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CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 3, Randomized, Double-Blind Study of Ociperlimab, an Anti-TIGIT Antibody, in Combination With Tislelizumab Compared to Pembrolizumab in Patients With Previously Untreated, PD-L1-Selected, and Locally Advanced, Unresectable, or Metastatic Non-Small Cell Lung Cancer
Protocol Identifier:	BGB-A317-A1217-302 (AdvanTIG-302)
Phase:	3
Investigational Products:	Tislelizumab (BGB-A317) and Ociperlimab (BGB-A1217)
Indication:	Locally advanced, unresectable, or metastatic non-small cell lung cancer (NSCLC)
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive, Third Floor San Mateo, California 94404 USA
Reference Number:	EudraCT 2020-004985-21 NCT04746924
Sponsor Medical Monitor:	[redacted] Telephone: [redacted] Email: [redacted]
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Protocol Amendment 5.0	22 December 2023

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FINAL PROTOCOL APPROVAL SHEET

A Phase 3, Randomized, Double-Blind Study of Ociperlimab, an Anti-TIGIT Antibody, in Combination With Tislelizumab Compared to Pembrolizumab in Patients With Previously Untreated, PD-L1-Selected, and Locally Advanced, Unresectable, or Metastatic Non-Small Cell Lung Cancer

BeiGene, Ltd., Approval:

Approved Date 12/22/2023

See electronic signature	*See electronic signature*
Sponsor's Representative	Date

INVESTIGATOR SIGNATURE PAGE

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

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SYNOPSIS

Study Title	A Phase 3, Randomized, Double-Blind Study of Ociperlimab, an Anti-TIGIT Antibody, in Combination With Tislelizumab Compared to Pembrolizumab in Patients With Previously Untreated, PD-L1-Selected, and Locally Advanced, Unresectable, or Metastatic Non -Small Cell Lung Cancer
Brief Study Title	BGB-A317-A1217-302 (AdvanTIG-302)
Brief Summary	The purpose of this study is to evaluate the efficacy and safety of ociperlimab + tislelizumab compared with that of pembrolizumab in adults with PD-L1 high, locally advanced/recurrent or untreated metastatic NSCLC. Two interim analyses for OS (primary endpoint) are planned in the study. The interim analyses and final analysis will be conducted when 245, 303 and 379 deaths are observed, which are expected approximately 37 months, 44 months, and 58 months after the first patient randomized, respectively.
Sponsor	BeiGene
Amendment Version	Protocol Amendment 5.0
Regulatory Agency Identifier Number(s)	EudraCT 2020-004985-21 NCT04746924
Rationale	Results from similar studies indicated that anti-TIGIT antibodies have the potential to significantly improve and/or extend the therapeutic benefit of anti-PD-1 therapy in NSCLC. Pembrolizumab, as standard of care for first line therapy patients with metastatic NSCLC, is considered the most suitable comparator to test whether the anti-TIGIT antibody ociperlimab in combination with the anti-PD-1 antibody tislelizumab improves patient outcomes.

Objectives and Endpoints

Objectives	**Endpoints**
Primary: • To compare overall survival (OS) between Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo) in the ITT Analysis Set	**Primary:** • OS (time from the date of randomization to the date of death due to any cause) in the ITT Analysis Set of Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo)
Secondary: • To compare progression free survival (PFS) between Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo) in the Intent to Treat (ITT) Analysis Set as assessed by investigators according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)	**Secondary:** • PFS as assessed by investigators (time from the date of randomization to the date of the first objectively documented tumor progression per RECIST v1.1, or death, whichever occurs first) in the ITT Analysis Set of Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo)

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• To compare the overall response rate (ORR) and duration of response (DOR) between Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo) in the ITT Analysis Set as assessed by investigators according to RECIST v1.1 • To compare health-related quality of life (HRQoL) and time to deterioration (TTD) between Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo) in the ITT Analysis Set • To further investigate the safety and tolerability of ociperlimab in combination with tislelizumab	• ORR as assessed by investigators (proportion of patients with a documented, confirmed complete response [CR] or partial response [PR] per RECIST v1.1) and DOR as assessed by investigators (time from the first determination of an objective response per RECIST v1.1 until the first documentation of progression or death, whichever occurs first) in Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo) • HRQoL as assessed via patient-reported outcomes (PRO) using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), its lung cancer module Quality of Life Questionnaire Lung Cancer 13 (QLQ-LC13), and the 5-Level EuroQol 5-Dimension (EQ-5D-5L) questionnaire in Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo). PRO endpoints include the EORTC QLQ-C30's global health status/QoL (GHS), physical function and fatigue scales, and the QLQ-LC13's index score, dyspnea, coughing, hemoptysis and pain in chest, pain in arms/shoulders and peripheral neuropathy scales. • TTD, defined as time from randomization to the first occurrence of worsening scores (10-point change, to be defined in the Statistical Analysis Plan [SAP] if otherwise) for 2 consecutive assessments or 1 assessment followed by death from any cause before the next scheduled data collection • The incidence and severity of adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) in Arm A (ociperlimab in combination with tislelizumab)
Study Design	This is a randomized, double-blind, multicenter, Phase 3 study, which will be carried out at approximately 242 centers, including a minimum of 26 centers in Japan. Preliminary safety and tolerability will be evaluated in a safety run-in substudy before Japanese patients are randomized in this Phase 3 study.

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	All study treatments will be administered until intolerable toxicity, withdrawal of informed consent, or the timepoint at which, in the opinion of the investigator, the patient is no longer benefiting from study therapy. Crossover is not permitted. An Independent Data Monitoring Committee (IDMC) will be established to regularly monitor the safety and efficacy of study treatment.
Description of Patients	The patients enrolled in this study are at least 18 years of age with a diagnosis of histologically or cytologically documented locally advanced or recurrent NSCLC that is not eligible for curative surgery and/or definitive radiotherapy with or without chemoradiotherapy, or metastatic nonsquamous or squamous NSCLC. Patients should have no prior systemic treatment for metastatic NSCLC and no prior checkpoint inhibitor treatment. As determined centrally (or locally in the US and Japan), eligible patients should have PD-L1 expressed in ≥ 50% tumor cells. Patients with known mutations in *EGFR*, *ALK* fusion oncogene, BRAF V600E, or *ROS1* will not be eligible.
Number of Patients	Approximately 660 patients will be enrolled in the main study and a minimum of 6 patients are planned to be enrolled into the safety run-in substudy in Japan
Study Drug/Treatments	Eligible patients will be randomized in a 5:5:2 ratio to receive ociperlimab + tislelizumab (Arm A), pembrolizumab + placebo (Arm B), or tislelizumab + placebo (Arm C): • Arm A: Tislelizumab 200 mg intravenously followed by ociperlimab 900 mg intravenously once every 3 weeks Note: As of Protocol Amendment Version 3.0, the ociperlimab dose that will be administered to Japanese patients allocated in Arm A was determined to be 900 mg based on the results from the safety run-in substudy. • Arm B: Pembrolizumab 200 mg intravenously followed by placebo intravenously once every 3 weeks • Arm C: Tislelizumab 200 mg intravenously followed by placebo intravenously once every 3 weeks.
Ethical Considerations	PD-1 blockade by tislelizumab has been evaluated in 1992 patients as monotherapy with a safety and efficacy profile similar to what has been reported for other anti-PD-1/PD-L1 therapies, such as nivolumab and pembrolizumab. The preliminary results from an anti-TIGIT/ anti-PD-L1 competitor combination study suggest that ociperlimab has the potential to improve and/or extend the therapeutic benefits of tislelizumab in the treatment-naive setting. As of 28 July 2023, 346 patients had received ociperlimab in combination with tislelizumab only across a variety of solid tumor types. The actual effectiveness of tislelizumab in combination with ociperlimab in patients is not yet fully known. Ociperlimab has been well tolerated. A pooled analysis of combination therapies conducted to provide a comprehensive safety assessment showed that AEs were generally reversible and manageable.

	Based on the mechanism(s) of action, and the nonclinical and available clinical data, the combined blockade of TIGIT and PD-1 by ociperlimab and tislelizumab, respectively, is expected to result in immune-mediated toxicities similar to what has been observed with tislelizumab alone. However, the actual side effects that each patient experiences may vary.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BGB-A317	tislelizumab
CBR	clinical benefit rate
cCRT	concurrent chemoradiotherapy
CR	complete response
CRT	chemoradiotherapy
CT	computed tomography
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
EBUS-TBNA	endobronchial ultrasound-guided transbronchial needle aspiration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture (system)
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	End-of-Treatment
EQ-5D-5L	5-Level EuroQol 5-Dimension
Fc	fragment crystallizable region (typically, of immunoglobulin G)
FDG	fluorodeoxyglucose
GEP	gene expression profiling
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life

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Abbreviation	Definition
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	immunoglobulin G
imAE	immune-mediated adverse event
IRB	Institutional Review Board
ITT	Intent-to-Treat
MHLW	Ministry of Health, Labour and Welfare
MRI	magnetic resonance imaging
MSI	microsatellite instability
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death ligand-1
PET	positron emission tomography
PFS	progression-free survival
PFS2	progression-free survival after next line of treatment
PGI-S	patient global impression of severity
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcomes
PRTSE	patient reported treatment-related side-effect burden
QLQ-LC13	Quality of Life Questionnaire Lung Cancer 13
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
TEAE	treatment-emergent adverse event

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Abbreviation	Definition
TIGIT	T-cell immunoglobulin and ITIM domain
TIL	tumor-infiltrating immune cell
TMB	tumor mutation burden
TPS	Tumor Proportion Score
TTD	time to deterioration
TTR	time to response
ULN	upper limit of normal

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1. INTRODUCTION

1.1. Background Information on Non-Small Cell Lung Cancer

Lung cancer is the most common cancer, with approximately 2.21 million new diagnoses and 1.8 million deaths worldwide in 2020, which corresponds to the second highest incidence among cancers and the most common cancer-related mortality (WHO Cancer 2021). The disease is more common in men than women, representing 16.8% of all cancers in men and 8.8% of all cancers in women. In China, lung cancer is the leading cause of cancer-related death in both men and women, with an estimated 610,200 deaths and an estimated 733,300 new cases in the year 2015 (Chen et al 2016). Non-small cell lung cancer (NSCLC) originates from the epithelial cells of the lung and accounts for 80% to 85% of all lung cancers. There are 3 main histological subtypes of NSCLC, adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, which constitute 40%, 25%, and 10% of lung cancers, respectively (PDQ Adult Treatment Editorial Board [NSCLC] 2020).

The prognosis for lung cancer patients is relatively poor, although it greatly depends on the stage at which the cancer is detected. Lung cancer staging is performed worldwide according to the tumor, lymph node, and metastasis (TNM) Classification of Malignant Tumors, Eighth Edition (Amin et al 2017). If lung cancer is diagnosed in its earliest stages, cure is possible through surgery or chemo-radiation therapy. Unfortunately, lung cancer cases are most often detected at a relatively late stage. Approximately one third of patients with NSCLC present with locally advanced Stage III disease (including involvement of locoregional mediastinal lymph nodes or organs). The 5-year survival rates for patients with Stage III disease range from 36% (Stage IIIA) to 13% (Stage IIIC) (American Cancer Society 2023). Fifty-five percent of patients with newly diagnosed NSCLC have distant metastases (Stage IV). Stage IVA patients (any T, any N, M1a or M1b) present with separate tumor nodule(s) in a contralateral lung lobe, pleural or pericardial nodule(s), or malignant pleural or pericardial effusion (M1a) or with metastases in a single location outside the chest, for instance, a distant lymph node or organ such as brain, liver, or bone (M1b). The 5-year survival rate for Stage IVA is 10% (Goldstraw et al 2016). Stage IVB patients (any T, any N, and M1c) present with disease that has spread to multiple locations (either distal lymph nodes or organs, M1c). The overall 5-year survival rate for patients with Stage IV NSCLC is 5% (Siegel et al 2020).

1.2. Current Treatment for Locally Advanced, Unresectable, and Metastatic Non-Small Cell Lung Cancer

1.2.1. Concurrent Chemotherapy and Radiotherapy in the Management of Locally Advanced, Unresectable Stage III NSCLC

Concurrent chemoradiotherapy (cCRT) is the backbone part of first-line standard of care for patients with locally advanced, unresectable stage III NSCLC (National Comprehensive Cancer Network [NCCN] 2020) (European Society for Medical Oncology [ESMO] 2020). A meta-analysis of platinum-based chemotherapies from 1764 patients (Aupérin et al 2006) demonstrated that adding sequential or concurrent chemotherapy to radiotherapy improved survival in patients with locally advanced NSCLC. A direct comparison of data from 1205 patients enrolled in 6 clinical studies, showed a significant benefit of cCRT over sequential

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chemoradiotherapy (CRT) on overall survival (OS) (hazard ratio [HR], 0.84; 95% confidence interval [CI]: 0.74 to 0.95; p = 0.004), with an absolute benefit of 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% at 5 years. Concurrent CRT decreased locoregional progression (HR, 0.77; 95% CI: 0.62 to 0.95; p = 0.01), but not distal progression (HR, 1.04; 95% CI: 0.86 to 1.25; p = 0.69). Concurrent CRT increased acute esophageal toxicity compared with sequential CRT, but there was no significant difference in acute pulmonary toxicity (Aupérin et al 2010). Induction and consolidation chemotherapy have also been studied but neither has been shown improvement in OS compared to cCRT alone (Vokes et al 2007; Tsujino et al 2013).

