessed by ORR by both IRC and investigator review
- To evaluate the efficacy of BGB-A1217 combined with tislelizumab and tislelizumab monotherapy as measured by DOR, PFS, time to response (TTR), disease control rate (DCR), and clinical benefit rate (CBR) by both IRC and investigator review
- To evaluate the efficacy of BGB-A1217 combined with tislelizumab and tislelizumab monotherapy as measured by OS
- To evaluate Health Related Quality of Life (HRQoL) via cancer-specific patient-reported outcomes (PROs) in patients treated with BGB-A1217 combined with tislelizumab and tislelizumab monotherapy
- To evaluate the safety and tolerability of BGB-A1217 combined with tislelizumab and tislelizumab monotherapy
- To characterize the PK of BGB-A1217 and tislelizumab
- To assess host immunogenicity to BGB-A1217 and tislelizumab

2.1.3. Exploratory Objectives

- To evaluate quality of life (QoL) via a generic PRO in patients treated with BGB-A1217 combined with tislelizumab and tislelizumab monotherapy
- To evaluate potential association of biomarkers with patient prognosis, response, or resistance of BGB-A1217 in combination with tislelizumab or tislelizumab alone

2.2. Study Endpoints

2.2.1. Primary Endpoints

- ORR, defined as the proportion of patients who had CR or PR assessed by IRC per RECIST v1.1 for Cohort 1

2.2.2. Secondary Endpoints

- ORR, defined as above assessed by investigator's review per RECIST v1.1 for Cohort 1
- ORR, defined as above assessed by both IRC and investigator's review per RECIST v1.1 for Cohort 2
- DOR, defined as the time from the first confirmed objective response until the first documentation of progression or death, whichever comes first, assessed by both IRC and investigator's review according to RECIST v1.1 for Cohorts 1 and 2
- Other efficacy endpoints (PFS, TTR, DCR, and CBR) that need tumor assessments by both IRC and investigator's review per RECIST v1.1 for Cohorts 1 and 2
  - PFS, defined as the time from the date of first dose of study drug to the date of first documentation of disease progression or death, whichever occurs first
  - TTR, defined as the time from the date of first dose of study drug to first documentation of response
  - DCR, defined as the proportion of patients who achieve CR, PR, or SD
  - CBR, defined as the proportion of patients who achieve CR, PR, or durable SD (SD $\geq$ 24 weeks)
- OS, defined as the time from the date of first dose of study drug until the date of death from any cause for Cohorts 1 and 2
- HRQoL questionnaires, assessment of the patient's overall health status using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cervical Cancer Module (EORTC QLQ-CX24), for Cohorts 1 and 2
- AEs and SAEs as characterized by type, frequency, severity (as graded by National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0 [NCI-CTCAE v5.0]), timing, seriousness, and relationship to study drugs, physical examinations, electrocardiograms (ECGs), and laboratory assessments for Cohorts 1 and 2
- Serum BGB-A1217 and tislelizumab concentrations at specified timepoints
- Immunogenic responses to BGB-A1217 and tislelizumab, evaluated through the detection of ADAs

2.2.3. Exploratory Endpoints

- Evaluate status of exploratory biomarkers including but not limited to expression of TIGIT, CD226, CD155, CD112 and PD-L1; gene expression profiling; tumor mutation burden; tumor infiltrating immune cells in archival and/or fresh tumor tissue and blood before study treatment, during study treatment, or at disease progression/reoccurrence; and the association between these biomarker and clinical efficacy, disease status, and resistance

- QoL is measured by assessment of the European Quality of Life 5-Dimensional - 5-Level Questionnaire (EQ-5D-5L)

3. STUDY DESIGN

3.1. Summary of Study Design

This is an open-label, 2-cohort, multicenter, Phase 2 study to evaluate the efficacy and safety of tislelizumab (BGB-A317) combined with or without BGB-A1217 in patients with previously treated recurrent or metastatic cervical cancer. The study is composed of two stages:

- **Stage 1 (randomization)**: Approximately 80 patients whose tumor regardless of PD-L1 expression will be randomized at a 1:1 ratio to receive either tislelizumab (200 mg IV Q3W) combined with BGB-A1217 (900 mg IV Q3W) or tislelizumab (200 mg IV Q3W) monotherapy.
- **Stage 2 (expansion)**: After the enrollment is completed in Stage 1, the sample size of the **combination** therapy cohort will continue to be expanded in Stage 2 with approximately 87 additional patients. These patients will receive tislelizumab (200 mg IV Q3W) combined with BGB-A1217 (900 mg IV Q3W).

The total sample size of the combination therapy cohort (Cohort 1) will be approximately 127 patients. The total sample size of the tislelizumab monotherapy cohort (Cohort 2) will be approximately 40 patients.

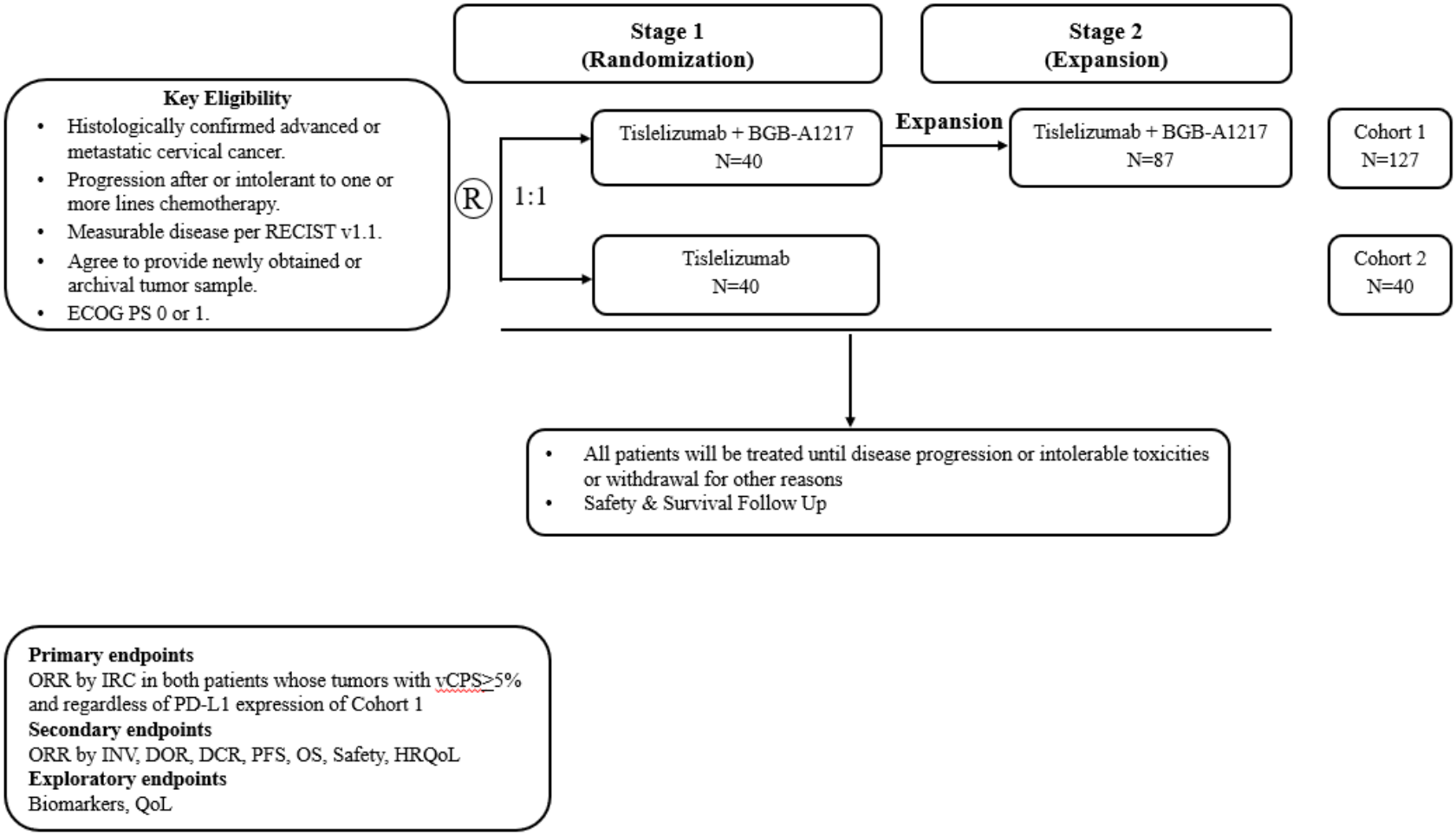
In Stage 1, the PD-L1 expression will be retrospectively tested centrally. In Stage 2, PD-L1 expression will be prospectively tested centrally and only patients whose tumors are evaluable for PD-L1 expression will be enrolled.

For Cohort 1 (including patients enrolled in Stage 1 and Stage 2), the percentage of patients whose tumors have PD-L1 vCPS < 5% or whose tumors are not evaluable for PD-L1 expression would be capped to be no more than 40%, to reflect the natural distribution of PD-L1 expression in cervical cancer (Section 1.5.3). vCPS is the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining and tumor-associated immune cells with PD-L1 staining at any intensity.

Study drugs will be administered until disease progression per RECIST v1.1, unacceptable toxicity, or withdrawal for other reasons, whichever occurs first. End-of-Treatment (EOT), safety follow-up, and survival follow-up visits will be conducted following study drug discontinuation.

The 2-stage schema is presented in Figure 1.

Figure 1: Study Schema



Abbreviations: DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, Health-Related Quality of Life; INV, investigator; IRC, Independent Review Committee; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death protein-ligand 1; PFS, progression-free survival; QoL, Quality of Life; RECIST, Response Evaluation Criteria in Solid Tumors; vCPS, visually-estimated Combined Positive Score.

For all study procedures see Section 7 and Appendix 1.

3.2. Screening Period

Screening evaluations will be performed within 28 days before the first dose of study drug. Patients who agree to participate in this study will sign the informed consent form (ICF) before undergoing any screening procedure. Screening evaluations may be repeated as needed within the screening period; the investigator is to assess preliminary patient eligibility according to the latest screening assessment results.

Archival tumor tissue must be collected for the purpose of biomarker analysis. If no archival samples are available, a fresh tumor biopsy at baseline is mandatory (Section 7.7).

3.3. Treatment Period

3.3.1. Stage 1

After completing all screening activities, approximately 80 patients confirmed to be eligible by the sponsor will be randomized in a 1:1 ratio to receive either tislelizumab and BGB-A1217 combination treatment or tislelizumab monotherapy.

Patients will receive:

Cohort 1: Tislelizumab 200 mg and BGB-A1217 900 mg IV once every 3 weeks until disease progression assessed per RECIST v1.1, unacceptable toxicity, or withdrawal for other reasons, whichever should occur first.

Cohort 2: Tislelizumab 200 mg IV once every 3 weeks until disease progression assessed per RECIST v1.1, unacceptable toxicity, or withdrawal for other reasons, whichever should occur first.

3.3.2. Stage 2

After 80 patients were enrolled in Stage 1, the enrollment will continue for Cohort 1 in Stage 2 with approximately 87 additional patients. These patients will receive tislelizumab 200 mg and BGB-A1217 900 mg IV once every 3 weeks until disease progression assessed per RECIST v1.1, unacceptable toxicity, or withdrawal for other reasons, whichever should occur first.

For Both Stage 1 and 2:

All patients will undergo tumor assessments at baseline (≤ 28 days before the first dose of study drugs) and every 6 weeks (± 7 days) for the first 54 weeks and then every 12 weeks (± 7 days) thereafter based on RECIST v1.1.

Response and PD will be assessed using RECIST v1.1. When PD is assessed by the investigator, IRC is required to complete central image review and convey the results to the investigator as soon as possible. If PD is NOT confirmed by IRC, it is recommended to continue the study treatment until PD is confirmed by IRC, if this is in the best interest of the patient as discussed with the medical monitor. In the situation where the investigator believes the patient must urgently discontinue study treatment without waiting for IRC confirmation, the investigator must contact the medical monitor to inform the decision of treatment discontinuation.

A patient who discontinues study drugs early for reasons other than disease progression by IRC (e.g., toxicity, PD by the investigator) will continue to undergo tumor assessments following the

original plan until the patient experiences PD per RECISTv1.1 by IRC, withdraws consent, is lost to follow-up, death or until the study terminates, whichever occurs first.

If at the investigator's discretion a patient could continue to benefit from tislelizumab and BGB-A1217 or tislelizumab alone (original assigned treatment) after PD per RECIST v1.1 by IRC, the patient may continue their original assigned treatment. The following criteria must be met in order to treat patients who may continue to benefit from study treatment after PD:

- Absence of clinical symptoms and signs of PD (including clinically significantly worsening of laboratory values)
- Stable ECOG Performance Status ≤ 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic PD and inform patients that this practice is not considered standard in the treatment of cancer.

The decision to continue study drugs beyond initial progression must be agreed by the medical monitor and documented in the study records. Patients who receive study treatment beyond progression will have tumor assessments performed according to the original schedule until study treatment discontinuation.

To determine the PK properties of tislelizumab and BGB-A1217 and host immunogenic response to tislelizumab and BGB-A1217, blood samples will be collected at various timepoints as outlined in Appendix 1.

An optional blood sample will be taken at baseline (predose at Day 1 of Cycle 1), at the time of first tumor response (predose at Day 1 of the following Cycle) and at EOT after disease progression (10 mL each timepoint) for all patients to explore the association of blood-based biomarkers with response, prognosis and resistance to tislelizumab in combination with BGB-A1217 and/or tislelizumab alone.

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, ECG results, and other examinations will also be used for safety assessment. Safety assessments are further detailed in Section 7.4 and the Schedule of Assessments (Appendix 1).

3.4. End of Treatment/Safety Follow-up

The EOT Visit is conducted when the investigator determines that study drugs will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT Visit, these tests need not to be repeated. Tumor assessment is not required at the EOT Visit and should follow the regular schedule of assessment in Appendix 1.

Patients who discontinue study treatment for any reason will be asked to return to the clinic for the EOT Visit, which is required to be conducted within 7 days of the EOT decision is made unless otherwise specified or before the initiation of a new anticancer treatment, whichever occurs first. An on-site Safety Follow-up Visit at 30 days (± 7 days) after last dose of study drugs is required. If the time windows of this Safety Follow-up Visit and EOT Visit are overlapped, the

safety follow-up can be exempted and the tests required at Safety Follow-up Visit will be conducted at EOT Visit. In addition, 2 Safety Follow-up Visits (by telephone) with patients should be conducted to assess imAEs and concomitant medications (if appropriate, such as being associated with an imAE or is a new anticancer therapy) at 60 (± 14 days) and 90 days (± 14 days) after the last dose of study drugs regardless of whether patients started a new subsequent anticancer therapy. If patients report a suspected imAE at a Safety Follow-up Visit, 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.

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

Optional biopsy will also be taken at the EOT Visit for the patients who have confirmed disease progression during the study from accessible tumor sites to obtain samples, which could be used for exploratory study including but not limited to the resistance mechanism. If feasible, any follow-up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written informed consent is required before fresh tumor biopsies.

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

3.5. Survival Follow-up

Patients will be followed for survival and further anticancer therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the last Safety Follow-up Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or end of study.

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 discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue study treatment for reasons other than disease progression should be followed for assessments of antitumor activity (Section 7.5), safety (Section 7.4), and survival (Section 3.5), 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:

- Radiographic disease progression per RECIST v1.1
- AE
- Patient decision
- Pregnancy

- Any medical condition that the investigator determines may jeopardize the patient's safety, if he or she were to continue the study treatment
- Use of any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese herbal medicine and Chinese 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 who are consistently noncompliant.

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

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

- Patient withdrawal of consent
- 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. In that case, the date that the last patient is followed-up upon the study termination would be the Last Patient Last Visit (LPLV).

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
- A rollover study or other post-trial supply program becomes available.

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for EOT Visits.

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

At the end of study, any patients who, in the opinion of the investigator, continue to benefit from tislelizumab/BGB-A1217 at study termination, may be offered the option to continue treatment in a company-sponsored clinical trial until it is commercially available in the country of the patient's residence.

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

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

3.7.1. Study Drug Treatment for Russian Patients After End of Study

In Russia, the long-term extension study or the post-trial supply program may not be available at the time of end of study.

At the end of the study, Russian patients who do not meet the treatment discontinuation criteria by the time of study closure, but may continue to benefit from the study drugs in the opinion of the investigator, may be offered the option to have continuous treatment (per current assignment).

For patients who receive the post-study drug treatment, the study drugs will be administered per current assignment until investigator-assessed disease progression, adverse events, the patient receives approximately 3 years of study drug treatment, or reasons specified in Section 3.6.1, whichever occurs first. The study drugs will be managed manually via the local depot per local regulation.

The investigator is encouraged to communicate with the sponsor for any questions regarding patient management and monitoring during study drug treatment. Patient management and monitoring including tumor and response evaluations, safety assessments, study drug modifications, and follow-ups will be generally concordant with the current approved protocol or per investigator's discretion, with guidance provided below.

Tumor and Response Evaluations

- The patient will continue to undergo tumor assessments following the current plan per Section 7.5 or per investigator's discretion.

Safety Assessment, Monitoring, and Reporting

- Safety will be assessed and monitored per Section 7.4 and Section 8 or per investigator's discretion.
- Safety tests (eg, laboratory tests, ECGs, hepatitis B and C testing) will be performed by qualified local laboratories.

- While all adverse events should be adequately evaluated and recorded in the clinical source documents, only SAEs will be reported to BeiGene's Global Patient Safety.

Pharmacokinetic and Biomarker Testing

- No blood or tissue samples will be collected for PK, ADA, biomarker, or other exploratory analysis.

End of Treatment/Safety Follow-up

- The study drugs will be discontinued when disease progression is assessed by the investigator, and no IRC confirmation will be conducted.
- Treatment beyond investigator-assessed PD is not suggested unless otherwise specified.
- The EOT Visit and 30-day Follow-up Visit are required to be conducted per Section 3.4.
- The 60-day Safety Follow-up, 90-day Safety Follow-up, or Survival Follow-up Visits will not be conducted.

Data Collection and Management

- All the data generated after study termination will not be collected into the eCRFs.
- As part of patient management, the investigator must collect and maintain patient clinical source documents per the requirement of local institutions.

4. STUDY POPULATION

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

4.1. Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be considered eligible for participation in this study:

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments
2. Age ≥ 18 years on the day of signing the ICF (or the legal age of consent in the jurisdiction in which the study is taking place)
3. Histologically or cytologically confirmed squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix
4. Progression on or after one or more lines of chemotherapy for management of recurrent or metastatic disease and is not amenable to curative treatment (eg, systemic chemotherapy, surgery, or radiotherapy)
    a. Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer would not be counted as a line of chemotherapy
    b. Patients intolerant to most recent regimen due to Grade 4 hematologic toxicity or Grade 3 or 4 non-hematologic toxicity may also be eligible
5. Measurable disease as assessed by RECIST v1.1. Note: A lesion in an area subjected to prior loco-regional therapy, including previous radiotherapy, is not considered measurable unless there has been demonstrated progression in the lesion since the therapy as defined by RECIST v1.1
6. Patients must submit qualified archival tumor tissue (formalin-fixed paraffin-embedded block containing tumor [preferred] or approximately 15 [at least 6] unstained slides) with an associated pathology report, or agree to a tumor biopsy for determination of PD-L1 expression and other biomarker analyses (fresh tumor biopsies are strongly recommended at baseline in patients with readily accessible tumor lesions and who consent to the biopsies). PD-L1 expression will be assessed centrally. For Stage 2, patients with evaluable PD-L1 expression are eligible
7. ECOG performance status of 0 or 1
8. Life expectancy of at least 12 weeks
9. Patient must have adequate organ function as indicated by the following screening laboratory values obtained within 7 days before the first study treatment:
    a. Patients must not have required blood transfusion or growth factor support ≤ 14 days before sample collection at screening for the following:
        i. Absolute neutrophil count ≥ 1.5 x 10^9/L

ii. Platelets ≥ 75 x 10^9/L

iii. Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol /L (Note: Criteria must be met without a transfusion within 14 days of obtaining the sample)

b. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated Glomerular Filtration Rate ≥ 60 mL/min/1.73 m2 by Chronic Kidney Disease Epidemiology Collaboration equation (Appendix 7)
c. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilberts syndrome)
d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN or ≤ 5 x ULN if hepatic metastases present

10. Women of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and for ≥ 120 days after the last dose of study drug, as well as have a negative urine or serum pregnancy test ≤ 7 days before first dose of study drug

4.2. Exclusion Criteria

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

1. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, TIGIT or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways
2. Prior randomization in a tislelizumab or BGB-A1217 study, regardless of the treatment arm, until the primary and key secondary endpoints of the study have read out
3. Active leptomeningeal disease or uncontrolled, untreated brain metastasis

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

   a. Brain imaging at screening shows no evidence of progression, clinically stable for at least 2 weeks, and have no evidence of new brain metastases
   b. Measurable and/or evaluable disease outside the central nervous system
   c. No ongoing requirement for corticosteroids as therapy for central nervous system disease; off steroids 3 days before the first study treatment; anticonvulsants at a stable dose are allowed
   d. No stereotactic radiation or whole-brain radiation within 14 days before the first study treatment

4. Active autoimmune diseases or history of autoimmune diseases (Appendix 4) 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

5. Any active malignancy ≤ 2 years before first dose of study drug except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of breast)
6. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before first dose of study drug

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. 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 of study drug
8. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence within 2 weeks of intervention)
9. History of interstitial lung disease, non-infectious pneumonitis, or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc. Patients with significantly impaired pulmonary function, or who require supplemental oxygen at baseline must undergo an assessment of pulmonary function at screening
10. Infection (including tuberculosis infection, etc.) requiring systemic antibacterial, antifungal, or antiviral therapy within 14 days before the first dose of study drugs

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 > 2 weeks before enrollment.