Most of the chemotherapy regimens administered as part of cCRT are combinations of cisplatin with either pemetrexed, etoposide, vinblastine, or vinorelbine, but no chemotherapy regimen has been shown to be better than others. The NCCN guidelines (NCCN 2020) also recommend carboplatin as an alternative to cisplatin in the pemetrexed-containing doublet. Weekly carboplatin with paclitaxel during radiation with optional consolidation is another acceptable cCRT regimen (NCCN 2020) that has been shown to be superior to mitomycin + vindesine, weekly irinotecan + carboplatin, or single agent cisplatin or carboplatin with radiation therapy (Yamamoto et al 2010).

The accepted standard of care for radiotherapy concomitant to chemotherapy is approximately 60 Gy in 2 Gy fractions (NCCN 2020) (ESMO 2020 guidelines [ESMO 2020])

1.2.2. Chemotherapy in the Management of Advanced/Metastatic Stage IV NSCLC

Treatment of Stage IV NSCLC patients depends on disease histology, the presence of actionable mutations, age, performance status (PS), comorbidities, and patient's preferences.

Patients without actionable mutations regardless of programmed cell death ligand-1 (PD-L1) status and with PS 0 to 2 may receive 4 to 6 cycles of platinum-based doublets with or without maintenance. Patients with higher risk of neurotoxicity may receive carboplatin/nab paclitaxel. Carboplatin based doublets are also considered for patients with PS2 (ESMO 2019 guidelines [ESMO 2019]).

Patients with squamous NSCLC and PS 0-2 may receive platinum-based doublets with either gemcitabine, vinorelbine, or taxanes. Patients with nonsquamous NSCLC are given pemetrexed-based combination chemotherapy with carboplatin or cisplatin (ESMO 2019).

1.2.3. Targeted Therapy for Patients With Advanced/Metastatic Stage IV NSCLC and Selected Actionable Mutations

Targeted therapy is recommended for patients with metastatic NSCLC harboring anaplastic lymphoma kinase (*ALK*) or *ROS1* rearrangements or carrying epidermal growth factor receptor (EGFR) or BRAF V600 mutations (NCCN 2020). Patients with sensitizing *EGFR* mutations are offered treatment with tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, osimertinib or dacomitinib as first-line treatment. Erlotinib in combination with bevacizumab is another available option. Patients with *ALK* rearrangements may receive treatment with ALK TKIs, such as crizotinib, ceritinib, alectinib, or brigatinib. Patients with ROS1 rearrangements may be treated with crizotinib, entrectinib, or ceritinib. Patients with BRAF V600 mutations are offered BRAF/MEK inhibition using dabrafenib/trametinib (ESMO 2019).

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1.2.4. Anti-PD-1/PD-L1 Therapy for Locally Advanced or Metastatic Non-Small Cell Lung Cancers

Anti-programmed cell death protein-1 (PD-1) therapy has emerged as an effective treatment for those patients with tumors expressing varying degrees of PD-L1 (Hanna et al 2017). Anti-PD-1 and anti-PD-L1 therapies target the programmed death receptor pathway of T lymphocytes; this checkpoint has been found to be activated in cancers allowing tumors to evade the host immune system.

Single agent pembrolizumab was approved by the US Food and Drug Administration (FDA) as first line therapy for patients with metastatic NSCLC whose tumors express a high level of PD-L1 (Tumor Proportion Score [TPS] ≥ 50%) based on results from the KEYNOTE 024 trial (Reck et al 2016). In this study, pembrolizumab showed a significant improvement in the OS rate at 6 months (80.2% versus 72.4% [95% CI: 0.4 to 0.9]) and in progression-free survival (PFS; 10.3 months versus 6 months [95% CI: 6.7 to NR]) compared to platinum-based chemotherapy.

Single-agent atezolizumab was approved by the FDA as first-line therapy for patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1-stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1-stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]) with no *EGFR* or *ALK* genomic tumor aberrations based on results from the Phase 3 IMpower110 study. The study showed that atezolizumab monotherapy demonstrated a 7.1-month improvement in OS versus chemotherapy, with a median OS of 20.2 months and 13.1 months, respectively (HR = 0.59; 95% CI: 0.40 to 0.89; p = 0.0106; Herbst et al 2020).

Most recently, the FDA has approved single-agent cemiplimab as first-line treatment for patients with advanced NSCLC (locally advanced who are not candidates for surgical resection or definitive chemoradiation or whose cancer is metastatic) whose tumors have high PD-L1 expression (Tumor Proportion Score [TPS] > 50%) as determined by an FDA-approved test, with no *EGFR*, *ALK*, or *ROS1* aberrations based on results from the Phase 3 EMPOWER-Lung1 study. The study showed that cemiplimab monotherapy significantly improved median OS (NR versus 14.2 month, HR = 0.57; 95% CI: 0.42 to 0.77; p = 0.0002) and median PFS (8.2 month versus 5.7 month; HR = 0.54; 95% CI: 0.43 to 0.68; p< 0·0001) compared with chemotherapy (Sezer et al 2021).

Pembrolizumab in combination with pemetrexed and platinum-based therapy has also been granted accelerated approval by the FDA as a first-line treatment for patients with Stage IIIB or IV nonsquamous NSCLC and no *EGFR* or *ALK* genomic aberrations based on the results from KEYNOTE 021, Cohort G (Langer et al 2016). These findings were recently confirmed in the KEYNOTE 189 study, which enrolled metastatic NSCLC patients (Gandhi et al 2018). Based on results from the IMpower130 trial, atezolizumab in combination with carboplatin/nab paclitaxel was approved as a first-line treatment for patients with metastatic nonsquamous NSCLC who have no *EGFR* or *ALK* genomic tumor aberrations. Both median OS and median PFS were significantly improved in the atezolizumab arm versus the chemotherapy arm (OS: 18.6 months [95% CI: 16.0 to 21.2] versus 13.9 months [95% CI: 12.0 to 18.7]; PFS: 7.0 months [95% CI: 6.2 to 7.3] versus 5.5 months [95% CI: 0.54 to 0.77]) (West et al 2019).

Based on the results from the PACIFIC trial (Antonia et al 2017), the FDA-approved durvalumab as consolidation therapy for the treatment of unresectable stage III NSCLC whose

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cancer had not progressed after CRT. Based on results from the KEYNOTE 042 trial, pembrolizumab was also approved as a first-line treatment of patients with Stage III NSCLC who are not candidates for surgical resection or definitive CRT, or who have metastatic NSCLC *a*nd who h*a*ve no EGFR or ALK genomic aberrations and express PD-L1 (TPS > 1%). This study showed that pembrolizumab significantly improved median OS compared with carboplatin-based regimens (16.7 versus 12.1 months, 95% CI: 0.71 to 0.93) (Mok et al 2019).

There are multiple ongoing studies evaluating anti-PD-1 or PD-L1 therapies in combination with radiation or CRT. Emerging retrospective and prospective data suggest that anti-PD-1 therapy (at the established monotherapy dosing) in combination with radiation has similar toxicity to that anticipated with either treatment alone (Nomura et al 2018; Fiorica et al 2018).

1.2.5. New Immunotherapy-Immunotherapy Combinations for Locally Advanced or Metastatic NSCLC: Ipilimumab and Tiragolumab

The combinations of anti-PD-L1 therapy with other immunotherapy agents including anti-CTLA-4 and anti-TIGIT with or without chemotherapy are being evaluated in clinical studies in NSCLC patients.

Nivolumab in combination with ipilimumab (anti-CTLA-4) is approved by the FDA as first-line treatment for patients with metastatic NSCLC whose tumors express PD-L1 (≥ 1%), as determined by an FDA-approved test, with *EGFR* or *ALK* genomic tumor aberrations. In the CheckMate 227 study, nivolumab in combination with ipilimumab significantly prolonged median OS (17.1 months versus 14.9 months; HR = 0.79; 95% CI: 0.67 to 0.94; p = 0.0066) compared with the platinum-doublet chemotherapy arm (Hellmann et al 2018).

The combination of nivolumab plus ipilimumab and 2 cycles of platinum-doublet chemotherapy is approved by the FDA as first-line treatment for patients with metastatic or recurrent NSCLC with no *EGFR* or *ALK* genomic tumor aberrations based on results from the CheckMate 9LA study. The study showed that the median OS was significantly prolonged in patients who received nivolumab plus ipilimumab plus chemotherapy compared to patients who received chemotherapy alone (14.1 months versus 10.7 months; HR = 0.69; 96.71% CI: 0.55 to 0.87; p=0·00065); the same trend was seen with median PFS (6.8 months versus 5 months; HR = 0.70; CI: 0.57 to 0.86) (Paz-Ares et al 2021).

CITYSCAPE is a Phase 2 randomized study evaluating the anti-TIGIT antibody tiragolumab in combination with atezolizumab versus atezolizumab and placebo as a first-line therapy for PD-L1-selected NSCLC patients with no *EGFR* or *ALK* genomic aberrations (Rodriguez-Abreu et al 2020). At the time of the report, the study had enrolled 135 patients, 58 of whom had high PD-L1 expression (TPS ≥ 50%). Results from this study demonstrated improvement in overall response rate (ORR) and median PFS in a subset of PD-L1-high patients treated with tiragolumab and atezolizumab (ORR: 37.3% [95% CI: 25.0 to 49.6]; PFS: 5.6 months [95% CI: 4.2 to 10.4]) compared with those treated with atezolizumab and placebo (ORR: 20.6% [95% CI: 10.2 to 30.9]; PFS: 3.9 months [95% CI: 2.7 to 4.5]). A slightly higher percentage of treatment-related treatment-emergent adverse events (TEAEs) occurred in patients receiving tiragolumab and atezolizumab compared with patients receiving atezolizumab and placebo (81% versus 72%). The most common TEAEs observed in patients treated with tiragolumab and atezolizumab were low grade fatigue, pruritus and arthralgia; the most common immune-mediated AEs (imAEs) were low grade rash infusion related reactions and

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hypothyroidism. Similarly, Grade 3 events were slightly more frequent in the tiragolumab and atezolizumab arm (19%) versus the atezolizumab and placebo arm (15%). Anemia and dyspnea were the most common Grade 3 events, whereas Grade 4 pancreatitis was the most common imAE.

Study NCT02964013 is a Phase 1b study evaluating the anti-TIGIT antibody vibostolimab in combination with pembrolizumab in therapy-naïve or previously treated, advanced metastatic NSCLC patients who had never received anti-PD-L1 or anti-PD-1 therapy (Niu et al 2020). At the time of the report, the study had enrolled 41 patients in this arm, out of whom 13 were considered PD-L1 positive (TPS ≥ 1%) and 12 had a TPS ≤ 1%. Results from this study showed a better ORR and median PFS in patients with TPS ≥ 1% (N = 13; confirmed ORR: 31.0%, 95% CI: 9.0 to 61.03; median PFS: 8.4 months, 95% CI: 3.9 to 10.2) compared with patients with TPS ≤ 1% (N = 12; confirmed ORR: 25.0%, 95% CI: 6.0 to 57.0; median PFS: 4.1 months, 95% CI: 1.9 to NR). Ten percent of patients experienced SAEs deemed related to study drug. Eighty-three percent of patients experienced a related TEAE of any grade, the majority of which were low grade. The most common related TEAEs were pruritus (34.0%), hypoalbuminemia (29.0%), pyrexia (20.0%), decreased lymphocyte counts (17.0%), fatigue and rash (12.0% each), and infusion related reactions (10.0%). Decreased lymphocyte counts (7.0%) and rash (2.0) were the most common ≥ Grade 3 events.

1.3. Background Information on Ociperlimab, a TIGIT inhibitor

1.3.1. Nonclinical Summary

1.3.1.1. Pharmacology

Ociperlimab is a humanized immunoglobulin G (IgG) 1 monoclonal antibody against T-cell immunoglobulin and ITIM domain (TIGIT) under clinical development for the treatment of human malignancies.

Ociperlimab binds to the extracellular domain of human TIGIT with high specificity and affinity (equilibrium dissociation constant [KD] = 0.135 nM), as demonstrated by target-binding assays and SPR characterization. Ociperlimab has shown antitumor activity 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, ociperlimab in combination with anti–mouse PD-1 significantly inhibited tumor growth compared with either therapy alone.

Ociperlimab has the constant region of a wild-type human immunoglobulin G1 (IgG1) to enable the Fc-mediated effector functions. Ociperlimab has demonstrated competent binding to C1q and all FcγRs and induces antibody-dependent cellular cytotoxicity against a TIGIT-overexpressing cell line, but no antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity against primary T cells in the cell-based assays.

Refer to the Ociperlimab Investigator's Brochure for detailed information regarding pharmacology studies.

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1.3.1.2. Toxicology

Humanized TIGIT knock-in mice containing human TIGIT gene and cynomolgus monkeys were selected for nonclinical safety evaluation of ociperlimab based on the homology of TIGIT amino acid sequence, binding affinity, and efficacy studies. The humanized TIGIT knock-in mouse is considered the more relevant model due to the much higher binding affinity of ociperlimab to human TIGIT compared with monkey TIGIT.