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 > 2 weeks before enrollment.

13. Known history of HIV infection
14. Any major surgical procedure ≤ 28 days before first dose of study drug. Patients must have recovered adequately from the toxicity and/or complications from the intervention before the first dose of study drug
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 of study drug
    b. Pulmonary embolism ≤ 28 days before first dose of study drug
    c. Any history of acute myocardial infarction ≤ 6 months before first dose of study drug
    d. Any history of heart failure meeting New York Heart Association (NYHA) Classification III or IV ≤ 6 months before first dose of study drug
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before first dose of study drug
    f. Any history of cerebrovascular accident ≤ 6 months before first dose of study drug
    g. Uncontrolled hypertension that cannot be managed by standard anti-hypertension medications ≤ 28 days before first dose of drug
       For France only, specify: Systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg on repeated measurements
    h. Any episode of syncope or seizure ≤ 28 days before first dose of study drug
17. A history of severe hypersensitivity reactions to other monoclonal antibodies
18. Has received any chemotherapy, immunotherapy (eg, interleukin, interferon, thymosin, etc.) or any investigational therapies within 14 days or 5 half-lives (whichever is longer) before the first dose of study drug or has received palliative radiation treatment or other local regional therapies within 14 days before the first dose of study drug
19. Patients with toxicities (as a result of prior anticancer therapy) who have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
20. Administration of a live vaccine ≤ 28 days before first dose of study drug

    Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
21. 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
22. Women who are pregnant or breastfeeding

23. Concurrent participation in another therapeutic clinical study

Note: Concurrent participation in observational or non-interventional 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

5.1.1. BGB-A1217

BGB-A1217 is a monoclonal antibody formulated for intravenous injection in a single-use vial (20 mL glass vial, United States Pharmacopeia Type I) containing a total of 200 mg antibody in 10 mL (or 300 mg antibody in 15 mL) of buffered isotonic solution. BGB-A1217 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 condition as specified on the label. Shaking should be avoided.

Refer to the Pharmacy Manual for details regarding intravenous administration, accountability, and disposal. Refer to the BGB-A1217 Investigator's Brochure for other details regarding BGB-A1217.

5.1.2. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous injection in a single-use vial (20R glass, United States Pharmacopeia 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 condition as specified on the label. Shaking should be avoided.

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

5.2. Dosage, Administration, and Compliance

Planned dosage and dosing frequency for BGB-A1217 and tislelizumab are presented in Table 7.

The first dose of study drug is to be administered within 2 business days of randomization. The initial infusion (Cycle 1 and Cycle 2, Day 1) will be delivered over 60 minutes for each drug of tislelizumab and BGB-A1217; if this is tolerated well, then the subsequent infusions may be administered over 30 minutes of each drug, which is the shortest period permissible for infusion (Table 8 and Table 9).

All patients will be monitored continuously for AEs. Treatment modifications (eg, dose delay, interruption, or discontinuation) will be based on specific laboratory and AE criteria, as described in Section 5.5. 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 11.

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

Table 7: Planned Dose, Frequency of Administration, and Route of Administration for BGB-A1217 and Tislelizumab

Study Drugs	Dose	Frequency of Administration	Route of Administration	Duration of Treatment
BGB-A1217	900 mg	Day 1 of each cycle (21 days)	Intravenous	Refer to Section 3.3
Tislelizumab	200 mg	Day 1 of each cycle (21 days)	Intravenous	Refer to Section 3.3

Table 8: Administration of BGB-A1217 and Tislelizumab and Monitoring Time

Cycle	BGB-A1217 and Tislelizumab Combination (Cohort 1)
C1D1 and C2D1	Tislelizumab infusion over 60 (± 5) minutes followed by BGB-A1217 infusion over 60 (± 5) minutes Patient monitoring for ≥ 120 minutes
C3D1 onwards	Tislelizumab infusion over 30 (± 5) minutes followed by BGB-A1217 infusion over 30 (± 5) minutes Patient monitoring for ≥ 30 minutes

Table 9: Administration of Tislelizumab and Monitoring Time

Cycle	Tislelizumab Monotherapy (Cohort 2)
C1D1 and C2D1	Tislelizumab infusion over 60 (± 5) minutes Patient monitoring for ≥ 60 minutes
C3D1 onwards	Tislelizumab infusion over 30 (± 5) minutes Patient monitoring for ≥ 30 minutes

5.2.1. BGB-A1217 and Tislelizumab

Patients will receive tislelizumab 200 mg on Day 1 of each 21-day cycle (ie, once every 3 weeks) followed by the administration of BGB-A1217 900 mg.

Tislelizumab and BGB-A1217 must be administered by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2- or 0.22 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

Use of a volumetric pump is recommended to control the infusion speed and to avoid potential infusion reactions associated with too rapid administration. The pump may not be needed if the infusion speed is controlled through alternative means and consistent with approved institutional procedures.

At the end of the infusion period, flush the line with enough normal saline to ensure all study drugs are administrated to the patient.

As a routine precaution, after infusion of tislelizumab and BGB-A1217 on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for ≥ 2 hours afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, at least a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

Tislelizumab and BGB-A1217 must not be concurrently administered with any other drug (Section 6).

5.2.2. Tislelizumab

Tislelizumab 200 mg will be administered on Day 1 of each 21-day cycle (Q3W).

Tislelizumab will be administered by IV infusion through an IV line containing a sterile, nonpyrogenic, 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.

Use of a volumetric pump is recommended to control the infusion speed and to avoid potential infusion reactions associated with too rapid administration. The pump may not be needed if the infusion speed is controlled through alternative means and consistent with approved institutional procedures.

At the end of the infusion period, flush the line with enough normal saline to ensure all study drug is administrated to the patient.

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

Tislelizumab must not be concurrently administered with any other drug (Section 6).

5.3. Incorrect Administration or Overdose

Any incorrect administration of BGB-A1217 or overdose of tislelizumab (defined as ≥ 600 mg in a 24-hour period) should be noted in the patient's chart and on the appropriate eCRF.

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

5.4. Investigational Medicinal Product Accountability

The investigational medicinal products required for completion of this study (BGB-A1217 and tislelizumab) will be provided by the sponsor. The investigational site will acknowledge receipt of investigational medicinal products. 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.

5.5. Dose Delay or Modification

Every effort should be made to administer the study drugs 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 and/or BGB-A1217, 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 patient
- Grade 4: Permanent discontinuation from study. Exceptions may be considered following consultation with the medical monitor.

5.5.1. Dose Interruption or Delay for BGB-A1217 and Tislelizumab

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

If a dose delay is required, both study drugs are to be delayed (ie, BGB-A1217 and tislelizumab must both be delayed and, if applicable, re-started at the same time). Exceptions may be considered following consultation between the investigator and the medical monitor.

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

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

If a dose is delayed for ≤ 10 days for a planned dosing cycle (eg, Cycle 3 Day 1), the study drug should be administered. If the delay is > 10 days, the patient should skip both tislelizumab and BGB-A1217. Both tislelizumab and BGB-A1217 will be administered on Day 1 of the next planned cycle (eg, Cycle 4 Day 1).

If immune-mediated AEs are persistent without any improvement for more than 12 weeks, permanent discontinuation of the study drug should be considered. In the combination treatment cohort, the treatment discontinuation in response to treatment-related AEs should be applied to both tislelizumab and BGB-A1217 because the causality of imAEs may not be distinguished from one study drug to the other.

If the patient recovers from the treatment-related AE after 12 weeks, re-initiation of study drug is permitted only in patients who are deemed to be deriving clinical benefit per the opinion of the investigator following agreement between the investigator and the medical monitor.

Management guidelines for imAEs and infusion-related reactions in patients treated with tislelizumab and BGB-A1217 are presented in Section 8.7 and Appendix 11.

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

5.5.2. Dose Reductions for BGB-A1217 and Tislelizumab

There will be no dose reductions allowed for tislelizumab or BGB-A1217.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

The exclusion criteria (Section 4.2) specify that patients should not have received prior therapies targeting PD-1, PD-L1, PD-L2, TIGIT, T-cell costimulation or checkpoint pathways, chemotherapy, immunotherapy (eg, interleukin, interferon, or thymosin), or investigational therapy ≤ 14 days or 5 half-lives (whichever is longer) before the first dose of study drugs.

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. Opiates and other medication required for palliative management of patients are allowed.

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

Bisphosphonates and RANKL inhibitors are allowed for bone metastases if initiated before enrollment and at a stable dose. Bisphosphonates are permitted during the study for a nonmalignant indication. Use of potentially hepatotoxic drugs in patients with impaired hepatic function is allowed but should be carefully monitored.

6.2.1. Systemic Corticosteroids

Systemic corticosteroids administered for the control of imAEs must be tapered gradually (see Appendix 11) and must be administered at nonimmunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next tislelizumab and BGB-A1217 or tislelizumab administration. The short-term use of steroids as prophylactic treatments (eg, 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 treatment 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 antivirals agent 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.

6.2.4. Radiation Therapy

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

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

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

6.3. Prohibited Concomitant Medications/Procedures

The following medications are prohibited during the study:

- 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])
- Live vaccines within 28 days before the first dose of study drugs and 60 days following the last dose of study drugs
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (eg, hypericin)

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
- Radiation therapy, except for palliative radiation therapy described in Section 6.2.4

6.5. Potential Interactions Between the Study Drugs and Concomitant Medications

Information regarding clinical drug interactions with BGB-A1217 is not available, and no dedicated drug-drug interaction studies are planned. However, the potential for drug-drug interaction between the study drugs (BGB-A1217 and tislelizumab) and other drug products is very low because BGB-A1217 and tislelizumab are therapeutic monoclonal antibodies. Because BGB-A1217 and tislelizumab are expected to be degraded into amino acids and recycled into other proteins, they are unlikely to influence drug-metabolizing enzymes or transporters.

7. STUDY ASSESSMENT 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 (that must be available before any dosing) have been reviewed and found to be acceptable per protocol guidelines.