Ociperlimab demonstrated a comparable binding affinity in TIGIT receptor occupancy assays with CD3+ splenocytes from humanized TIGIT knock-in mice compared to CD3+ human peripheral blood mononuclear cells (with EC50 of 48.8 ng/ml versus 63.2 ng/ml, respectively). In addition, ociperlimab showed a significant inhibition of GL261 tumor growth in humanized TIGIT knock-in mice at a dose of ≥ 0.4 mg/kg administered once weekly.

The toxicity and safety profile of ociperlimab was characterized in a 4- and 13-week repeated-dose toxicology study in humanized TIGIT knock-in mice and a 13-week repeated-dose toxicology study in cynomolgus monkeys. Ociperlimab was also evaluated in a 4-week repeated-dose study in humanized TIGIT knock-in mice with subcutaneous MC-38 tumors.

No apparent toxicity was observed in the 4- or 13-week humanized TIGIT knock-in mouse or in the 13-week cynomolgus monkey studies. A dose-proportional increase in systemic exposure (AUC and C_{max}) was noted in both species without apparent sex difference while excluding the impact of positive antidrug antibodies (ADAs) in individual animals with lower systemic exposure and/or faster clearance. No accumulation was observed in monkeys following once-every-2-week dosing for 13 weeks. A trend of accumulation was shown in mice following once weekly dosing for 4 and 13 weeks. The no-observed-adverse-effect level (NOAEL) of ociperlimab was 50 mg/kg in mice and 100 mg/kg in monkeys, which were the highest doses tested in each species.

The tissue cross-reactivity of ociperlimab was evaluated in frozen normal human tissues using a validated immunohistochemistry method, with appropriate positive and negative cell controls. No specific staining was observed under the conditions of testing.

In an in vitro cytokine release assay using human PBMCs, ociperlimab did not induce significant increases in interferon gamma (IFN-γ), IL-2, IL-6, tumor necrosis factor-alpha (TNF-α), IL-1β, and granulocyte-macrophage colony-stimulating factor (GM-CSF) as commonly seen in the "cytokine storm." Selective induction of monocyte chemoattractant protein-1 (MCP-1) and IFN-γ-inducible protein 10 (IP-10) in PBMCs by ociperlimab was observed and was not considered to be a risk in causing acute cytokine release syndrome.

The safety profile of ociperlimab was considered adequate to support human studies.

Refer to the Ociperlimab Investigator's Brochure for detailed information regarding toxicology studies.

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1.3.2. Prior Clinical Experience With Ociperlimab

1.3.2.1. Safety

1.3.2.1.1. Pooled Safety Data From Ociperlimab Investigator Brochure

As of 28 July 2023, there are 10 ongoing clinical studies of ociperlimab as monotherapy or in combination across a variety of solid tumors, including non-small cell lung cancer. Preliminary safety data are available from 6 studies: Study AdvanTIG-101 (patients with relapsed or refractory diffuse large B cell lymphoma); Study AdvanTIG-105 (patients with unresectable locally advanced or metastatic solid tumors); Study AdvanTIG-202 (patients with previously treated recurrent or metastatic cervical cancer); Study AdvanTIG-204 (patients with untreated limited-stage small cell lung cancer); Study AdvanTIG-206 (patients with advanced hepatocellular carcinoma); and Study AdvanTIG-301 (patients with locally advanced, unresectable, PD-L1-selected non-small cell lung cancer whose disease has not progressed after concurrent chemoradiotherapy).

As of 28 July 2023, 729 patients had received ociperlimab, including ociperlimab as monotherapy (n = 9), in combination with tislelizumab only (n = 370), in combination with tislelizumab plus chemotherapy (n = 214), in combination with tislelizumab plus concurrent chemoradiotherapy (n = 63), or in combination with tislelizumab plus BAT1706 (a bevacizumab biosimilar, a vascular endothelial growth factor [VEGF] inhibitor) (n = 62), or in combination with rituximab (n = 11) across a variety of tumor types.

Ociperlimab has been well tolerated. A pooled analysis of monotherapy and combination therapies conducted to provide a comprehensive safety assessment showed that AEs were generally reversible and manageable. One hundred and fifty-two patients (20.9%) experienced ≥ Grade 3 treatment-emergent adverse events (TEAEs) related to ociperlimab, and 107 patients (14.7%) experienced TEAEs leading to discontinuation of ociperlimab. Furthermore, 52 patients (7.1%) experienced a TEAE that led to death, and 7 patients (1.0%) had fatal TEAEs that were assessed as related to ociperlimab. Dose-limiting toxicity (DLT) data were only collected in Study AdvanTIG-101, Study AdvanTIG-105 and Study AdvanTIG-206. One patient (8.3%) in Study AdvanTIG-101 experienced a DLT (Grade 3 febrile neutropenia). No TEAE was considered to be a DLT in Study AdvanTIG-105 or Study AdvanTIG-206.

Of the 9 patients in the ociperlimab monotherapy group, one patient (11.1%) experienced an ociperlimab-related ≥ Grade 3 TEAE of hypertension, 1 (11.1%) experienced a TEAE of pneumonia that led to ociperlimab discontinuation, and no patient experienced ≥ 1 ociperlimab-related TEAE leading to death. No patient in the ociperlimab monotherapy group experienced serious TEAEs related to ociperlimab.

Of the 346 patients in the ociperlimab plus tislelizumab group, 37 patients (10.7%) experienced ≥ 1 serious ociperlimab-related TEAE, 55 (15.9%) experienced ≥ 1 ociperlimab-related TEAE ≥ Grade 3 in severity, 47 (13.6%) experienced ≥ 1 TEAE leading to ociperlimab discontinuation, and 3 patients (0.9%) experienced ≥ 1 ociperlimab-related TEAE leading to death.

Please refer to the latest Ociperlimab Investigator's Brochure for detailed safety information.

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1.3.2.1.2. Safety Data From BGB-900-105 Cohort 3

A Phase 1/1b study (AdvanTIG-105 [BGB-900-105]) is investigating the safety/tolerability, pharmacokinetic (PK), and preliminary antitumor activity of ociperlimab in combination with tislelizumab with or without chemotherapy in patients with unresectable locally advanced or metastatic solid tumors. As of 28 July 2023, 431 patients had been enrolled in Study AdvanTIG-105 and treated with ociperlimab either as monotherapy (n = 9), in combination with tislelizumab only (n = 208), or in combination with tislelizumab plus chemotherapy (n = 214) across a variety of solid tumor types (Ociperlimab Investigator's Brochure).

As of 05 April 2022, 40 patients with PD-L1 positive TC ≥ 1%, untreated metastatic squamous and nonsquamous non-small cell lung cancer had been enrolled in Cohort 3 of dose expansion part and had been treated with the recommended phase 2 dose (RP2D) of ociperlimab 900 mg and tislelizumab 200 mg every 3 weeks (Rajiv et al 2022). Among the 40 patients in Cohort 3, TEAEs were reported in 38 patients (95.0%) as of the data cut-off date. The most common TEAEs were pruritus (32.5%), pyrexia (30.0%), decreased appetite (20.0%), rash (20.0%), anemia (17.5%), nausea (17.5%), and dyspnea (17.5%). Treatment-related TEAEs ≥ Grade 3 and serious treatment-related TEAEs occurred in 4 patients (10.0%) each. One patient (2.5%) experienced a TEAE leading to death with no treatment-related death reported. The combination of ociperlimab plus tislelizumab had a manageable safety profile, with most TEAEs being Grade 1 or 2 in severity.

1.3.2.2. Clinical Pharmacology

Preliminary PK data are available from a total of 52 patients in Study AdvanTIG-105. In the dose escalation part, 32 patients were treated with ociperlimab at dose levels ranging from 50 mg to 1800 mg once every 3 weeks. During Cycle 1, ociperlimab was administered as a single agent on Study Day 1; tislelizumab 200 mg was then administered on Day 8. For subsequent cycles, ociperlimab and tislelizumab were administered on the same day at the beginning of each cycle beginning on Day 29 (Cycle 2) and once every 3 weeks thereafter.

In the China dose verification part, 20 patients were treated with 900 mg ociperlimab, either as monotherapy (n = 9) or in combination with tislelizumab 200 mg (n = 11).

Ociperlimab exposures increased approximately dose proportionally from the 50 mg to the 1800 mg dose level for maximum observed serum concentration (C_{max}) and area under the AUC. There was minimal accumulation observed in Cycle 5 following multiple doses. The mean serum concentration-time profiles of ociperlimab from dose escalation are shown in (Figure 1).

Peripheral TIGIT receptor occupancy data were available for 32 enrolled patients treated with ociperlimab at 50 mg, 150 mg, 450 mg, 900 mg, and 1800 mg dose levels in Study AdvanTIG-105. Complete TIGIT receptor occupancy (100%) was observed on $CD8^+$ T cells, $CD4^+$ T cells, and regulatory T cells in peripheral blood at all the tested dose levels.

Refer to the Ociperlimab Investigator's Brochure for detailed information on ociperlimab clinical pharmacokinetics and pharmacodynamics.

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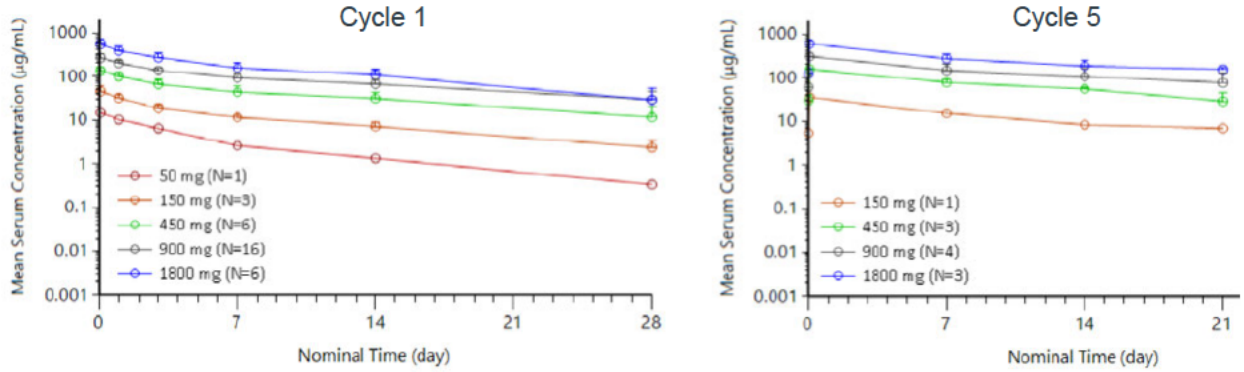
Figure 1: Cycles 1 and 5 Mean (+SD) Serum Concentration-Time Profiles of Ociperlimab in Study AdvanTIG-105



Note: For the 1800 mg dose, only 3 concentrations were available on Day 28.

1.3.2.3. Efficacy

Efficacy data from Study AdvanTIG-105 Dose Expansion Cohort 3 (as of the data cutoff date of 05 April 2022) were presented at World Conference of Lung Cancer (WCLC) (Rajiv et al 2022).

A total of 39 patients with PD-L1 TC ≥ 1%, untreated metastatic squamous or non-squamous NSCLC who received ociperlimab 900 mg plus tislelizumab 200 mg were evaluable for efficacy. The unconfirmed objective response rate was 53.8% (95% CI: 37.2, 69.9) in the PD-L1 TC ≥ 1% population. In patients with PD-L1 TC 1-49% and PD-L1 TC ≥ 50%, the unconfirmed ORR was 44.0% and 71.4%, respectively. The DCR was 89.7%, 88.0%, and 92.9%, in the PD-L1 TC ≥ 1%, PD-L1 TC 1-49%, and PD-L1 TC ≥ 50% populations, respectively. The median DoR was not evaluable across the 3 patient groups, and the median PFS was 5.4 months, 5.2 months, and 5.6 months in the PD-L1 TC ≥ 1%, PD-L1 TC 1-49%, and PD-L1 TC ≥ 50% populations, respectively.

1.4. Background Information on Tislelizumab

1.4.1. Pharmacology

Tislelizumab (also known as BGB-A317) is a humanized, immunoglobulin G4 (IgG4)-variant monoclonal antibody against programmed cell death protein-1 (PD-1) under clinical development for the treatment of several human malignancies.

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity and affinity (dissociation constant [K_D] = 0.15 nM). It competitively blocks binding of 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 dose-dependently enhance the functional activity of human T cells and pre-activated primary peripheral blood mononuclear cells. Tislelizumab has demonstrated in vivo antitumor activity in several allogeneic xenograft models, in which peripheral blood mononuclear cells were coinjected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

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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; Zhang et al 2018). 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. 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. In addition, tislelizumab clearly exhibited relatively high selective binding to the intended target, PD-1 protein, and had weak binding to only one off-target protein in a Retrogenix microarray assay for the screening of potential off-target binding, in which > 6400 different human plasma membrane and/or secreted proteins were screened. The toxicokinetic profile showed 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-A317-A1217-302 (AdvanTIG-302).

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

1.4.3. Clinical Pharmacology

Based on pooled data from 2596 patients across 12 clinical studies, 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 C_{max} and AUC increased in a nearly dose-proportional manner from 0.5 mg/kg to 10 mg/kg. The terminal $t_{1/2}$ was estimated to be approximately 23.8 days, and the steady state is expected to be reached after 12 weeks. Tislelizumab PK was generally similar between Chinese patients and patients of other ethnic groups and across tumor types. Please refer to the Tislelizumab Investigator's Brochure for more detailed information.

1.4.4. Prior Clinical Experience With Tislelizumab

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

A pooled monotherapy analysis was conducted to provide a comprehensive review of the tislelizumab safety profile. Patients included in this analysis (N = 1992) had a median age of

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60.0 years with 72.1% of them being male. Median treatment exposure duration was 4.07 months (range: 0.10 to 55.46) and median study follow-up duration was 11.65 months (range: 0.07 to 58.91).

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. Treatment-Emergent Adverse Events Assessed as Related to Tislelizumab

Of the 1992 patients with solid tumors treated with tislelizumab monotherapy, 1398 (70.2%) experienced ≥ 1 treatment-related TEAE. The most commonly occurring treatment-related TEAEs (≥ 5% of patients) assessed as related to tislelizumab irrespective of grade were AST increased (260 patients, 13.1%), alanine aminotransferase (ALT) increased (249 patients, 12.5%), hypothyroidism (197 patients, 9.9%), anemia (183 patients, 9.2%), rash (160 patients, 8.0%), pruritus (148 patients, 7.4%), fatigue (138 patients, 6.9%), decreased appetite (116 patients, 5.8%), blood bilirubin increased (113 patients, 5.7%), diarrhea (107 patients, 5.4%), and nausea (100 patients, 5.0%).

Two hundred sixty-nine patients (13.5%) experienced ≥ 1 tislelizumab-related TEAE of ≥ Grade 3 severity. The most frequent ≥ Grade 3 tislelizumab-related TEAEs (occurring in ≥ 1% of the patients) were AST increased (24 patients, 1.2%), ALT increased (21 patients, 1.1%), and anemia (20 patients, 1.0%).

1.4.4.2. Treatment-Emergent Serious Adverse Events

Of the 1992 patients with solid tumors treated with tislelizumab monotherapy, 712 (35.7%) experienced ≥ 1 treatment-emergent serious adverse event (SAE). The most commonly occurring treatment-emergent SAEs (irrespective of relationship to study drug) were pneumonia (95 patients, 4.8%), pneumonitis (27 patients, 1.4%), dysphagia (24 patients, 1.2%), pyrexia (21 patients, 1.1%), and pleural effusion (20 patients, 1.0%).

One-hundred ninety-seven patients (9.9%) experienced ≥ 1 tislelizumab-related treatment-emergent SAE. The most common treatment-emergent SAE assessed as related to tislelizumab that occurred in ≥ 1% of the patients was pneumonitis (26 patients, 1.3%).

1.4.4.3. Immune-Mediated Adverse Events

Anti-PD-1 therapies are known to cause imAEs in some patients and therefore have been defined as adverse events (AEs) of special interest (AESI) in tislelizumab clinical studies and as such are being monitored closely.

Immune-mediated AEs are consistent with an immune-related mechanism or immune-related 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 were exacerbated by the induction of autoimmunity. There is a potential temporal relationship between the initiation of treatment with tislelizumab and onset of an imAE that spans a window of days to several months.

All imAEs presented here are assessed as related to study drug by the investigator and categorized and adjudicated by the BeiGene Safety/Pharmacovigilance Team. Certain imAEs

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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.

Of the 1912 patients with solid tumors included in the pooled analysis of imAEs, 312 (16.3%) experienced ≥ 1 imAE of any grade. The most commonly occurring imAEs of any grade that occurred in ≥ 1% of the patients were hypothyroidism (121 patients, 6.3%) and pneumonitis (41 patients, 2.1%). Analysis of the patients with ≥ 1 imAE that was also ≥ Grade 3 in severity showed that 83 patients (4.3%) experienced such events. The most commonly occurring imAEs that were ≥ Grade 3 in severity were pneumonitis (16 patients, 0.8%), interstitial lung disease (7 patients, 0.4%), ALT increased (7 patients, 0.4%), AST increased (5 patients, 0.3%), and hepatitis (5 patients, 0.3%).

1.4.4.4. Infusion-Related Reactions

Infusion-related reactions, including high-grade hypersensitivity reactions, following administration of tislelizumab are uncommon. Of the 1992 patients in the solid tumor group treated with tislelizumab monotherapy, 55 (2.8%) experienced ≥ 1 infusion-related reaction of any grade. The most commonly occurring infusion-related reactions of any grade were infusion-related reactions (28 patients, 1.4%), pyrexia (16 patients, 0.8%), rash (5 patients, 0.3%), hypotension (3 patients, 0.2%), and nausea (4 patients, 0.2%).

1.4.4.5. Liver Laboratory Abnormalities

Of the 1678 patients with solid tumors included in the analysis of drug-induced liver injury (excluding Study BGB-A317-208), 30 patients (1.8%) experienced ALT or AST levels > 3 x upper limit of normal (ULN) with a concurrent total bilirubin level ≥ 2 x ULN. Concurrent elevation of alkaline phosphatase (ALP) (ie, ALP ≥ 2 x ULN) was observed in 25 of these 30 patients. Of the remaining 5 patients, none met the criteria for a Hy's law case.

1.4.4.6. Fatal Adverse Events

Out of 1992 patients treated with tislelizumab monotherapy who were included in the analysis, 141 patients (7.1%) experienced a fatal AE. A total of 19 patients (1.0%) experienced fatal AEs that were deemed related to tislelizumab, including pneumonia (0.1%), "death" (0.1%), hepatic failure (0.1%), multiple organ dysfunction syndrome (0.1%), and pneumonitis (0.1%). All other events occurred in single patient.

1.4.5. Efficacy Assessment of Tislelizumab

As of 20 July 2022, 7 studies with tislelizumab have been completed and 18 studies are ongoing. Please refer to the Tislelizumab Investigator's Brochure for more detailed information on efficacy data for tislelizumab when given as monotherapy or in combination therapies.

Efficacy data are available from 2 of the completed Phase 1 monotherapy studies in solid tumors, BGB-A317_Study_001 (data cutoff 20 May 2019) and BGB-A317-102 (data cutoff 01 December 2018), which are summarized below, and from a Phase 3 combination study, BGB-A317-304, in NSCLC (data cutoff 23 January 2020).

Study BGB-A317_Study_001 is a Phase 1a/1b study consisting of a dose escalation phase (1a) and a dose expansion phase (1b) designed to establish the maximum tolerated dose (MTD) and

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schedule, determine the RP2D, and investigate the preliminary efficacy of tislelizumab in previously treated patients with select tumor types, including NSCLC.

The RP2D and schedule for tislelizumab was determined to be 200 mg administered once every 3 weeks. Across all disease cohorts (N = 451), 6 patients (1.3%) experienced a complete response (CR) and 54 patients (12.0%) had a confirmed partial response (PR), yielding an ORR of 13.3%. Stable disease was observed in 141 patients (31.3%). Disease control rate (DCR) was 44.6% (95% CI: 39.92 to 49.29) and clinical benefit rate (CBR) was 25.9% (95% CI: 21.96 to 30.25). Of the 49 NSCLC patients enrolled in the study, ORR was observed in 12.2% (95% CI: 4.63 to 24.77).

Study BGB-A317-102 is a nonrandomized, Phase 1/2 study of tislelizumab monotherapy evaluating the activity and safety of tislelizumab at the RP2D and schedule of 200 mg given once every 3 weeks in previously treated Chinese patients with select advanced solid tumors, including NSCLC.

Across all disease cohorts and study phases (N = 249), 1 patient (0.4%) experienced a CR and 44 patients (17.7%) had a confirmed PR, yielding an ORR of 18.1%. Stable disease was observed in 91 patients (36.5%). DCR was 54.6% (95% CI: 48.2 to 60.9) and CBR was 36.5% (95% CI: 30.6 to 42.9).

In the PD-L1+ NSCLC cohort (n = 18), no patients (0%) experienced a CR and 2 patients (11.1%) had a confirmed PR. Stable disease was observed in 7 patients (38.9%). DCR was 50% (95% CI: 26.0 to 74.0) and CBR was 27.8% (95% CI: 9.7 to 53.5).

In the PD-L1- NSCLC cohort (n = 24), no patients (0%) had a CR and 5 patients (20.8%) had a confirmed PR. Stable disease was observed in 11 patients (45.8%). DCR was 66.7% (95% CI: 44.7 to 84.4) and CBR was 33.3% (95% CI: 15.6 to 55.3).

Study BGB-A317-304 is an ongoing randomized Phase 3 study evaluating tislelizumab in combination with a platinum compound plus pemetrexed versus a platinum compound plus pemetrexed alone as a first-line treatment in patients with Stage IIIB or IV nonsquamous NSCLC.

At the time of data cut-off, a total of 223 patients were randomized to the tislelizumab plus a platinum compound plus pemetrexed treatment arm (Arm A), and 111 patients were randomized to the platinum compound plus pemetrexed alone treatment arm (Arm B). ORR per Independent Review Committee (IRC) review was greater in Arm A than in Arm B (57.4% versus 36.9%). Median PFS was significantly higher in the tislelizumab-containing arm (9.7 months, 95% CI: 7.72 to 11.53) compared to the chemotherapy only arm (7.6 months, 95% CI: 5.55 to 8.02) with a stratified HR ratio of 0.645 (95% CI: 0.462 to 0.902).

1.5. Study Rationale

1.5.1. Rationale for Tislelizumab and Ociperlimab in the Treatment of NSCLC

Upregulation of TIGIT expression in tumor-infiltrating lymphocytes has been reported in NSCLC (Tassi et al 2017). 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

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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). As mentioned in Section 1.2, anti–PD-1/PD-L1 antibodies have been shown to be efficacious in NSCLC independently of histology; furthermore, results from other anti-TIGIT/PD-L1 or PD-1 combination studies in NSCLC showed promising antitumor activity suggesting that anti-TIGIT antibodies have the potential to significantly improve and/or extend the therapeutic benefit of anti-PD-1 therapy in this indication.

1.5.2. Rationale for the Selection of Ociperlimab Dose in Combination With Tislelizumab

The ociperlimab dose of 900 mg once every 3 weeks (Q3W) combined with tislelizumab 200 mg Q3W was selected as the RP2D for further investigations based on clinical safety, tolerability, PK, and pharmacodynamic data from the ongoing Phase 1/1b Study AdvanTIG-105.

Complete TIGIT receptor occupancy was observed in circulating T cells in peripheral blood at all the tested doses of ociperlimab in Study AdvanTIG-105. However, the correlation between TIGIT receptor occupancy in the periphery and in tumor tissues is unknown. In a previous Phase 1 study of tiragolumab, another anti-TIGIT antibody, complete peripheral receptor occupancy was reached at the 30 mg dose level, but the clinical dose of 600 mg was determined as the RP2D, which was 20 times the 30 mg dose (Bendell et al 2020). Similarly, although complete peripheral receptor occupancy was observed at the 50 mg dose level of ociperlimab, the RP2D of 900 mg is approximately 20 times the dose of 50 mg. As of 12 May 2021, a total of 3 patients were assessed to have a confirmed partial response, 1 patient each in the 450 mg, 900 mg, and 1800 mg cohorts. Ociperlimab exposure in all 3 patients with a partial response is consistent with that expected at the 900 mg dose level. The confirmed disease control rates observed in the 450 mg, 900 mg, and 1800 mg cohorts were 60% (3/5), 64.3% (9/14), and 60% (3/5) of patients, respectively.

Although the best overall response and disease control rate were numerically comparable at the 450 mg and 900 mg dose levels, the 900 mg dose was chosen as the RP2D for the following reasons:

- 900 mg was well tolerated in Study AdvanTIG-105
- Exposure in all 3 patients with a partial response was consistent with that expected at the 900 mg dose
- Lack of sufficient information on the impact of immunogenicity on ociperlimab PK
- An overall intent to minimize exposure overlap with doses < 450 mg

1.5.3. Rationale for Selection of Tislelizumab Dose

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

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

Additionally, tislelizumab is currently approved and marketed in China at the recommended dosage of 200 mg once every 3 weeks for multiple indications. Please refer to the Tislelizumab Investigator's Brochure for additional details.

1.5.4. Rationale for Pembrolizumab as the Comparator

Pembrolizumab is considered standard of care for first line therapy patients with metastatic NSCLC whose tumors express a high level of PD-L1 (TPS ≥ 50%) and bear no genomic aberrations in the *EGFR* and *ALK* genes. Pembrolizumab has been approved by several health authorities outside the European Union (eg, US FDA) for the treatment of first line patients with Stage III NSCLC who are not candidates for surgical resection or definitive CRT, have no *EGFR* or *ALK* genomic aberrations and express PD-L1 (TPS > 1%), irrespective of histology. Since the population to be evaluated in this study includes the populations for which pembrolizumab has been approved, it is considered the most suitable comparator to test whether ociperlimab in combination with the anti-PD-1 antibody tislelizumab improves patient outcomes.

Pembrolizumab will be administered at the dose and schedule (200 mg once every three weeks) recommended for NSCLC.

1.5.5. Rationale for Biomarker Strategy

Biomarker analyses, including but not limited to PD-L1 expression, TIGIT pathway molecules, gene expression profiling (GEP), tumor mutation burden (TMB), microsatellite instability (MSI), extracellular vesicles (EVs), and tumor-infiltrating immune cells (TILs), will be performed to explore potential predictive and prognostic biomarkers and mechanisms of resistance.