7.1. Screening Period

Screening evaluations will be performed ≤ 28 days before the first dose of study drugs. A patient who agrees to participate in this study will sign the ICF before undergoing any screening assessment. The screening period begins on the first day that a screening assessment is conducted. Screening evaluations may be repeated as needed within the screening period. The investigator is to assess patient eligibility according to the latest screening assessment results.

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

Procedures conducted only during the Screening Visit are described in this section. For the description of other assessments that are conducted during screening as well as throughout the study, refer to Safety Assessments (Section 7.4), Tumor and Response Evaluations (Section 7.5), PK and ADA Assessments (Section 7.6) and Biomarkers (Section 7.7) sections.

Rescreening under limited conditions may be allowed after consultation with sponsor (eg, when a patient's laboratory result narrowly miss laboratory criterion and it is correctable and not due to rapidly deteriorating condition or PD). Rescreening is allowed only once.

7.1.1. 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 the first dose of study drugs. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

7.1.2. Patient Numbering

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

7.1.3. 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, 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 the first dose of study drugs.

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

7.1.4. Females of Childbearing Potential and Contraception

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

7.1.5. Pulmonary Function Tests

Patients who are suspected of having or known to have serious/severe respiratory conditions, exhibiting significant respiratory symptoms unrelated to the underlying cancer, or having a history of thoracic radiotherapy will undergo pulmonary function testing that may include but is not limited to spirometry and assessment of diffusion capacity done during the screening period to assist the determination of suitability on the study.

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

7.2. Enrollment

7.2.1. Confirmation of Eligibility

The investigator will assess and the sponsor will confirm the eligibility of each patient. All screening procedure results and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met, and none of the exclusion criteria may apply. No eligibility waivers will be granted.

After a patient is screened and the investigator determines the patient is eligible for enrollment, study site personnel will complete an Eligibility Authorization Packet and send it to the medical monitor or designee to confirm the eligibility before enrollment. Study site personnel should ensure that a medical monitor's confirmation has been received before proceeding with study procedures.

7.2.2. Randomization

Site personnel will access the IRT system to randomize the patient to treatment assignment and assign study drugs in Stage 1 in the study. Study treatment must commence within 2 business days after randomization/treatment assignment.

7.3. Study Drug Dispensation

Tislelizumab and BGB-A1217 will be dispensed and administered as described in Section 5.2.

7.4. Safety Assessment

7.4.1. Vital Signs

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

7.4.2. Physical Examinations

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

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

7.4.3. Eastern Cooperative Oncology Group Performance Status

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

7.4.4. Laboratory Safety Tests

Local and/or central laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined 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.

Laboratory assessments will include the following:

- Hematology (complete blood count [CBC], including red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count with differential [neutrophils, lymphocytes, monocytes, basophils, eosinophils], and platelet count)
- Serum chemistry (glucose, blood urea nitrogen or urea, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, direct bilirubin, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, total protein, albumin, creatine kinase, CK-MB)

- Coagulation test (international normalized ratio, prothrombin time, and activated partial thromboplastin time)
- Urine or serum pregnancy test (for women of childbearing potential, including premenopausal women who have had a tubal ligation) ≤ 7 days before the first dose of study drugs
- Urinalysis (complete [including, but not limited to specific gravity, pH, glucose, protein, ketones, blood] and/or microscopic at screening and if clinically indicated)
- Thyroid function testing (thyroid stimulating hormone [TSH], free triiodothyronine [T3], free Thyroxine [T4]).

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.

7.4.4.1. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune checkpoint inhibitors, serum creatine kinase and creatine kinase cardiac isoenzyme are monitored in all tislelizumab studies to protect study patients and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 11 for guidelines for management of suspected immune-mediated myocarditis, respectively).

Serum creatine kinase and CK-MB testing will be implemented for all patients at screening, predose at Day 1 of every scheduled cycle, at the EOT Visit, and at the on-site Safety Follow-up Visit. In the event that CK-MB fractionation is not available, serum troponins (troponin I and/or T) measurements will be performed instead per local guidelines if used consistently throughout the study.

7.4.5. Electrocardiograms

The ECG recordings will be obtained during screening, the EOT Visit, the on-site Safety Follow-up Visit, and as clinically indicated.

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

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

7.4.6. Adverse Events

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

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

7.4.7. Hepatitis B and C Testing

Testing will be performed by a central laboratory and/or the local laboratory at screening -and as clinically indicated till EOT Visit and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody) and viral load assessment (HBV DNA and HCV RNA). For patients who have detectable HBV DNA or HCV RNA at screening, a respective viral load test will be performed every 4 cycles (ie, Day 1 of Cycle 5, 9, 13, etc) starting from Cycle 5.

7.5. Tumor and Response Evaluations

Tumor imaging will be performed ≤ 28 days before the first dose of study drug. Results of standard-of-care tests or examinations performed before obtaining informed consent and ≤ 28 days before the first dose of study drug may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days), from Day 1 of Cycle 1, for 54 weeks, then every 12 weeks (± 7 days) thereafter, based on RECIST v1.1. If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted according to the planned schedule.

Screening assessments and each subsequent assessment must include computed tomography (CT) scans (with oral/IV contrast) of the chest, abdomen, and pelvis. If contraindication exists, other modalities can be allowed after consultation with the medical monitor (eg. magnetic resonance imaging [MRI], CT with contrast). CT/MRI of the head at baseline is required for patients who are suspected to have central nervous system metastases. Bone scan or positron emission tomography (PET) scan is required if clinically indicated. Other known or suspected sites of disease must be included in the imaging assessments (neck, extremities, etc).

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

- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a PET/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- Bone scans (Technetium-99m [TC-99m]) or PET scans should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans, TC-99m or PET bone scans should be repeated when a CR is suspected in target lesion or when progression in bone is suspected.
- Images of brain, neck, or extremities should be performed at screening, only if clinically indicated, and followed throughout the study, if there is evidence of metastatic disease in these regions at screening.

- At the investigator's discretion, other methods of assessment of target lesion and non-target lesions per RECIST v1.1 may be used.

Response will be assessed by the IRC and the investigator using RECIST v1.1 (see Appendix 12). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

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

When PD is assessed by the investigator, IRC is required to complete central image review and convey the results to the investigator as soon as possible. If PD is NOT confirmed by IRC, it is recommended to continue the study treatment until PD is confirmed by IRC, if this is in the best interest of the patient as discussed with the medical monitor. In the situation where the investigator believes the patient must urgently discontinue study treatment without waiting for IRC confirmation, the investigator must contact the medical monitor to inform the decision of treatment discontinuation.

A patient who discontinues study drugs early for reasons other than disease progression by IRC (eg, toxicity, PD by the investigator) will continue to undergo tumor assessments following the original plan until the patient experiences PD per RECISTv1.1 by IRC, withdraws consent, is lost to follow-up, death or until the study terminates, whichever occurs first.

If at the investigator's discretion a patient could continue to benefit from tislelizumab and BGB-A1217 combination treatment or tislelizumab monotherapy (original assigned treatment) after PD per RECIST v1.1 criteria by IRC, the patient may continue their assigned treatment. The following criteria must be met in order to treat patients who may continue to benefit from study treatment after PD:

- Absence of clinical symptoms and signs of PD (including clinically significantly worsening of laboratory values)
- Stable ECOG Performance Status ≤ 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic PD and inform patients that this practice is not considered standard in the treatment of cancer.

The decision to continue study drugs beyond initial progression must be agreed to with the medical monitor and documented in the study records.

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

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

7.6. Pharmacokinetic and Antidrug Antibody Testing

BGB-A1217 and tislelizumab may elicit an immune response. Patients with signs of any potential immune response will be closely monitored. Validated screening and confirmatory assays will be employed to detect ADA at multiple timepoints throughout the study. In addition, blood samples will be collected for characterization of BGB-A1217 and tislelizumab PK at the timepoints specified in the Schedule of Assessments (Appendix 1).

PK and ADA assays of BGB-A1217 and tislelizumab will be managed through a central laboratory. Serum samples will be assayed for BGB-A1217 and tislelizumab concentrations using validated immunoassays.

- ADA assays: serum samples will be tested for the presence of ADAs to BGB-A1217 and tislelizumab using a validated immunoassay
- PK assay: serum samples will be assayed for BGB-A1217 and tislelizumab concentration with use of a validated immunoassay

Refer to the laboratory manual for instructions regarding sample collection, handling, labeling, storage, and shipping of laboratory samples.

7.7. Biomarker

Shipping, storage, and handling of blood as well as archival tumor and/or fresh tumor tissues for the assessment of biomarkers will be handled by a central laboratory. Refer to the laboratory manual for details of sample handling and the Schedule of Assessments (Appendix 1) for timepoints.

Patients are required to provide tumor tissues (archival tumor tissues [formalin-fixed paraffin embedded blocks or approximately 15 freshly cut unstained slides (at least 6)] or fresh biopsy) for biomarker analysis, including but not limited to expression of PD-L1, TIGIT pathway related markers (including but not limited to TIGIT, CD226, CD155, and CD112), TILs, gene expression profiling, and tumor mutation burden/gene mutation/MSI. If archival tumor tissues are not available, a fresh tumor biopsy is mandatory at baseline. Acceptable fresh biopsy samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

If clinically feasible, it is highly recommended to obtain a tumor biopsy at the time of confirmed disease progression to explore the immune- or tumor-related biomarkers and biological changes that might drive disease progression or acquired resistance to tislelizumab in combination with BGB-A1217 and tislelizumab alone (written informed consent is required before fresh tumor biopsy).

Optional blood samples will be collected at baseline (pre-dose of C1D1), at the time of first tumor response (predose at Day1 of the following cycle) and at the time of confirmed PD (Appendix 1) to explore association of blood based biomarkers with response, resistance and prognosis.

Written informed consent is required for any of the fresh tumor biopsies and blood. Tumor tissue should be of good quality in terms of total and viable tumor content. Fine needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

7.8. Health Related Quality of Life/Quality of Life

Patients will be asked to complete three PROs, that include EORTC QLQ-CX24, EORTC QLQ-C30, and EQ-5D-5L before any clinical activities are performed during on-study clinic visits according to the schedule in Appendix 1. The questionnaires will be provided in the patient's preferred language.

7.9. Visit Windows

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted (see Appendix 1). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed before any study treatment is given unless otherwise noted. Laboratory results must be reviewed before dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled for the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule every 3 weeks from Day 1 of Cycle 1.

7.10. Unscheduled Visits

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

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

8. SAFETY MONITORING AND REPORTING

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

8.1. Risks Associated With Study Drugs

8.1.1. Risks Associated With BGB-A1217 and Tislelizumab

BGB-A1217 and tislelizumab are investigational agents that are currently in clinical development. Limited safety data are available in patients, and the full safety profile has not been characterized. The following recommendation is based on results from nonclinical and clinical studies with tislelizumab and BGB-A1217 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 enhancement of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Section 8.7.3. BGB-A1217-mediated TIGIT inhibition may increase the risk of immune-mediated AEs. However, no apparent immunotoxicity, or toxicity in general, have been observed in animal models treated with BGB-A1217. Furthermore, in the absence of activation, peripheral effector T-cells do not typically express TIGIT, thereby minimizing any potential negative additive affect as it relates to peripheral immune tolerance.

Although most imAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested workup procedures for suspected imAEs are provided in Appendix 11.

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies and clinical data with BGB-A1217 and tislelizumab, as well as the nonclinical/clinical data from other TIGIT and PD-L1/PD-1 inhibitors, were considered. Specifically, patients at risk for study-emergent active autoimmune diseases or with a history of autoimmune diseases that may relapse, patients who have undergone allogeneic stem cell or organ transplantation, and patients who have received a live vaccine ≤ 28 days before the first dose of study drug 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 10), 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, study drug(s) will be administered only after clinical laboratory results have been reviewed. Administration of study drugs 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).

Serum samples will be drawn for determination of ADAs to BGB-A1217 and tislelizumab in all patients.

Investigators are instructed to report all AEs (includes 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 study drugs, whether considered related to study drugs or not.

Examples of AEs include:

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

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records 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 best clinical judgement. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, and other risk factors, and the temporal relationship of the AE or SAE to the study drugs should be considered and investigated. The investigator should consult the Tislelizumab Investigator's Brochure and the BGB-A1217 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 1 of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality considering follow-up information, amending the SAE report accordingly.

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 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[s]). 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-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and that worsen significantly during the study. The definition of clinically significant is based on the 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 x 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 adverse event. 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 that hypothetically might have caused death if it was 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 with or prevent everyday life functions but do not constitute a substantial disruption.

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

The following are NOT considered 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 (SADR), the specificity or severity of which is not consistent with those noted in Tislelizumab Investigator's Brochure or BGB-A1217 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 drugs, only SAEs should be reported to the sponsor.

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

AEs and SAEs should be recorded according to the details in Table 10. For the follow-up period for AEs, see Section 8.3.4. For the definition of treatment-emergent adverse events (TEAEs), see Section 9.3.2.

Table 10: Guidance for Duration of Recording New or Worsening Adverse Events in All Cohorts

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 PD	Do not record (see Section 8.6.4)	
All nonserious AEs, except those due to PD	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; PD, progressive disease; SAE, serious adverse event.
[a] All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

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 11.

Table 11: Time Frames and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Time Frame for Sending Initial Report	Documentation Method	Time Frame 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 form

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

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, 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, including all available details of the event, and forwarded to the sponsor or designee within the designated time frames.

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

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

The sponsor will provide contact information for SAE receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

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

The investigator, or the 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 BGB-A1217 and tislelizumab studies.

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

8.6.3. Eliciting Adverse Events

The investigator or designee will ask 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

PD, 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 AE. If the only information available is death and the cause of death is unknown, then the death is reported as an event (eg, "death," "death of unknown cause," or "death unexplained").

8.6.6. Pregnancies

If a patient becomes pregnant while receiving study drugs or within 120 days after the last dose of study drugs, a pregnancy report form must be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 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 always be reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drugs 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 documents:

- Tislelizumab Investigator's Brochure
- BGB-A1217 Investigator's Brochure

8.6.8. Assessing and Recording Immune-Mediated Adverse Events

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

Investigators should consult the guidance on diagnostic evaluation and management of imAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 11.

An extensive list of potential imAEs appears in Section 8.7.3, Table 13. All conditions like those listed should be evaluated to determine whether they are imAEs based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 11.

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. Individual signs and symptoms of an infusion reaction should be recorded each as a separate AE in the eCRF and identified as an infusion-related reaction.

8.7. Management of Adverse Events of Special Interest

As a routine precaution, patients must be monitored for ≥ 2 hour after infusion of tislelizumab combined with BGB-A1217 (Cohort 1) and for ≥ 1 hour after infusion of tislelizumab monotherapy (Cohort 2) on Day 1 of Cycle 1 and Cycle 2 in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, at least a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The management for 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 study drugs are provided in Table 12.

Table 12: Treatment Modifications for Symptoms of Infusion-Related Reactions Due to Study Drugs

NCI-CTCAE Grade	Treatment Modification for BGB-A1217 and Tislelizumab
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, nonsteroidal anti-inflammatory drugs, 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.

NCI-CTCAE Grade	Treatment Modification for BGB-A1217 and Tislelizumab
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: IV, intravenous; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Once the BGB-A1217 or 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, the infusion should be discontinued, and the patient should be withdrawn from BGB-A1217 + tislelizumab combination treatment or tislelizumab monotherapy.

NCI-CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted, as indicated per the type of reaction. This includes but is not limited to an antihistamine (eg, diphenhydramine 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 oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and 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 hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice as described in the complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (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 discontinued from the study. Systemic anaphylactic/anaphylactoid reactions typically manifest within minutes following administration of the drug/antigen and are characterized by: respiratory distress; laryngeal edema; and/or intense bronchospasm; and are often followed by vascular collapse or shock without antecedent respiratory difficulty; cutaneous manifestations such as pruritus and urticaria with/without edema; and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea.

The patient will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed, and then the patient should be placed on monitor immediately and 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 drug infusion. Alternative treatments for fever (ie, paracetamol) may be administered to the patient 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, PD, or other neoplastic causes) with appropriate diagnostic tests that may include but are not limited to serologic, immunologic, and histologic (biopsy) data. If alternative causes have been ruled out, the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy and is consistent with an immune-mediated mechanism of action, the imAE indicator on the eCRF AE page should be checked.

A list of potential imAEs is shown below in Table 13. All conditions similar to those listed should be evaluated in patients receiving tislelizumab or BGB-A1217 to determine whether they are immune-mediated.

Recommendation for diagnostic evaluation and management of imAEs is based on European Society for Medical Oncology and American Society of Clinical Oncology guidelines (Haanen et al 2017; Brahmer et al 2018) and common immune-mediated toxicities are detailed in Appendix 11. For any AEs not included in Appendix 11, refer to the American Society of Clinical Oncology Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Table 13: 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

Body System Affected	Events
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 11.

If a toxicity does not resolve to ≤ Grade 1 within 12 weeks, study drugs 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. Data will be listed and summarized using SAS® Version 9.3 or higher (SAS Institute, Inc., Cary, North Carolina) per sponsor agreed reporting standards, where applicable. Details of the statistical analyses will be included in a separate Statistical Analysis Plan (SAP).

9.1. Statistical Analysis

The following descriptive statistics will be used to summarize the trial data on the basis of their nature unless otherwise specified:

- Continuous variables: number of non-missing observations, mean, standard deviation, median, minimum, and maximum
- Categorical variables: frequencies and percentages
- Time-to-event variables: number of non-missing observations (N), median, minimum and maximum. Kaplan-Meier event rates may also be provided if applicable for specific time to event variables

9.1.1. Analysis Sets

The Safety Analysis Set (SAS) includes all patients who received ≥ 1 dose of study drugs of each cohort. This will be the primary analysis set for efficacy analysis, and the analysis set for safety analysis.

The Efficacy Evaluable Analysis Set (EAS) includes all treated patients (SAS) without critical protocol deviation of each cohort who had measurable disease at baseline per RECIST v1.1 and who had ≥ 1 evaluable post-baseline tumor assessment unless discontinued due to clinical PD or death within 7 weeks after the first dose. It will be used for the sensitivity analysis of the primary efficacy endpoint ORR.

The PK Analysis Set includes all patients who received ≥ 1 dose of any component of study drug per the protocol, for whom any postdose PK data are available.

The Immunogenicity Analysis Set includes all patients who received at least 1 dose of any component of study drug for whom both baseline antidrug antibody result and at least 1 post-baseline antidrug antibody result are available.

9.1.2. Patient Disposition

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

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

9.1.3. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in the Safety Analysis Set. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, time since advanced/metastatic disease diagnosis, etc. Categorical variables include gender, ECOG Performance Status, region/country, race, PD-L1 subgroup, prior systemic therapies, stage of disease, metastatic site, etc.

9.1.4. Prior and Concomitant Medications

Prior medications will be defined as medications that stopped before the day of first dose of study drugs. Concomitant medications will be defined as medications that 1) started before the first dose of study drugs and were continuing at the time of the first dose of study drugs, or 2) started on or after the date of the first dose of study drugs up to 30 days after the patient's last dose (as of the on-site Safety Follow-up Visit).

Concomitant medications will be coded using the WHO Drug Dictionary drug codes and 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.

9.2. Efficacy Analyses

ORR is the primary objective in the study. Response assessments will be determined by IRC and by investigator using RECIST v1.1.

Efficacy Analyses will be provided by subgroups as appropriate, such as PD-L1 subgroups, etc. Per-patient listings may be generated with limited patients for analysis.

General statistical considerations of efficacy analysis will be demonstrated here and more details will be provided in the Statistical Analysis Plan (SAP).

9.2.1. Primary Efficacy Analysis

The primary efficacy endpoint is confirmed ORR as determined by IRC using the RECIST v1.1 in Cohort 1.

ORR is defined as the proportion of patients achieving BOR of CR or PR. BOR is defined as the best response recorded from the first dose of study drug until data cut or the initiation of new anticancer treatment, whichever occurs earlier. Patients with no postbaseline response assessment (due to any reason) will be considered as nonresponders for BOR. The proportion of patients in each response category will be presented.

The binomial exact test will be performed among the patients whose tumor with PD-L1 vCPS $\geq$ 5% and patients whose tumor regardless of PD-L1 expression in Safety Analysis Set in a sequential way:

Patients whose tumor with vCPS ≥ 5%

The ORR in this population is assumed as 30%, which is deemed a clinically meaningful improvement based on a historical control of 15%. Hence, the null and alternative hypotheses are set as the following:

H_0: ORR ≤ 15%

H_a: ORR > 15%

Patients whose tumor regardless of PD-L1 expression

The ORR in this population is assumed as 25%, which is deemed a clinically meaningful improvement based on a historical control of 15%. Hence, the null and alternative hypotheses are set as the following:

H_0: ORR ≤ 15%

H_a: ORR > 15%

If the obtained one-sided p-value is ≤ 0.025, it will be concluded that BGB-A1217 combined with tislelizumab statistically significantly increases ORR compared with the historical controls in the PD-L1 vCPS ≥ 5% or/and regard less of PD-L1 expression population. Therefore, the superiority of BGB-A1217 combined with tislelizumab will be demonstrated. A Clopper-Pearson 95% confidence interval (CI) of ORR will be constructed to assess the precision of the rate estimate in the Safety Analysis Set.