PD-L1 is expressed in tumor and TILs in advanced NSCLC, and its expression level was shown to be correlated with clinical efficacy of anti-PD-1 treatment in multiple studies (Topalian et al 2012; Herbst et al 2014; Borghaei et al 2015; Fehrenbacher et al 2016; Herbst et al 2016; Rosenberg et al 2016). PD-L1 IHC 22C3 pharmDx was approved as a companion diagnostic (CDx) to identify patients with NSCLC for treatment with KEYTRUDA (pembrolizumab). However, the role of PD-L1 in predicting response to therapies combining 2 immunotherapeutic

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agents in patients with NSCLC is still poorly understood. In the CITYSCAPE study, NSCLC patients with tumors with PD-L1 TPS ≥ 50% derived significant benefit from atezolizumab (anti-PD-L1) plus tiragolumab (anti-TIGIT) compared to atezolizumab alone (PFS HR 0.3 [0.15-0.61]; ORR of 66% versus 24%). No obvious differences in PFS and ORR were observed between the 2 arms (PFS HR 0.89 [0.53, 1.49]; ORR of 16% versus 18%) for patients with 1% to 49% PD-L1 expression, suggesting PD-L1 could be a predictive biomarker of response for the anti-TIGIT and anti-PD-L1 combination treatment in NSCLC (Rodriguez-Abreu et al 2020). In this study, PD-L1 expression level on tumor cells will be assessed centrally and its predictive role will be assessed in ociperlimab in combination with tislelizumab, pembrolizumab alone, and tislelizumab alone.

In addition to PD-L1, clinical data from various studies suggested TMB, MSI, abundance and location of TILs, and immune-related GEP 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; Le et al 2017; Lemery et al 2017; Gandara et al 2018; Jiang et al 2018). Therefore, TMB, MSI, TILs, and GEP will be studied in relationship with clinical response to ociperlimab in combination with tislelizumab treatment to explore potential predictive biomarkers.

Mechanisms of resistance to immunotherapies are also not well understood and need more exploration. Identification of tumor and immune-related features associated with disease progression or acquired resistance to ociperlimab and tislelizumab may increase the understanding of disease pathobiology and provide biological evidence for the combination strategy. In this regard, high TIGIT/CD226 ratio on T-reg cells was shown to correlated with poor clinical outcomes in melanoma patients treated with anti-PD-1 or anti-PD-L1 antibodies (Fourcade et al 2018). In addition, a higher frequency of $TIGIT^+$ T cells among $PD\text{-}1^+CD8^+$ T cells was associated with hyperprogressive disease during PD-1/PD-L1 blockade and inferior survival rate in patients with NSCLC (Kim et al 2019). These results suggest that signaling through the TIGIT pathway in tumor tissues might contribute to resistance to immune checkpoint inhibitors targeting PD-1 or PD-L1. Here, the expression levels of TIGIT pathway molecules including TIGIT, CD226, CD155, and CD112 will also be studied to explore its correlation with the clinical efficacy of ociperlimab plus tislelizumab combined treatment.

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1.6. Benefit-Risk Assessment

Study BGB-A317-A1217-302 (AdvanTIG-302) will evaluate the safety and efficacy of tislelizumab in combination with the anti-TIGIT antibody ociperlimab in previously untreated, PD-L1-selected patients with locally advanced, unresectable, or metastatic NSCLC with no *EGFR* or *ALK* genomic aberrations. There are extensive evidences supporting TIGIT's role in regulating immune response and the interaction between the TIGIT and PD-1 pathways has been shown to promote tumor immune escape. The clinical efficacy demonstrated for tislelizumab (Section 1.4.5) and preliminary results from an anti-TIGIT/ anti-PD-L1 competitor combination study, suggest that ociperlimab has the potential to improve and/or extend the therapeutic benefits of tislelizumab in the treatment-naïve setting. As discussed earlier (Section 1.5.1), based on the mechanism(s) of action, and the nonclinical and preliminary clinical data, the combined blockade of TIGIT and PD-1 by ociperlimab and tislelizumab, respectively, is expected to result in immune-mediated toxicities similar to what has been observed with tislelizumab alone. Preliminary safety results from the CITYSCAPE study (N=135 patients) are in agreement with this hypothesis and show that patients treated with the anti-TIGIT/PD-L1 combination experienced less than 10% increase in overall and Grade 3 or 4 TEAEs compared to patients treated with anti-PD-1 and placebo.

The risk of observing augmented safety signals as has been shown for other anti-PD-1 based immuno-oncology combinations still remains, therefore, a monitoring plan derived from the European Society for Medical Oncology and American Society for Clinical Oncology has been established to monitor, diagnose, and manage imAEs (Appendix 7). It is important to note that peripheral effector T cells typically do not express TIGIT, which is in contrast to TILs stimulated by the antigens in tumor microenvironment. Therefore, the combination provides an opportunity to specifically augment the activity of effector T cells in the tumor rather than periphery and/or nontumor tissue (Johnston et al 2014), which should help control toxicity.

Blockade of the PD-1 pathway has demonstrated strong antitumor efficacy either alone or in combination with standard of care in multiple cancer indications. As discussed in Section 1.4.4, PD-1 blockade by tislelizumab has been evaluated in 1992 patients as monotherapy with a safety and efficacy profile similar to what has been reported for other anti-PD-1/PD-L1 therapies, such as nivolumab and pembrolizumab.

Safety data will be continuously monitored by the sponsor's study team in consultation with investigator(s) as needed. Refer to Section 7.5 and Section 8 for information regarding additional safeguards and considerations related to potential risk.

In summary, there is strong scientific rationale that the combined blockade of the TIGIT pathway and PD-1 pathway may result in enhanced antitumor activity and benefit a larger patient population than single agent anti-PD-1 therapy without a major increase in the risk of immune-mediated toxicities.

An Independent Data Monitoring Committee (IDMC) will be established to regularly monitor the safety and efficacy of tislelizumab in combination with ociperlimab when compared with pembrolizumab. Two interim analyses are planned in the study (Section 9.7).

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2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- To compare overall survival (OS) between Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo) in the ITT Analysis Set

2.1.2. Secondary Objectives

- To compare progression free survival (PFS) between Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo) in the Intent to Treat (ITT) Analysis Set as assessed by investigators according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)
- To compare overall response rate (ORR) and duration of response (DOR) between Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo) in the ITT Analysis Set as assessed by investigators according to RECIST v1.1
- To compare health-related quality of life (HRQoL) and time to deterioration (TTD) between Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo) in the ITT Analysis Set
- To further investigate the safety and tolerability of ociperlimab in combination with tislelizumab

2.1.3. Exploratory Objectives

- To compare disease control rate (DCR), clinical benefit rate (CBR), and time to response (TTR) between Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo) in the ITT Analysis Set as assessed by investigators according to RECIST v1.1
- To evaluate OS, as well as ORR, DOR, PFS, DCR, CBR, and TTR as assessed by investigators according to RECIST v1.1, in the ITT Analysis Set of Arm C (tislelizumab followed by placebo)
- To evaluate PFS after next line of treatment (PFS2)
- To characterize the pharmacokinetics (PK) of ociperlimab and tislelizumab
- To evaluate the potential association of exploratory biomarkers with response or resistance to treatment with ociperlimab and tislelizumab and with patient prognosis.
- To determine host immunogenicity to ociperlimab and tislelizumab
- To further investigate the safety and tolerability of tislelizumab

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- To evaluate patient reported global impression of severity (PGI-S) and patient reported treatment-related side-effect burden (PRTSE) in Arms A, B, and C in the ITT Analysis Set
- To measure HRQoL in Arm C in the ITT Analysis Set

2.2. Study Endpoints

2.2.1. Primary Endpoint

- OS (time from the date of randomization to the date of death due to any cause) in the ITT Analysis Set of Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo)

2.2.2. Secondary Endpoints

- PFS as assessed by investigators (time from the date of randomization to the date of the first objectively documented tumor progression per RECIST v1.1, or death, whichever occurs first) in the ITT Analysis Set of Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo)
- ORR as assessed by investigators (proportion of patients with a documented, confirmed CR or PR per RECIST v1.1) and DOR as assessed by investigators (time from the first determination of an objective response per RECIST v1.1 until the first documentation of progression or death, whichever occurs first) in Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo)
- HRQoL as assessed via patient-reported outcomes (PRO) using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), its lung cancer module Quality of Life Questionnaire Lung Cancer 13 (QLQ-LC13), and the 5 Level EuroQol 5 Dimension (EQ-5D-5L) questionnaire in Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo). PRO endpoints include the EORTC QLQ-C30's global health status/QoL (GHS), physical function and fatigue scales, and the QLQ-LC13's index score, dyspnea, coughing, hemoptysis and pain in chest, pain in arms/shoulders and peripheral neuropathy scales
- TTD, defined as time from randomization to the first occurrence of worsening scores (10-point change, to be defined in the Statistical Analysis Plan [SAP] if otherwise) for 2 consecutive assessments or 1 assessment followed by death from any cause before the next scheduled data collection
- The incidence and severity of AEs according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) in Arm A (ociperlimab in combination with tislelizumab)

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2.2.3. Exploratory Endpoints

- DCR (proportion of patients with confirmed CR + PR + stable disease), CBR (proportion of patients with confirmed CR + PR + durable stable disease), and TTR per RECIST v1.1 as assessed by investigators in Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo)
- OS, as well as ORR, DOR, PFS, DCR, CBR, and TTR per RECIST v1.1 as assessed by investigators, in Arm C (tislelizumab followed by placebo)
- PFS2 – defined as the time from randomization to objective disease progression after next line of treatment, or death from any cause, whichever occurs first
- Evaluate status of exploratory biomarkers including but not limited to expression of TIGIT, CD226, CD155, CD112, and PD-L1, GEP, TMB, MSI, mutational profiles, EVs, and TILs in archival and/or fresh tumor tissue and blood before and after study treatment or at disease progression/reoccurrence, and the association between these biomarkers and clinical efficacy, disease status, and resistance.
- Serum concentrations of ociperlimab and tislelizumab at specified timepoints.
- Immunogenic responses to ociperlimab and tislelizumab, evaluated through detection of antidrug antibodies (ADAs)
- The incidence and severity of AEs according to NCI-CTCAE v5.0 in Arm C (tislelizumab followed by placebo)
- Patient-reported changes in NSCLC symptom severity from baseline via the PGI-S questionnaire and patient reported treatment-related side-effect burden via the PRTSE questionnaire in Arms A, B, and C
- HRQoL measured by PROs using EORTC QLQ-C30, QLQ-LC13, and EQ-5D-5L questionnaires in Arm C

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3. STUDY DESIGN

3.1. Summary of Study Design

This is a randomized, double-blind, multicenter, Phase 3 study designed to evaluate the efficacy and safety of ociperlimab + tislelizumab compared with that of pembrolizumab in patients with PD-L1-selected NSCLC who have locally advanced or recurrent disease that is unresectable or not amenable to radiotherapy, with or without chemoradiotherapy, or previously untreated metastatic disease, and whose tumors do not harbor known *EGFR*-sensitizing mutations, *ALK* translocations, BRAF V600E mutations, or *ROS1* mutations. The efficacy and safety of tislelizumab alone will be explored in a small cohort of the same patient population.

The study will be carried out at approximately 242 centers, including a minimum of 26 centers in Japan. Details on study administrative information for Japanese sites are available in Clinical Study BGB-A317-A1217-302 Appendix 1, Appendix 2, and Appendix 3 for domestic use.

A safety run-in substudy investigating the safety, tolerability, PK, and preliminary efficacy of ociperlimab in combination with tislelizumab in Japanese patients is planned; preliminary safety and tolerability will be evaluated before Japanese patients are randomized in this Phase 3 study (see Appendix 16).

Patients will be required to sign a prescreening informed consent form (ICF) to undergo prescreening collection of tissue samples (archival tissue or fresh biopsy) for central evaluation of PD-L1 status. Patients in the US and Japan will be required to sign a prescreening ICF for collection of local PD-L1 testing results if used for randomization. Patients will be required to sign the main ICF to undergo screening procedures. Approximately 660 patients will be enrolled in the main study. The initial number of patients planned in the study was 605 in Protocol Amendment Version 1.0 (Version 1.1 in Japan, Version 1.2.1 in Germany, and Version 1.4 in France), which included a randomization ratio of 5:5:1 (275, 275, and 55 patients in Arms A, B, and C, respectively). With the randomization ratio changed to 5:5:2 in Protocol Amendment Version 2.0 (Version 2.1 in Japan, Version 2.2 in Germany, and Version 2.3 in the US), the total number of patients in the study will increase by 55 patients (from 605 to 660). The randomization ratio update was implemented after Protocol Amendment Version 2.0 was finalized and approved at each participating site (Version 2.1 in Japanese sites, Version 2.2 in German sites, and Version 2.3 in the US sites); therefore, it is estimated that approximately 300 patients will be randomized with a ratio of 5:5:1 and approximately 360 patients will be randomized with a ratio of 5:5:2. The final total number of patients in Arms A, B, and C is estimated to be approximately 286, 286, and 88, respectively. It is noted that the randomization ratio between Arm A and Arm B will remain unchanged.

Blinding will be accomplished using placebo infusions of normal saline in Treatment Arms B and C (Section 5.1.4) so that all patients will receive 2 infusions on Day 1 of each cycle. Study treatments will be prepared by unblinded pharmacists, who will mask treatments to ensure that patients and study staff remain blinded (Section 5.6). Eligible participants will be randomized in a 5:5:2 ratio to receive ociperlimab + tislelizumab (Arm A), pembrolizumab + placebo (Arm B), or tislelizumab + placebo (Arm C).