The primary efficacy analysis will be conducted when ORR data is mature, which is 6 months (approximately 4 tumor assessments) after the last patient receives the first dose of study drug in Stage 2 and will be based on the Safety Analysis Set.

Approximately 4 months after the enrollment is completed in Stage 1, there will be a preliminary analysis of ORR and safety (using descriptive statistics) for the first 40 patients in Cohort 1 and all 40 patients in Cohort 2. Enrollment of Stage 2 will continue in parallel. At the time of preliminary analysis, if no more than 5 responders are observed in Cohort 1 at Stage 1, which corresponds to a Bayesian predictive probability of success less than 0.1 (Chen et al 2019; Lee and Liu 2008), the study will be terminated.

9.2.2. Secondary Efficacy Analysis

Objective Response Rate (ORR)

ORR as assessed by investigator's review will be summarized for secondary efficacy analysis in the Safety Analysis Set in Cohort 1, and ORR as assessed by both IRC and investigator will be summarized in Cohort 2. A 2-sided Clopper-Pearson 95% CI of ORR will be constructed to assess the precision of the point estimate of ORR.

Other efficacy endpoints with necessary tumor assessments, as well as OS, will be summarized for secondary efficacy analysis. The secondary efficacy analysis will be conducted by both IRC and investigator (if applicable) in Cohort 1 and Cohort 2.

Disease Control Rate (DCR)

DCR is defined as the proportion of patients who achieve CR, PR, or SD. DCR will be summarized similarly as ORR in the Safety Analysis Set and also in Efficacy Evaluable Analysis Set for sensitivity analysis.

Clinical Benefit Rate (CBR)

CBR is defined as the proportion of patients who achieve CR, PR, or durable SD (SD ≥ 24 weeks).

CBR will be summarized similarly as ORR in the Safety Analysis Set and also in the Efficacy Evaluable Analysis Set for sensitivity analysis.

Duration of Response (DOR)

DOR is defined as the time from the first confirmed objective response to disease progression documented after treatment initiation or death, whichever occurs first.

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

More details, including the censoring rules, will be provided in the SAP.

Progression-Free Survival (PFS)

PFS is defined as the time from treatment initiation to disease progression or death due to any cause, whichever occurs first.

PFS will be analyzed in the Safety Analysis Set using methods similar to those described for DOR. The PFS censoring rule will follow the same as followed by DOR. PFS rates at 3 months, 6 months, 9 months, and 12 months will be calculated based on Kaplan-Meier method.

Overall Survival (OS)

OS is defined as the time from treatment initiation to death due to any cause.

OS will be analyzed in the Safety Analysis Set using similar methods to those described for PFS similarly, except for censoring rules. For OS, patients will be censored either at the date that the patient was last known to be alive or the date of data cutoff, whichever comes earlier, in the absence of death. OS rates at 3 months, 6 months, 9 months, and 12 months will be calculated based on Kaplan-Meier method.

Time to Response (TTR)

TTR is defined as the time from treatment initiation to the first documented response.

TTR will be summarized for responders (who have achieved an objective response) only using sample statistics such as mean, median, and standard deviation.

Health Related Quality of Life (HRQoL)

HRQoL is measured by assessment of a patient's overall health status using the EORTC QLQ-C30 and EORTC QLQ-CX24. The postbaseline scores will be summarized for Cohorts 1 and 2, and the changes from the baseline scores will be summarized descriptively.

9.2.3. Sensitivity Analysis

A sensitivity analysis of ORR will be carried out in the Efficacy Evaluable Analysis Set.

9.3. Safety Analyses

Safety will be assessed by the 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 safety. Descriptive statistics will be used to analyze all safety data in the Safety Analysis Set.

9.3.1. Extent of Exposure

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

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

Patient data listings will be provided for all dosing records.

9.3.2. Adverse Events

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

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drugs up to 30 days following the last treatment of monotherapy/combination therapy or initiation of subsequent anticancer therapy, whichever comes first. The TEAE classification also applies to imAEs that are recorded up to 90 days after the last dose of the study drugs, regardless of whether the patient starts a subsequent anticancer therapy. Only those AEs that were treatment emergent will be included in summary tables. 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 system organ class (SOC) and preferred term (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 preferred term.

The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drugs. Treatment-related AEs include those events considered by the investigator to be related to study drug or with missing assessment of the causal relationship.

SAEs, deaths, ≥ Grade 3 TEAEs, imAEs, treatment-related TEAEs, and TEAEs that led to treatment discontinuation, dose interruption, or dose delay will be summarized.

9.3.3. Laboratory Analyses

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

Laboratory parameters that are graded in NCI-CTCAE v5.0 or newer 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.

9.3.4. Vital Signs

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

9.4. Pharmacokinetic Analyses

Pharmacokinetic samples will be collected in this study as outlined in Appendix 1.

Tislelizumab and BGB-A1217 serum concentration data will be tabulated and summarized by visit/cycle at which these concentrations are collected. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

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

9.5. Immunogenicity Analyses

Samples to assess anti-BGB-A1217 and anti-tislelizumab antibodies will be collected only in patients who receive study drugs and at sites that are able to adequately perform sampling, handling, and processing as outlined in the laboratory manual.

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

9.6. Other Exploratory Analyses

Summary statistics might be provided for exploratory biomarkers including but not limited to expression of PD-L1, TIGIT, CD226, CD155, CD112 in tumor tissues, and tumor mutation burden/gene mutation/MSI and gene expression profiling in tumor tissues and/or peripheral blood.

An exploratory analysis on a potential correlation of these tumor tissue or blood-based biomarkers with response, resistance, and prognosis might be performed to understand disease pathobiology and explore potential predictive biomarkers.

QoL is measured by the assessment of the EQ-5D-5L. The postbaseline scores will be summarized for Cohorts 1 and 2, as appropriate.

9.7. Sample Size Consideration

The sample size calculation of Cohort 1 was based on the power of the comparison between estimated ORR in the study and the historical rate in a sequential way with patients whose tumor with PD-L1 vCPS ≥ 5% followed by patients whose tumor regardless of PD-L1 expression. An assumed ORR of 30% in the patients whose tumor with PD-L1 vCPS ≥ 5% as compared to historical rate of 15%; an assumed ORR of 25% in the patients whose tumor regardless of PD-L1 expression as compared to historical rate of 15%.

- With 76 patients (60% whose tumor with PD-L1 vCPS ≥ 5%), the power is 0.860 to demonstrate that the ORR in patients whose tumor with PD-L1 vCPS ≥ 5% is statistically higher than the historical rate of 15% using a binomial exact test; the 95% CI of an observed 30% ORR is (20.2%, 41.9%).
- With 89 patients (70% whose tumor with PD-L1 vCPS ≥ 5%), the power is 0.927 to demonstrate that the ORR in patients whose tumor with PD-L1 vCPS ≥ 5% is statistically higher than the historical rate of 15% using a binomial exact test; the 95% CI of an observed 30% ORR is (21.0%, 40.0%).
- With 102 patients (80% whose tumor with PD-L1 vCPS ≥ 5%), the power is 0.940 to demonstrate that the ORR in patients whose tumor with PD-L1 vCPS ≥ 5% is statistically higher than the historical rate of 15% using a binomial exact test; the 95% CI of an observed 30% ORR is (21.7%, 40.3%).
- With 127 patients, the power is 0.807 to demonstrate that the ORR in the patient population whose tumor regardless of PD-L1 expression is statistically higher than the historical rate of 15% using a binomial exact test; the 95% CI of an observed 25% ORR is (17.9%, 33.7%).

The PD-L1 expression will be closely monitored for Cohort 1, and enrollment of patients whose tumors are PD-L1 vCPS < 5%/not evaluable will be stopped as necessary when reaching ~40%. This is to ensure that the percentage of patients whose tumor with PD-L1 vCPS ≥ 5% is no less than 60% of the Safety Analysis Set.

In addition, 40 patients will be enrolled in Cohort 2 to investigate the safety and efficacy of tislelizumab monotherapy in patients with previously treated recurrent or metastatic cervical cancer.

10. STUDY COMMITTEES

10.1. Independent Review Committee

An Independent Review Committee (IRC) will be established to perform an independent review of all radiological images for the efficacy analysis and to determine all instances of response and disease progression based on RECIST v1.1 criteria, in addition to the local investigator review of radiographs. The results from the investigator's review of radiographic images will be used to determine whether patients should be enrolled or should continue study treatment. The tumor assessment by the IRC will be used for the reporting of the study results.

All decisions made during the performance of the study will be based on the local investigator's assessments of radiographic images, clinical status, and relevant examination of the patients. Sites will submit specific radiographic image files to the centralized data review facility during the study at an ongoing basis or at the sponsor's request. Detailed rules and guidelines for radiographic imaging and tumor assessments by the IRC are outlined separately in the Imaging Manual and the IRC Charter.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

11.1. Access to Information for Monitoring

In accordance with International Council for Harmonisation 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.

11.2. Access to Information for Auditing or Inspections

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

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

12.2. Quality Assurance

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

12.3. Study Site Inspections

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

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

12.4. Drug Accountability

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

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

13. ETHICS/PROTECTION OF HUMAN PATIENTS

13.1. Ethical Standard

This study will be conducted by the principal investigator and the study center in full conformance with the International Council for Harmonisation 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 International Council for Harmonisation E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

13.2. Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted, 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.

13.2.1. Protocol Amendments

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

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

13.3. Informed Consent

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

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

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

Patients must 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.

13.4. Patient and Data Confidentiality

The principal investigator and sponsor will maintain confidentiality and privacy standards by following applicable data privacy laws covering the collection, storage, transmission, and processing of patients' personal and medical information.

The principal investigator shall code the medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. This approach ensures that patients' names are not included in any data set transmitted to any sponsor location.

Patient 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 the event of a breach of the confidentiality of a patient's personal and medical information, the principal investigator and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable data privacy 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.

Data generated during this study must be available for inspection upon request by representatives of the National Medical Products Administration 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 must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator agrees that all information received from the sponsor, including but not limited to Tislelizumab Investigator's Brochure, BGB-A1217 Investigator's Brochure, this protocol, eCRFs, the Investigational New Drug, and any other study information, 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 provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

13.5. Financial Disclosure

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

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data 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.

14.1.2. 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 sign the completed casebooks to attest to their accuracy, authenticity, and completeness.

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

14.1.3. Data Management/Coding

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

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

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

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

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

14.2. Data Integrity and In-house Blinding

Due to the open-label design of the study, access to the patient-level clinical data in the EDC system will be assigned to predefined study personnel only. 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. In addition, the central imaging vendor will perform the central imaging review without knowledge of treatment arm assignment. Although the study is open label, analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented.

14.3. Study Records Retention

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

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

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

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

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

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

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

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

14.4. Protocol Deviations

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

14.5. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). The sponsor will ensure that the report meets the standards set out in the International Council for Harmonisation 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 2019).

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

14.6. Study and Study Center Closure

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

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

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

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons 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 the return of all unused study drugs 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.

14.7. Information Disclosure and Inventions

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

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

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

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

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an 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 14.5

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

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16. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Screening [a]	Treatment Cycles					Safety Follow-up Visits[c]			Survival Follow-up[d]
		Cycles 1 to 3 (Every 21 Days)			≥ Cycle 4 (Every 21 Days)	End of Treatment Visit[b]				
Days (Window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**0 to 7 Days**	**30 (±7) Days After Last Dose (On-site)**	**60 (±14) Days After Last Dose (Phone Call)**	**90 (±14) Days After Last Dose (Phone Call)**	**Every 3 Months**
Informed consent[a]	X									
Inclusion/exclusion criteria	X									
Randomization[e]	X									
Demographics/medical history/prior medications[f]	X									
Vital signs/ height and weight[g]	X	X			X	X	X			
Physical examination[h]	X	X			X	X	X			
ECOG Performance Status	X	X			X	X	X			
12-lead ECG[i]	X	As clinically indicated				X	X			
Adverse events[j]	X	X	X[z]	X[z]	X	X	X	X	X	
Concomitant medications	X	X	X[z]	X[z]	X	X	X	X	X	
Hematology[k]	X[1]	X			X	X	X			
Serum chemistry[k]	X[1]	X			X	X	X			

Assessment	Screening [a]	Treatment Cycles					Safety Follow-up Visits[c]			Survival Follow-up[d]
		Cycles 1 to 3 (Every 21 Days)			≥ Cycle 4 (Every 21 Days)	End of Treatment Visit[b]				
Days (Window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**0 to 7 Days**	**30 (±7) Days After Last Dose (On-site)**	**60 (±14) Days After Last Dose (Phone Call)**	**90 (±14) Days After Last Dose (Phone Call)**	**Every 3 Months**
Total CK and CK-MB[k,l]	X[1]	X			X	X	X			
Coagulation parameters[k,m]	X	As clinically indicated				X	X			
Urinalysis[k]	X	As clinically indicated								
Pregnancy test[n]	X	As clinically indicated								
Thyroid function[o]	X[1]	X[14] (Every 3 cycles)				X	X			
HBV/HCV tests[p]	X	Every 4 cycles (as clinically indicated)								
Pulmonary function tests[q]	X	As clinically indicated								
Pharmacokinetics[r]		X			X		X			
Anti-drug antibodies[s]		X			X		X			
Tumor assessment[t]	X	Every 6 weeks (± 7 days) for the first 54 weeks. Every 12 weeks (± 7 days) thereafter.								
Archival/fresh tumor tissue[u]	X					X(optional)				
Blood biomarker (optional)[v]		X	First response and confirmed PD as clinically indicated							
Tislelizumab administration[w]		X			X					
BGB-A1217 administration[x]		X			X					

Assessment	Screening [a]	Treatment Cycles					Safety Follow-up Visits[c]			Survival Follow-up[d]
		Cycles 1 to 3 (Every 21 Days)			≥ Cycle 4 (Every 21 Days)	End of Treatment Visit[b]				
Days (Window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**0 to 7 Days**	**30 (±7) Days After Last Dose (On-site)**	**60 (±14) Days After Last Dose (Phone Call)**	**90 (±14) Days After Last Dose (Phone Call)**	**Every 3 Months**
EORTC QLQ-C30[y]		Every 2 cycles for the first 54 weeks. Every 4 cycles thereafter. (Cycle 1 as baseline)					X			
EORTC QLQ-CX24[y]		Every 2 cycles for the first 54 weeks. Every 4 cycles thereafter. (Cycle 1 as baseline)					X			
EQ-5D-5L[y]		Every 2 cycles for the first 54 weeks. Every 4 cycles thereafter. (Cycle 1 as baseline)					X			
Survival status										X

Abbreviations: ADA, antidrug antibody; AE, adverse event; CK, creatine kinase; CK-MB, creatine kinase cardiac muscle isoenzyme; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-CX24, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cervical Cancer Module; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30, EQ-5D-5L, European Quality of Life 5-Dimensional - 5-Level Questionnaire; FFPE, formalin-fixed paraffin-embedded; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IEC, Independent Ethics Committee; imAE, immune-mediated adverse event; IRB, Institutional Review Board; IRC, Independent Review Committee; IRT, interactive response technology; IV, intravenous; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, progressive disease; PET, position emission tomography; PK, pharmacokinetic; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; v, version.

Written informed consent is required before performing any study-specific tests or procedures. Results of standard of care tests or examinations performed before obtaining informed consent and within 28 days before the first dose of study drugs may be used for screening assessments rather than repeating such tests.

The End-of-Treatment Visit (EOT) is conducted when the investigator determines that study treatment(s) will no longer be used. Patients who discontinue treatment for any reason will be asked to return to the clinic for the EOT Visit within 7 days of when the EOT decision is made unless otherwise specified or before the initiation of a new anticancer treatment, whichever occurs first. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT Visit, these tests need not be repeated.

Patients who permanently discontinue BGB-A1217/tislelizumab will be asked to return to the clinic for the on-site Safety Follow-up Visit, which is required to be conducted 30 days (± 7 days) after the last dose of BGB-A1217/tislelizumab or before the initiation of subsequent anticancer therapy, whichever occurs first. If the time windows of this Safety Follow-up Visit and EOT Visit are overlapped, the safety follow-up can be exempted and the tests required at Safety Follow-up Visit will be conducted at the EOT Visit. In addition, 2 additional Safety Follow-up Visits (by telephone contact) should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of BGB-A1217/tislelizumab, regardless of whether patients started a new subsequent 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.

Survival Follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the last Safety Follow-up Visit until death, loss to follow-up, withdrawal of consent, or end of study. All patients will be followed for survival and subsequent anticancer therapy information except for patients that request to be withdrawn from follow-up.

Patients will be randomized into either Cohort 1 or Cohort 2 via IRT in Stage 1. After the Stage 1 enrollment completes, patients in Cohort 1 will continue to participate in Stage 2 receiving the same treatment as in Stage 1. An additional approximately 87 patients will be enrolled in Cohort 1 Stage 2. All patients are required to receive study treatment within 2 business days of randomization.

Includes age or date of birth, gender, and self-reported race/ethnicity; history of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Information on radiographic studies performed before study entry may be collected for review by the investigator.

Vital signs collected on study include temperature, pulse rate, respiratory rate, and blood pressure. The patient's vital signs are required to be recorded within 60 minutes before, during, and approximately 30 minutes after the first 2 cycles of study drugs. For subsequent cycles, 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.

During the Screening Visit, a complete physical examination (as detailed in Section 7.4.2) will be conducted. At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed.

The ECG recordings will be obtained during screening, EOT Visit, on-site Safety Follow-up Visit, and as clinically indicated at other timepoints. When coinciding with blood draws, ECG assessment should be performed before blood draws. Patients should be resting in semirecumbent supine position for ≥ 10 minutes in the absence of environmental distractions before each ECG measurement.

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 before the administration of study drug, only SAEs should be reported. After the first dose of study drug, 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 drugs, the initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, 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 drugs, regardless of whether the patient starts a new anticancer therapy, death, withdrawal of consent, or loss to follow-up. The investigator should report any SAEs that are assessed as related to tislelizumab/BGB-A1217 treatment, at any time after treatment discontinuation.

Laboratory assessments on serum chemistry, hematology, coagulation, total CK and CK-MB, and urinalysis will be conducted, of which certain elements will be collected as specified in Section 7.4.4. If laboratory tests at screening are not performed within 7 days before the first dose of study drugs, these tests should be repeated and reviewed before randomization. After Cycle 1, these laboratory tests are to be performed and 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.

Serum CK and CK-MB testing is included in total CK and CK-MB assessment, which will be implemented for all patients at screening, predose at Day 1 of every scheduled cycles, at EOT Visit, and at the on-site Safety Follow-up Visit. In the event that CK-MB fractionation is not available, serum troponins (troponin I and/or T) measurements will be performed instead.

Includes international normalized ratio, prothrombin time, and activated partial thromboplastin time.

Urine or serum pregnancy test would be conducted during screening and whenever clinically indicated only for women of childbearing potential, including women who have had a tubal ligation (see Appendix 5 for related definition). When indicated, the test must be performed and documented as negative within 7 days before the first dose of study drugs. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

Analysis of free T3, free T4, and TSH will be performed by a central laboratory or the local study site laboratory. Thyroid function tests will be performed at screening and every 3 cycles (ie, Cycles 4, 7, 10, etc), EOT Visit, and Safety Follow-up Visit. For sites where free T3 or free T4 test is not available, alternative tests can be considered by communication with medical monitor.

Testing will be performed by a central laboratory and/or the local laboratory at screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA). Patients who have detectable HBV DNA or HCV RNA at screening will perform the respective viral load test every 4 cycles (ie, Day 1 of Cycle 5, 9, 13, etc) from Cycle 5 onwards.

Pulmonary function testing includes spirometry and assessment of oxygenation, at a minimum pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity. Patients who are suspected of having serious/severe respiratory conditions, or who exhibit significant respiratory symptoms unrelated to the underlying cancer, or with a history of thoracic radiotherapy should be evaluated for the suitability on the study at screening. Tests may be repeated as clinically indicated while on study. Respective test results need to be submitted to the sponsor.

PK samples will be collected in all patients who received ≥ 1 dose of any component of study drug per the protocol and whose postdose PK data are available. For both tislelizumab and/or BGB-A1217, predose (within 60 minutes before starting infusion) samples are required to be collected at Day 1 of Cycles 1, 2, 5, 9, and 17. A postdose (within 30 minutes after completing tislelizumab and BGB-A1217 combination treatment or tislelizumab monotherapy) sample is required to be collected on Day 1 of Cycles 1 and 5. An additional PK sample is required to be collected at the Safety Follow-up Visit for both drugs. Should a patient present with any ≥ Grade 3 imAE, an additional blood PK sample may be taken to determine the serum concentration of tislelizumab and/or BGB-A1217. These tests are required when it is allowed by local regulations/IRBs/IECs.

ADA samples will be collected only in sites that are able to adequately perform ADA sampling and handling in all patients. Blood used to test for anti-tislelizumab and anti-BGB-A1217 antibodies should be collected within 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 5, 9 and 17, and at Safety Follow-up Visit. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/IECs.