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Study treatments will be given as follows:

- Arm A: Tislelizumab 200 mg intravenously followed by ociperlimab 900 mg intravenously once every 3 weeks

  Note: As of Protocol Amendment Version 3.0, the ociperlimab dose that will be administered to Japanese patients allocated in Arm A was determined to be 900 mg based on the results from the safety run-in substudy (see Appendix 16).

- Arm B: Pembrolizumab 200 mg intravenously followed by placebo intravenously once every 3 weeks
- Arm C: Tislelizumab 200 mg intravenously followed by placebo intravenously once every 3 weeks.

The study design schematic is presented in Figure 2.

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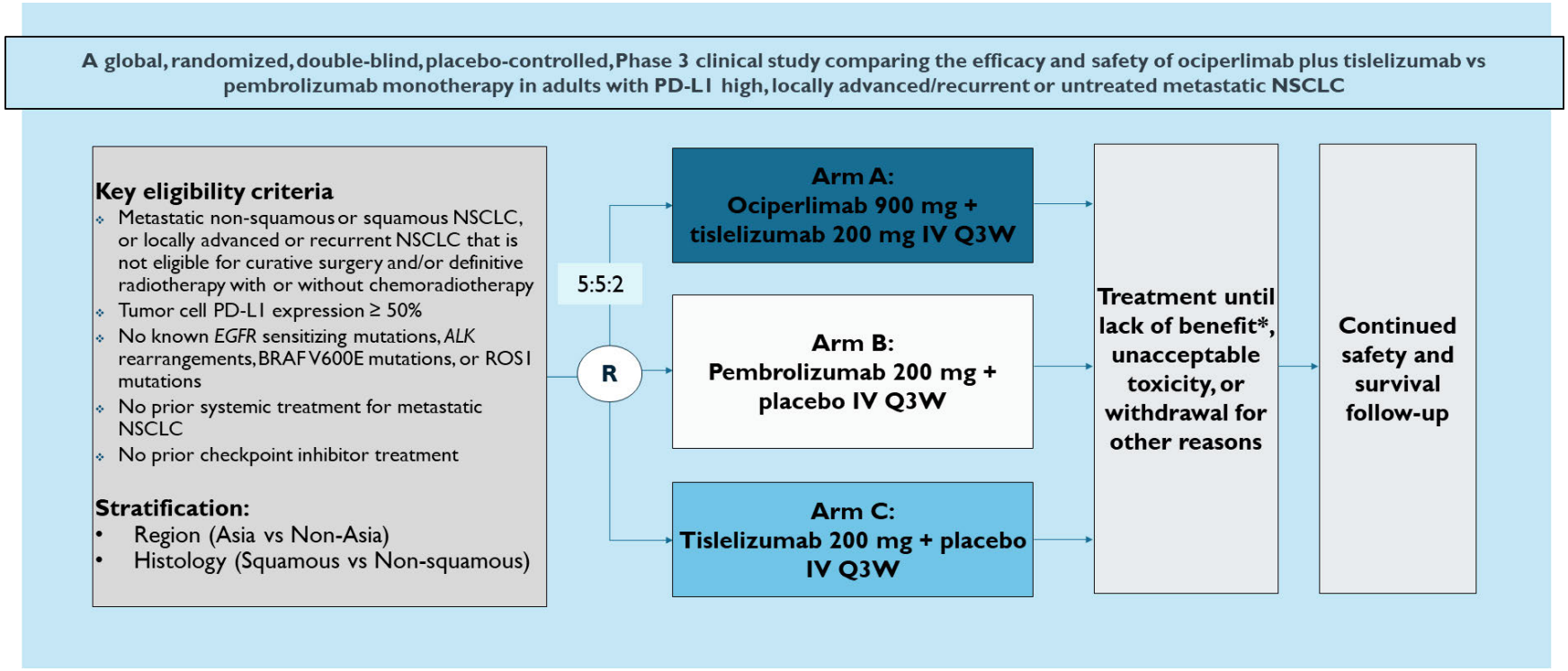
Figure 2: Study Schema



*The timepoint at which the investigator considers that the patient is no longer benefiting from study treatment;

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; IV, intravenous; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; Q3W, once every 3 weeks; R, randomization.

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

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3.2. Prescreening Period

All patients will undergo prescreening for central evaluation of PD-L1 status within 56 days to 28 days before randomization, unless the prescreening and screening periods are combined, in which case, PD-L1 status will be determined centrally within 28 days before randomization. Note, for the US and Japan only: Local PD-L1 testing may be used for patient randomization purposes, in which case, the local PD-L1 testing results will be collected in the electronic case report form (eCRF).

For all sites, local PD-L1 testing results, if available for patients who are randomized based on central PD-L1 testing results, may be collected in the eCRF if patients consent to this information being collected.

A separate prescreening informed consent must be obtained.

Archival tumor tissue must be collected for evaluation of PD-L1 status centrally. If no archival samples are available, a fresh tumor biopsy is required. Refer to Section 7.8 for details. Note, for the US and Japan only: If local PD-L1 testing will be used for patient randomization purposes, confirmation of tumor sample receipt by the central laboratory is required before patient randomization (preferably from the same block used for local PD-L1 testing). In the US and Japan, local PD-L1 testing must be performed using an FDA-approved or Ministry of Health, Labour and Welfare (MHLW)-approved assay, respectively (limited to 22C3, SP263, 28-8), at a certified laboratory and according to manufacturer's instructions.

EGFR, *ALK*, BRAF V600E, and *ROS1* mutational status, if known, will also be collected at this time.

Patients with nonsquamous NSCLC and unknown *EGFR* mutational status will be required to have a tissue-based EGFR test performed either locally or centrally, or an endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)-based EGFR test performed locally at Prescreening. Patients found to have EGFR-sensitizing mutations will not be eligible.

3.3. Screening Period

Screening evaluations will be performed within 28 days before randomization. Patients who agree to participate in this study will sign the main ICF before undergoing any screening procedure. Only patients whose tumors express a high level of PD-L1 (defined as ≥ 50% PD-L1 positive tumor cells) by central testing (or local testing in the US and Japan) will be considered eligible.

All patients must have a pulmonary function test performed during screening (refer to Section 7.2.3 and Appendix 1 for details). 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.

Tumor imaging (CT with or without contrast or MRI) must be performed within 28 days before randomization.

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3.4. Treatment Period

After completing all prescreening and screening activities, eligible patients will be randomized in a 5:5:2 ratio to receive ociperlimab + tislelizumab (Arm A), pembrolizumab + placebo (Arm B), or tislelizumab + placebo (Arm C).

Study treatments will be administered as follows:

- Arm A: Tislelizumab 200 mg intravenously followed by ociperlimab 900 mg* intravenously once every 3 weeks
- Arm B: Pembrolizumab 200 mg intravenously followed by placebo intravenously once every 3 weeks
- Arm C: Tislelizumab 200 mg intravenously followed by placebo intravenously once every 3 weeks.

* Note: As of Protocol Amendment Version 3.0, the ociperlimab dose that will be administered to Japanese patients allocated in Arm A was determined to be 900 mg based on the results from the safety run-in substudy (see Appendix 16).

All study treatments will be administered until intolerable toxicity, withdrawal of informed consent, or the timepoint at which, in the opinion of the investigator, the patient is no longer benefiting from study therapy. Crossover is not permitted. Treatment beyond the initial investigator-assessed, RECIST v1.1-defined disease progression is permitted in all arms if the criteria below are met:

- Absence of clinical symptoms and signs of progressive disease (including clinically significantly worsening of laboratory values)
- Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, spinal cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer. Patients must be informed that they may be forgoing treatment that has shown benefit by continuing treatment beyond progression
- The decision to continue study drug(s) beyond initial investigator-assessed progression must be agreed with the sponsor medical monitor

Patients who receive study treatment beyond progression will have tumor assessments performed according to the original schedule until study treatment discontinuation. Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held (ie, their schedule should not be adjusted for delays in cycles). Tumor response will be assessed by investigators using RECIST v1.1 criteria (Eisenhauer et al 2009). Radiological assessment of tumor-response status will be performed approximately every 9 weeks (±7 days) from randomization for the first 52 weeks and every 12 weeks (±7 days) thereafter. If a patient discontinues study treatment due to any reason other than disease

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progression, tumor assessments will continue as scheduled until, disease progression, death, loss to follow-up, withdrawal of consent, or until the study terminates, whichever occurs first. Details are provided in Section 7.6.

Patient-reported outcomes (PRO; see Section 7.9) will be collected using the EORTC QLQ-C30, QLQ-LC13, and EQ-5D-5L at baseline (Day 1 of Cycle 1), every other cycle through Cycle 13, then every 4 cycles thereafter, and at the End-of-Treatment (EOT) Visit (Section 3.5). PGI-S will be collected at baseline and Cycles 5 and 7; PRTSE will be collected at Cycles 5 and 7. At applicable dosing visits, PRO will be collected before any procedures or dose administration.

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

3.5. End of Treatment and Safety Follow-up

Patients who discontinue from 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 after the investigator decides to permanently discontinue study treatment or before the initiation of a new anticancer treatment, whichever occurs first. If routine laboratory tests (eg, hematology, serum chemistry) were completed within 7 days before the EOT Visit, these tests need not be repeated. A Safety Follow-up Visit at 30 days (± 7 days) after the last dose of study drug is required to assess AEs and concomitant medications, unless the time window overlaps the time window of the EOT Visit; the Safety Follow-up Visit may be a telephone call or an on-site visit if laboratory assessments are necessary.

Additional safety follow-up assessment of imAEs and relevant concomitant medications (ie, those associated with an imAE or any new anticancer therapy) will be made by telephone or, if a pregnancy test is also required, during a visit (see Appendix 1). These contacts will be made at approximately 60 and 90 days after the last dose of study drugs regardless of whether the patient starts a new subsequent anticancer therapy. For women of childbearing potential (see Appendix 9), an additional visit to perform a pregnancy test will occur at approximately 120 days after the last dose of study drugs. If a patient reports a suspected imAE at a safety follow-up telephone call, 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 from study treatment before disease progression will need to undergo tumor assessments as outlined in Section 7.6.

Patients who have progressive disease will be asked to provide an optional biopsy at the EOT Visit for the assessment of mechanism of resistance (Section 7.8).

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

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3.6. Survival Follow-up

Patients will be followed for survival and to obtain information on subsequent 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 EOT Visit or as directed by the sponsor until death, withdrawal of consent, loss to follow-up, or end of study.

3.7. Discontinuation From the Study Treatment or From the Study

3.7.1. Patient Discontinuation From Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue study treatment for reasons other than disease progression should be followed for assessments of antitumor activity (Section 7.6), safety (Section 7.5) and survival (Section 3.6), if possible.

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

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

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

Patients will be discontinued from the study for reasons that include, but are not limited to, the following:

- Patient withdrawal of consent
- Death

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- Lost to follow-up
- Patient has completed all study assessments

3.8. End of Study

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

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

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

The sponsor will notify the investigator (in Japan, the sponsor will notify the investigator, the head of the study center, and the regulatory authority) if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for an EOT Visit.

The investigators will 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 (in Japan, the head of the study center) will be responsible for informing Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) of the early termination of the study.

At the end of the study, any patients who, in the opinion of the investigator, continue to benefit from tislelizumab alone or in combination with ociperlimab at study termination, will be offered the option to continue treatment in a company-sponsored clinical study (if available in the patient's country) or patient supply treatment program until treatment 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
- Good Clinical Practice (GCP) noncompliance
- Study activity is completed (ie, all patients have completed, and all obligations have been fulfilled).

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4. STUDY POPULATION

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

4.1. Inclusion Criteria

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

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments.
2. Age ≥ 18 years on the day of signing the informed consent form (or the legal age of consent in the jurisdiction in which the study is taking place).
3. Histologically or cytologically documented locally advanced or recurrent NSCLC that is not eligible for curative surgery and/or definitive radiotherapy with or without chemoradiotherapy, or metastatic nonsquamous or squamous NSCLC.
4. No prior systemic treatment for metastatic NSCLC.
5. Agreement to provide archival tissue (formalin-fixed paraffin-embedded block containing tumor [preferred] or approximately 6 to 15 freshly cut unstained slides) or fresh biopsy (if archival tissue is not available) for central evaluation of PD-L1 levels and retrospective analysis of other biomarkers.

   Note, for the US and Japan only: If local PD-L1 testing will be used for patient randomization purposes, confirmation of tumor sample receipt by the central laboratory is required before patient randomization (preferably from the same block used for local PD-L1 testing).
6. Tumors with PD-L1 expressed in ≥ 50% tumor cells as determined centrally (or locally in the US and Japan).

   Note, for the US and Japan only: Local PD-L1 testing must be performed using an FDA-approved or MHLW-approved assay, respectively (limited to 22C3, SP263, 28-8), at a certified laboratory and according to manufacturer's instructions.
7. At least 1 measurable lesion as defined per RECIST v1.1.

   Note: A lesion in an area subjected to prior locoregional therapy, including previous radiotherapy, is not considered measurable unless there has been demonstrated progression in the lesion since the therapy as defined by RECIST v1.1.
8. ECOG Performance Status ≤ 1.
9. Adequate organ function as indicated by the following laboratory values during screening:

   a. Patients must not have required blood transfusion or growth factor support ≤ 14 days before sample collection at Screening for the following:
      - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
      - Platelets ≥ 75 x 10^9/L
      - Hemoglobin ≥ 90 g/L

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b. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated Glomerular Filtration Rate ≥ 60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation (Appendix 8).
Note, for France only: Serum creatinine ≤ 1.5 x ULN and estimated glomerular filtration rate or estimated creatinine clearance ≥ 60 mL/min/1.73 m^2 by CKD-EPI and Cockcroft and Gault equations, respectively (Appendix 8).
c. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilberts syndrome).
d. AST and ALT ≤ 2.5 x ULN or < 5 x ULN if hepatic metastases present.

10. Females 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, and must have a negative urine or serum pregnancy test ≤ 7 days before randomization. See Appendix 9.
11. Nonsterile males must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of study drug.

- A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
- Males with known "low sperm counts" (consistent with "subfertility") are not to be considered sterile for purposes of this study.

4.2. Exclusion Criteria

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

1. Known mutations in:
   a. *EGFR* gene

      (Note: Patients with nonsquamous NSCLC whose EGFR mutational status is unknown will be required to have a tissue-based EGFR test either locally or centrally, or endobronchial ultrasound-guided transbronchial needle aspiration [EBUS-TBNA]-based EGFR test locally at Prescreening). Patients found to have *EGFR*-sensitizing mutations will be excluded.

   b. *ALK* fusion oncogene
   c. BRAF V600E
   d. *ROS1*

   Note: If no targeted therapy approved by local health authority is available for BRAF V600E or *ROS1* mutations, then these patients are eligible. ALK testing is required for patients with nonsquamous NSCLC in Korea, if *ALK* status is unknown.
2. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-TIGIT, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways.
3. Active leptomeningeal disease or uncontrolled, untreated brain metastasis.

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

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- Brain imaging at Screening shows no evidence of interim progression, patient is clinically stable for at least 2 weeks and without evidence of new brain metastases.
- Measurable and/or evaluable disease outside the CNS.
- No ongoing requirement for corticosteroids as therapy for CNS disease; off steroids 3 days before randomization; anticonvulsants at a stable dose are allowed.
- No stereotactic radiation or whole-brain radiation within 14 days before randomization.

4. Active autoimmune diseases or history of autoimmune diseases that may relapse.

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

   a. Controlled Type I diabetes.
   b. Hypothyroidism (provided it is managed with hormone replacement therapy only).
   c. Controlled celiac disease.
   d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia).
   e. Any other disease that is not expected to recur in the absence of external triggering factors.

5. Any active malignancy ≤ 5 years before randomization except for the specific cancer under investigation in this study, those with a negligible risk of metastasis or death, and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, localized prostate cancer, or carcinoma in situ of the cervix or breast).

6. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone [in Japan, prednisolone] or equivalent) or other immunosuppressive medication ≤ 14 days before randomization.

   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 [in Japan, prednisolone] 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 randomization.

8. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence within 2 weeks of intervention). Patients with symptomatic pleural

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effusion are excluded unless the patient undergoes a therapeutic thoracentesis or has had pleurodesis (more than 2 weeks prior) and has subsequently stable effusions.

9. History of interstitial lung disease, noninfectious pneumonitis or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc. All patients must undergo an assessment of pulmonary function at Screening (see Section 7.2.3).
10. Infection (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal, or antiviral therapy within 14 days before randomization, or patients who tested positive for COVID-19 antigen by a licensed test during screening.

    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 (in Japan, defined as patients who are HBsAg-positive but asymptomatic), treated and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Patients with detectable hepatitis B surface antigen (HBsAg) or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at Screening should have been treated for > 2 weeks before randomization.
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 randomization.
13. Known history of human immunodeficiency virus (HIV) infection, or if HIV status is unknown, positive HIV test at Screening.
14. Any major surgical procedure ≤ 28 days before randomization. Patients must have recovered adequately from the toxicity and/or complications from the intervention before randomization.
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 randomization.
    b. Symptomatic pulmonary embolism diagnosed ≤ 28 days before randomization.
    c. Any history of acute myocardial infarction ≤ 6 months before randomization.
    d. Any history of heart failure meeting New York Heart Association (NYHA) Classification III or IV (Appendix 6) ≤ 6 months before randomization.
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before randomization.
    f. Any history of cerebrovascular accident ≤ 6 months before randomization.
    g. Uncontrolled hypertension that cannot be managed by standard antihypertension medications ≤ 28 days before randomization.

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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 randomization.

17. A history of severe hypersensitivity reactions to other monoclonal antibodies or a history of hypersensitivity to the ingredients of tislelizumab or ociperlimab.

18. Was administered a live vaccine ≤ 28 days before randomization.
    Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.

19. 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.

20. Women who are pregnant or are breastfeeding.

    Note, for Japan only: If pregnancy is suspected during physical examination or interview, patient is not eligible regardless of whether or not a negative urine or serum pregnancy test is subsequently obtained before randomization. Breastfeeding women who agree to stop breastfeeding prior to randomization are allowed to enroll and they shall not resume breastfeeding until ≥ 120 days after the last dose of study drugs.

21. Concurrent participation in another therapeutic clinical study.
    Note: Concurrent participation in observational or noninterventional studies is allowed. In addition, patients who have completed active treatment in a clinical study and are in the follow-up period can be enrolled in this study.

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5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous injection in a single-use vial (20R glass, United States Pharmacopeia [USP] type I), containing a total of 100 mg of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in a single-use glass vial with a rubber stopper and capped by an aluminum flip-off seal cap. Each vial is packaged into a single carton box.

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

The study drug must be kept at the temperature 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.

5.1.2. Ociperlimab

Ociperlimab is a monoclonal antibody formulated for intravenous injection in a single-use vial (20 mL glass vial, USP Type I) containing a total of 200 mg antibody in 10 mL (or 300 mg antibody in 15 mL) of buffered isotonic solution as available. Ociperlimab 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 Ociperlimab Investigator's Brochure for other details regarding ociperlimab.

5.1.3. Pembrolizumab

Pembrolizumab may be locally sourced by the investigational site or, in some circumstances (eg, Japan), provided by the sponsor. The actual appearance and composition of the product may depend on the respective marketed product sourced for the participating countries.

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.

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

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5.1.4. Placebo

Placebo infusions will be used in Treatment Arms B and C for the purpose of maintaining the study blind (Section 5.6). Placebo infusions will consist of a sterile, normal saline solution that will be locally sourced by the investigational site. The actual appearance and composition of the product may depend on the respective product sourced for the participating countries. Placebo treatments will be masked to preserve the study blind (Section 5.6).

Refer to the pharmacy manual for details regarding intravenous administration, accountability, and disposal.

5.2. Dosage, Administration, and Compliance

Dosing schedules for all arms, broken out by individual treatment arm, are provided in Table 1. Dosing administration and monitoring times, broken out by individual treatment arm, are provided in Table 2.

The first dose of study drug is to be administered within 2 business days of randomization.

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.

Table 1: Selection and Timing of Dose for Each Patient

Treatment arm	Study treatment	Dose	Frequency and sequence of administration	Route of administration	Duration of treatment
Arm A	Tislelizumab	200 mg	Day 1 of each cycle (21 days) Administer first	Intravenous	See Section 3.4
	Ociperlimab	900 mg*	Day 1 of each cycle (21 days) Administer after tislelizumab	Intravenous	See Section 3.4
Arm B	Pembrolizumab	200 mg	Day 1 of each cycle (21 days) Administer first	Intravenous	See Section 3.4
	Placebo infusion	NA	Day 1 of each cycle (21 days) Administer after pembrolizumab	Intravenous	See Section 3.4
Arm C	Tislelizumab	200 mg	Day 1 of each cycle (21 days) Administer first	Intravenous	See Section 3.4
	Placebo infusion	NA	Day 1 of each cycle (21 days) Administer after tislelizumab	Intravenous	See Section 3.4

Abbreviations: NA, not applicable.

*As of Protocol Amendment Version 3.0, the ociperlimab dose that will be administered to Japanese patients allocated in Arm A was determined to be 900 mg based on the results from the safety run-in substudy (see Appendix 16).

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Table 2: Administration of Study Treatments and Monitoring Time

Cycle	Treatment arm	Study treatment administration and monitoring times
C1D1 and C2D1	Arm A	Tislelizumab infusion for ≥ 55 minutes followed by ociperlimab infusion for ≥ 55 minutes Patient monitoring for ≥ 120 minutes
	Arm B	Pembrolizumab infusion for ≥ 55 minutes followed by placebo infusion for ≥ 55 minutes Patient monitoring for ≥ 120 minutes
	Arm C	Tislelizumab infusion for ≥ 55 minutes followed by placebo infusion for ≥ 55 minutes Patient monitoring for ≥ 120 minutes
C3D1 onwards	Arm A	Tislelizumab infusion for ≥ 25 minutes followed by ociperlimab infusion for ≥ 25 minutes Patient monitoring for ≥ 60 minutes
	Arm B	Pembrolizumab infusion for ≥ 25 minutes followed by placebo infusion for ≥ 25 minutes Patient monitoring for ≥ 60 minutes
	Arm C	Tislelizumab infusion for ≥ 25 minutes followed by placebo infusion for ≥ 25 minutes Patient monitoring for ≥ 60 minutes

Abbreviations: C1D1, Cycle 1 Day 1; C2D1, Cycle 2 Day 1; C3D1, Cycle 3 Day 1

Treatment Administration

In Arm A, tislelizumab 200 mg will be administered followed by ociperlimab 900 mg on Day 1 of each 21-day cycle (once every 3 weeks). Note: As of Protocol Amendment Version 3.0, the ociperlimab dose that will be administered to Japanese patients allocated in Arm A was determined to be 900 mg based on the results from the safety run-in substudy (see Appendix 16).

In Arm B, pembrolizumab 200 mg will be administered followed by a placebo infusion on Day 1 of each 21-day cycle (once every 3 weeks).

In Arm C, tislelizumab 200 mg will be administered followed by a placebo infusion on Day 1 of each 21-day cycle (once every 3 weeks).

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

The initial infusions (Day 1 of Cycle 1 and Cycle 2) will have a duration of ≥ 55 minutes; if this is well tolerated, then the subsequent infusions may have a duration of ≥ 25 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (Section 6).

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

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infusion speed is controlled through alternative means and consistent with approved institutional procedures.

At the end of each infusion period, the line will be flushed with enough normal saline to make sure the complete doses of study drugs are administered.

As a routine precaution, after infusion of all study treatment is complete on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for ≥ 120 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 60-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

Guidelines for treatment interruption, or discontinuation and for the management of imAEs and infusion-related reactions are provided in detail in Section 8.6 and Appendix 7.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

5.3. Overdose or Incorrect Administration

Any incorrect administration of any study drug or overdose of tislelizumab (defined as ≥ 600 mg in a 24-hour period), ociperlimab, or pembrolizumab should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration must be reported within 24 hours of awareness via the SAE reporting process described in Section 8.6.2. Supportive care measures should be administered as appropriate.

5.4. Investigational Medicinal Product Accountability

The investigational medicinal products (IMPs) required for completion of this study are tislelizumab, ociperlimab, and pembrolizumab. Tislelizumab and ociperlimab will be provided by the sponsor, as required by local or country-specific guidance. Pembrolizumab may be locally sourced by the investigational site or, in some circumstances, provided by the sponsor (eg, Japan). The investigational site will acknowledge receipt of IMPs. Any damaged shipments will be replaced.

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

5.5. Dose Delay or Interruption

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

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

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

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5.5.1. Dose Delay or Interruption for All Arms

There will be no dose reduction for any of the study drugs in this study.

In all treatment arms, treatment with study drugs may be temporarily suspended if the patient experiences a toxicity that is considered related to study drugs and requires a dose to be withheld. If temporary suspension is required in Treatment Arm A, both study drugs (ociperlimab and tislelizumab) must be suspended. Treatment with study drugs should resume as soon as possible after the AEs recover to Grade 1 or baseline (whichever is more severe) and within 12 weeks after the last dose of study drugs. If the administration of study drugs can resume within ≤ 10 days, study drugs should be administered in the current cycle. If study drugs need to be withheld for > 10 days, they should be omitted from the current cycle and administration should restart in the next cycle. If the patient is unable to resume study drugs within 12 weeks after the last dose of study drugs, then the patient should be discontinued from treatment. If the patient is not able to resume study drugs ≤ 12 weeks after the last dose for unforeseen non-drug-related reasons, and the patient is likely to benefit from the study treatment, resumption of study treatment may occur after discussion and agreement with the medical monitor.

Specific treatment modifications to manage study drug-related toxicities, such as to imAEs and infusion-related reactions, are described in Section 8.6 and Appendix 7.

5.6. Blinding

This is a randomized, double-blind, Phase 3 study. Patients will be randomized in a 5:5:2 ratio to receive ociperlimab + tislelizumab (Arm A), pembrolizumab + placebo (Arm B), or tislelizumab + placebo (Arm C) in a double-blind fashion.

Pharmacists will be unblinded; therefore, it is imperative to maintain the blind such that neither the investigator, nor the patient, nor the medical or ancillary medical staff, nor the sponsor's blinded staff or its designees will know which drug treatment is being administered. Pharmacists will mask the study treatments to ensure that patients and study staff remain blinded.