Radiological images captured as standard of care before obtaining written informed consent and ≤ 28 days before the first dose of study drugs may be used rather than repeating tests. All measurable and evaluable lesions are required to be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at Screening is required to be used throughout the study (eg, the same imaging protocol for CT or MRI). CT/MRI of the head at baseline is required for patients who are suspected to have central nervous system metastases; bone scan or PET is required if clinically indicated.

Patients will undergo tumor assessments approximately every 6 weeks (± 7 days) for the first 54 weeks and every 12 weeks (± 7 days) thereafter (based on RECIST v1.1 assessment). Tumor assessments must be performed on schedule regardless of whether study treatment has been administered or withheld. That is, they should not be adjusted for delays in cycles. Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer treatment, experiences disease progression per RECISTv1.1 by IRC, withdraws consent, is lost to follow-up, death, or until the study terminates, whichever occurs first. See also Section 7.5.

Patients are required to provide archival tumor tissues (FFPE blocks or approximately 15 [≥ 6] unstained slides) for biomarker analysis. Fresh biopsy: In the absence of sufficient archival tumor tissues, a fresh biopsy of a tumor lesion at baseline is mandatory. See Section 7.7 for more information. Patients who have PD will be asked to provide an optional biopsy for the assessment of mechanism of resistance (written informed consent is required before fresh tumor biopsy).

Blood samples will be taken optionally at baseline (predose, on Cycle 1 Day 1), at the time of first tumor response (predose of Day1 of the following cycle) and at the time of confirmed PD (10 mL each timepoint) for all patients to explore the association with response, resistance and prognosis to tislelizumab in combination with BGB-A1217 or tislelizumab alone. Written patient consent is required for blood sample collection.

Tislelizumab will be given IV Q3W for patients in Cohort 1 and Cohort 2. The initial infusion (Cycle 1 and Cycle 2, Day 1) will be delivered over 60 minutes, and then can be administered over 30 minutes for subsequent infusions if well tolerated. Patients must be monitored for ≥ 2 hours after infusion of tislelizumab combined with BGB-A1217 (Cohort 1) and for ≥ 1 hour after infusion of tislelizumab monotherapy (Cohort 2) on Day 1 of Cycle 1 and Cycle 2; from Cycle 3 onward, a monitoring period of ≥ 30 minutes is required. Treatment could continue beyond progression if clinical benefit is seen and treatment is tolerated per the investigator's discretion. Patients should sign an informed consent form for continued treatment beyond progression per RECIST v1.1.

BGB-A1217 will be given to patients in Cohort 1. The initial infusion (Cycle 1 and Cycle 2, Day 1) will be delivered over 60 minutes, and then can be administered over 30 minutes for subsequent infusions if well tolerated. Patients must be monitored for ≥ 2 hour after infusion of tislelizumab combined with BGB-A1217 on Day 1 of Cycle 1 and Cycle 2; from Cycle 3 onward, a monitoring period of ≥ 30 minutes is required. Treatment could continue beyond progression if clinical benefit is seen and treatment is tolerated per the investigator's discretion. Patients should sign an informed consent form for continued treatment beyond progression per RECIST v1.1.

To be completed before any clinical activities during on-study site study visits. The questionnaires will be completed at Cycle 1 (baseline), at every other cycle (i.e., Cycle 1, Cycle 3, Cycle 5, Cycle 7) in the first 54 weeks and then every 4 cycles thereafter, and at Safety Follow-up Visit.

Review of AEs and concomitant medications may be conducted by telephone on Day 8 and Day 15.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Serum Chemistry	**Hematology**	**Coagulation**	**Urinalysis (screening and as clinically indicated)**
Alkaline phosphatase	Red blood cell count	Prothrombin time	pH
Alanine aminotransferase	Hematocrit	Partial thromboplastin time or activated partial thromboplastin time	Specific gravity
Aspartate aminotransferase	Hemoglobin	International normalized ratio	Glucose
Albumin	Monocyte count		Protein
Total bilirubin	Basophil count		Ketones
Direct bilirubin	Eosinophil count		Blood
Blood urea nitrogen or urea	Platelet counts		24-hour protein[a]
Potassium	White blood cell count with differential		
Sodium	Neutrophil count		
Calcium	Lymphocyte count		
Phosphorus			
Magnesium			
Chloride			
Creatinine			
Glucose			
Lactate dehydrogenase			
Total protein			
Creatine kinase/ CK-MB[b]			

Abbreviations: CK-MB, creatine kinase-muscle/brain.

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

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

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 more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

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

APPENDIX 4. PREEXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

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

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

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

APPENDIX 5. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control. (Clinical Trials Facilitation Group 2014) These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation:
  - oral
  - injectable
  - implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized male partner, provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment).

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

  Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence for the duration of exposure to study drugs, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be combined with another acceptable method listed above.

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

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

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

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
  - < 55 years of age with no spontaneous menses for ≥ 12 months AND with a postmenopausal follicle-stimulating hormone (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 syndromes, 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

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. EORTC-QLQ-C30 QUESTIONNAIRE

EORTC QLQ-C30 (version 3)

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

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

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

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

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 8. EORTC-QLQ-CX24 QUESTIONNAIRE

EORTC QLQ – CX24

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

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had cramps in your abdomen?	1	2	3	4
32.	Have you had difficulty in controlling your bowels?	1	2	3	4
33.	Have you had blood in your stools (motions)?	1	2	3	4
34.	Did you pass water/urine frequently?	1	2	3	4
35.	Have you had pain or a burning feeling when passing water/urinating?	1	2	3	4
36.	Have you had leaking of urine?	1	2	3	4
37.	Have you had difficulty emptying your bladder?	1	2	3	4
38.	Have you had swelling in one or both legs?	1	2	3	4
39.	Have you had pain in your lower back?	1	2	3	4
40.	Have you had tingling or numbness in your hands or feet?	1	2	3	4
41.	Have you had irritation or soreness in your vagina or vulva?	1	2	3	4
42.	Have you had discharge from your vagina?	1	2	3	4
43.	Have you had abnormal bleeding from your vagina?	1	2	3	4
44.	Have you had hot flushes and/or sweats?	1	2	3	4
45.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46.	Have you felt less feminine as a result of your disease or treatment?	1	2	3	4
47.	Have you felt dissatisfied with your body?	1	2	3	4

During the past 4 weeks:	Not at all	A little	Quite a bit	Very much
48. Have you worried that sex would be painful?	1	2	3	4
49. Have you been sexually active?	1	2	3	4

Answer these questions only if you have been sexually active during the past 4 weeks:	Not at all	A little	Quite a bit	Very much
50. Has your vagina felt dry during sexual activity?	1	2	3	4
51. Has your vagina felt short?	1	2	3	4
52. Has your vagina felt tight?	1	2	3	4
53. Have you had pain during sexual intercourse or other sexual activity?	1	2	3	4
54. Was sexual activity enjoyable for you?	1	2	3	4

APPENDIX 9. EQ-5D-5L QUESTIONNAIRE

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

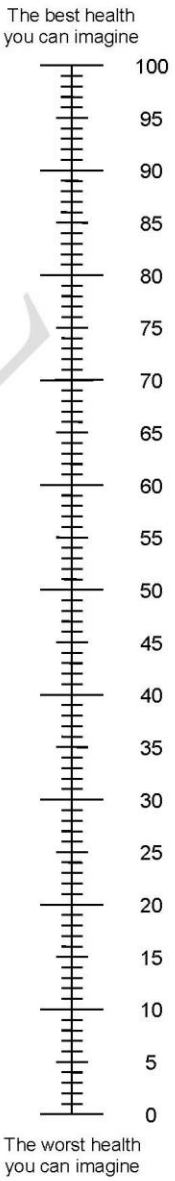
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX 10. 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

APPENDIX 11. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

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

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

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

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

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

Recommended diagnostic tests in the management of possible immune-mediated adverse events	
Immune-mediated toxicity	**Diagnostic evaluation guideline**
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, *Clostridium difficile* toxin, and cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain or distension, consider colonoscopy with biopsy and surgical intervention, as appropriate.
Eye disorders	If a patient experiences acute, new onset, or worsening of eye inflammation, blurred vision, or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if ≥ 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 I and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, troponin I, and refer to a cardiologist.

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

Treatment of Immune-Mediated Adverse Events

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

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

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
Thyroid disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 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/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1.
Hypophysitis	**1-2** Mild 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 Moderate-severe symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade 2 or less. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 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.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical 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.

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

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
Diabetes/ hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
Ocular toxicity	**1** Asymptomatic eye exam/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	4	Admit to hospital for emergency	Discontinue study

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	Acute abdominal pain, surgical emergency	management and appropriate referral.	treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment manage as a Grade 3 event.	Continue treatment or, if symptoms continue worsens, hold study treatment until symptoms improve to baseline or Grade 0-1.
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider IV corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2.	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 X ULN or worse initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	Hold study treatment until improved to Grade 0-1. Discontinue if any evidence of myocardial involvement.
Myocarditis	**< 2** Asymptomatic but	Admit to hospital and refer to a cardiologist.	Hold study treatment until completely

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Transfer all patients with moderate/severe cardiac symptoms or any increase in cardiac serum markers to the coronary care unit. Initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab or anti-thymocyte globulin.	resolved or myocarditis has been ruled out.
	2 Symptoms on mild-moderate exertion		Discontinue study treatment unless cardiac involvement has been excluded and symptoms have completely resolved.
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CK, creatine kinase; CK-MB, creatine kinase-muscle-brain; CHF, congestive heart failure; INR, international normalized ratio; IV, intravenous; LFT, liver function test; MMF, mycophenolate mofetil; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.

APPENDIX 12. 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 (Version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

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

Measurable Disease

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

- 10 mm by computed tomography (CT) scan (irrespective of scanner type) and magnetic resonance imaging (MRI) (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical examination (when superficial).
- 20 mm by chest x-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT or MRI scan (CT/MRI scan slice thickness recommended to be ≥ 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

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

Bone lesions:

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

MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other 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 or MRI scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph node" or "multiple liver metastases").

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and 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, because CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete

pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.

- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) to differentiate between response (or SD) and progressive disease (PD).

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.
- PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
- Stable Disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the “sum” of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, o 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 electronic case report form (eCRF). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially 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 Non-target Lesions

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

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- PD: Unequivocal progression (as detailed below) of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression.)
- Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The

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

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

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

While fluorine-18 [F-18] fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a 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 considering any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response."

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

Target lesions	**Non-target lesions**	**New lesions**	**Overall response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
Stable disease	Non-PD or not all evaluated	No	Stable disease

Target lesions	Non-target lesions	New lesions	Overall response
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

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

In trials where confirmation of response is required, repeated 'NE' timepoint assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with timepoint responses of PR-NE-PR as a confirmed response.

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

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

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

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

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

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

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not 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 PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

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

Duration of Stable Disease

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

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

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

[redacted]

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