Every effort should be made to avoid unblinding the patient's treatment assignment unless necessary. Unblinding may be indicated and permissible only in specific situations as described below and if necessary for the patient's welfare. Unblinding would occur through Interactive Response Technology (IRT) as per the instructions in the IRT site user manual. If unblinding has occurred, the sponsor must be notified immediately using the Unblinding Event Form. To ensure the continued blinding of study personnel, this form will not include the treatment assignment. Patients will remain on study for safety follow-up and, if applicable, for survival follow-up.

Refer to the pharmacy manual for details regarding unblinded pharmacists, masking of study treatments, and other details regarding study blinding.

5.6.1. Emergency Unblinding

In case of an emergency, such as when a patient has an AE suspected to be related to the investigational drug product and for which management of the AE with one or more drug products with substantial toxicity or invasive procedures is being considered, unblinding can

occur. The investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to inform the medical monitor of their intent before unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the sponsor must be notified immediately.

The investigator performs the emergency unblinding for AEs through an IRT System. Unblinded patients may remain on study treatment at the discretion of the investigator in consultation with the medical monitor and only as permissible per definitions in the study protocol.

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5.6.2. Non-Emergency Unblinding

Non-emergency unblinding to study treatment administration may occur on an individual patient basis and only after consultation with and approval from the medical monitor at the time of 1) investigator-assessed disease progression and the patient has discontinued all study treatments, or 2) when the patient has discontinued all study treatments for toxicity and a new anticancer treatment is going to be started.

5.6.3. Inadvertent Unblinding

Every effort will be made to blind both the patient and the investigator/site staff to the identity of the treatment assignment (ie, ociperlimab and tislelizumab [Arm A], pembrolizumab and placebo [Arm B], or tislelizumab and placebo [Arm C]), but the inadvertent unblinding of a patient may occur. If an investigator, site personnel (eg, those performing assessments), or patient is unblinded, the unblinding will not be a sufficient cause (in and of itself) for that patient to be discontinued from study therapy or excluded from any safety or efficacy analyses.

Additionally, there may be ethical reasons to have the patient remain on the study treatment. For patients to continue study treatment in the event of unblinding, the investigator must obtain specific approval from the medical monitor.

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6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

Patients should not have received chemotherapy, radiation, targeted therapy, biologic therapy, immunotherapy, or investigational agent used to control metastatic NSCLC (Section 4.1), with the exception of prior radiation to brain metastases, which is permitted. Patients should not have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-TIGIT, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways (Section 4.2).

Prior adjuvant, neoadjuvant, and/or chemoradiotherapy ≤ 12 months before randomization is not permitted.

Patients who have received low dose and limited-field palliative radiation of bone NSCLC metastatic sites, given strictly for pain control or prophylaxis of bone fracture are eligible provided:

- The patient has at least one measurable lesion per RECIST v1.1 that has not been previously irradiated or that has progressed since the therapy.
- The case is discussed with the medical monitor, and the medical monitor agrees that the patient is eligible.

6.2. Concomitant Therapy

6.2.1. Permitted Concomitant Medications/Procedures

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) and in a patient's interest are allowed. Opiates and other medication required for palliative management of patients are allowed. Patients must notify the investigator of all concurrent medications used during the study.

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

6.2.1.1. Systemic Corticosteroids

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

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6.2.1.2. Hepatitis B Treatment

Patients with active hepatitis B, defined as HBV DNA ≥ 500 IU/mL at Screening, must initiate treatment 2 weeks before randomization, and continue until 6 months after the last dose of study drug(s). Patients should continue effective antiviral treatment during the study to decrease potential viral reactivation risk. Tenofovir and entecavir are recommended in the American Association for the Study of Liver Disease (AASLD) guideline because they lack resistance with long-term use (Terrault et al 2016; AASLD/IDSA HCV Guidance Panel 2015). The investigator may use other antiviral agents, if appropriate, following local guidelines. However, interferon-based therapy for hepatitis B is not permitted on study.

Management of prophylactic antiviral therapy for patients with inactive, treated, and stable hepatitis B (HBV DNA < 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 randomization and continue treatment during the study and for 6 months after study drug treatment discontinuation.

6.2.1.3. 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 sofosbuvir alone or in combination with other antivirals following the AASLD guideline or the 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 randomization.

6.2.1.4. Radiation Therapy

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

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

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

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

6.2.2. Prohibited Concomitant Medications/Procedures

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

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The following medications are prohibited during screening (and ≤ 14 days or ≤ 5 half-lives before randomization, whichever is shorter) and through the EOT Visit:

- Any concurrent anti-cancer therapy, including chemotherapy, hormonal therapy, immunotherapy, standard anticancer agents, or investigational anticancer agents
- Herbal remedies for the treatment of cancer or Chinese patent medicines for use as anticancer treatment (regardless of cancer type; see Appendix 10)
- 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)

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

6.2.3. 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 [in Japan, prednisolone] 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 is not allowed, except for palliative radiation therapy described in Section 6.2.1.4

6.3. Potential Interactions Between the Study Drugs and Concomitant Medications

The potential for drug-drug interaction between the study drugs (tislelizumab, ociperlimab, and pembrolizumab), and small-molecule drug products is very low, given that the study drugs are therapeutic monoclonal antibodies. The study drugs are unlikely to have an effect on drug-metabolizing enzymes or transporters because they are expected to be degraded into amino acids and recycle into other proteins.

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7. STUDY ASSESSMENTS AND PROCEDURES

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

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

7.1. Prescreening

Prescreening assessments will be performed between 56 and 28 days before randomization, unless the prescreening and screening periods are combined, in which case, PD-L1 status will be determined within 28 days before randomization. Note, for the US and Japan only: Local PD-L1 testing may be used for patient randomization purposes, in which case, the local PD-L1 testing results will be collected in the eCRF.

For all sites, local PD-L1 testing results, if available for patients who are randomized based on central PD-L1 testing results, may be collected in the eCRF if patients consent to this information being collected.

A separate prescreening informed consent must be obtained.

Archival tumor tissue must be collected for central evaluation of PD-L1 status. If no archival samples are available, a fresh tumor biopsy is required. Refer to Section 7.8 for details. Note, for the US and Japan only: If local PD-L1 testing will be used for patient randomization purposes, confirmation of tumor sample receipt by the central laboratory is required before patient randomization (preferably from the same block used for local PD-L1 testing). In the US and Japan, local PD-L1 testing must be performed using an FDA-approved or MHLW-approved assay, respectively (limited to 22C3, SP263, 28-8), at a certified laboratory and according to manufacturer's instructions.

EGFR, *ALK*, BRAF V600E, and *ROS1* mutational status, if known, will also be collected at this time.

Only for patients with nonsquamous NSCLC: If *EGFR* mutational status is unknown, patients with nonsquamous NSCLC will be required to have a tissue-based *EGFR* test performed either locally or centrally, or EBUS-TBNA–based EGFR test locally, at Prescreening. Patients found to have EGFR-sensitizing mutations will not be eligible.

The following tasks will be performed during the Prescreening Visit:

- Obtain written informed consent (prescreening ICF) to obtain archival or fresh tumor tissue
- Collect *EGFR*, *ALK*, BRAF V600E, and *ROS1* mutational status if known; obtain agreement to have *EGFR* mutational status determined if unknown (for patients with nonsquamous NSCLC only)
- Prepare tumor samples and ship to the qualified central laboratory for analysis as specified in the study manual

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- For US and Japan sites only, collect local PD-L1 testing results if they will be used for patient randomization purposes. Confirmation of tumor sample receipt by the central laboratory is required before patient randomization (preferably from the same block used for local PD-L1 testing).

7.2. Screening

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

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

Procedures conducted during the Screening Visit only are described in this section. All patients must have a pulmonary function test performed during screening (refer to Appendix 1 for details). For the description of assessments that are conducted during screening, as well as throughout the study, refer to Safety Assessments (Section 7.5), Tumor and Response Evaluations (Section 7.6) and Biomarkers (Section 7.8) sections. The PK sampling schedule is shown in Appendix 1.

Rescreening under limited conditions may be allowed after consultation with the sponsor, eg, when a patient narrowly misses a laboratory criterion, and it is correctable and not due to rapidly deteriorating condition or disease progression. Rescreening is allowed only once.

7.2.1. Informed Consent and Prescreening and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures at the Prescreening Visit (Section 7.1, prescreening ICF) and at the Screening Visit (Section 7.2, main ICF). Informed consent forms for prescreened and enrolled patients and for patients who are screened but not enrolled will be maintained at the study site.

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

7.2.2. 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.

7.2.3. Pulmonary Function Tests

Pulmonary function testing including spirometry and assessment of oxygenation, either pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity, are to be

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performed for all patients during the screening period to assist the determination of suitability on the study. Respective test results will be evaluated by the investigator before randomization.

For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, forced expiratory volume (FEV1) < 60% or diffusing capacity of the lungs for carbon monoxide (DLCO) (if performed) < 60% of age and sex adjusted predicted performance levels (Pellegrino et al 2005), the medical monitor needs to be consulted to confirm eligibility.

Tests may be repeated as clinically indicated while on study.

7.3. Enrollment

7.3.1. Confirmation of Eligibility

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

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

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

7.3.2. Enrollment/Randomization

Site personnel will access the IRT system to randomize to treatment assignment and to enable study drug dispensation. Study treatment must commence within 2 business days after randomization/treatment assignment.

7.4. Study Drug Dispensation

All study drugs will be dispensed and administered as described in Section 5.2.

7.5. Safety Assessments

7.5.1. Vital Signs, Height, and Weight

Vital signs will include measurements of body temperature (˚C), pulse rate, and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be collected while the patient is in a seated position after resting for 10 minutes. Vital signs will be recorded at Screening, on Day 1 of each cycle, and at the EOT Visit (Appendix 1).

The patient's vital signs are required to be recorded within 60 minutes before, during, and approximately 30 minutes after completion of both study drug infusions on Day 1 of Cycle 1. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and, if clinically indicated, during and 30 minutes after both infusions.

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Height will be recorded at Screening only. Weight will be recorded at Screening, on Day 1 of each cycle, and at the EOT Visit.

7.5.2. Physical Examinations

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

At subsequent visits (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.

7.5.3. Pulmonary Assessments

For Japan sites only, chest x-rays, sialylated carbohydrate antigen Krebs von den Lungen-6 (KL-6) and peripheral capillary oxygen saturation (SpO2) evaluations will be performed as specified in Appendix 1.

7.5.4. Eastern Cooperative Oncology Group Performance Status

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

7.5.5. Laboratory Safety Tests

Local or central laboratory assessments of serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2.

If laboratory tests at Screening are not performed within 7 days before Day 1 of Cycle 1, these tests should be repeated and reviewed before randomization. Hematology and serum chemistry (including liver function tests) as specified in Appendix 2 should be performed weekly for the first 3 cycles, at the beginning of each subsequent cycle, and at the EOT Visit (Appendix 1). After Cycle 1, results are to be reviewed within 48 hours before study drug administration.

Coagulation assessments will be performed at timepoints as specified in Appendix 1.

Urinalysis is to be conducted at Screening and during the treatment period only if clinically warranted.

Thyroid assessments will be performed as specified in Appendix 1.

Details about sample collection and shipment will be provided in a separate instruction manual. Investigators may use results from local laboratories for assessing eligibility, safety monitoring, and dosing decisions.

7.5.5.1. Cardiac Enzyme Monitoring

Although immune-related myocarditis is a rare complication of immune checkpoint inhibitors, serum creatine kinase (CK) and CK cardiac muscle isoenzyme (CK-MB) is monitored to protect

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study participants and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 7 for guidelines for management of suspected immune-related myocarditis). Serum troponins may be substituted per local guidelines if used consistently throughout the study.

7.5.6. Electrocardiograms

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

The ECG recordings will be obtained during screening, the EOT Visit, and as clinically indicated at other timepoints (Appendix 1). When coinciding with blood draws at the same timepoint, ECG assessment should be performed before blood draws. Patients should rest in a semirecumbent supine position for at least 10 minutes before ECG collection.

7.5.7. Adverse Events

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

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

7.5.8. Hepatitis B, Hepatitis C, and HIV Testing

Testing will be performed by a local or central laboratory at Screening and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody), and HIV serology (antigen and/or antibodies), unless the patient's HIV status is already known. In the case of active HBV or HCV infection, these tests will be followed by viral load assessment (HBV DNA and HCV RNA).

Inactive hepatitis B surface antigen (HBsAg) carriers (in Japan, defined as patients who are HBsAg-positive but asymptomatic) and patients with treated and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Patients with detectable hepatitis B surface antigen (HBsAg) or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at Screening should have been treated for > 2 weeks before randomization. Patients who have detectable HBV DNA at Screening will perform a viral load test every 4 cycles (eg, Day 1 of Cycles 5, 9, 13).

Patients with a negative HCV antibody test at Screening or positive HCV antibody test followed by a negative HCV RNA test at Screening can be enrolled. The HCV RNA test will be performed only for patients testing positive for HCV antibody. Patients receiving antivirals at Screening should have been treated for > 2 weeks before randomization. Patients who had a positive antibody test at Screening will perform a viral load test every 4 cycles (eg, Day 1 of Cycles 5, 9, 13).

7.6. Tumor and Response Evaluations

Tumor imaging will be performed within 28 days before randomization. Radiological images captured as standard of care before obtaining written informed consent and ≤ 28 days before randomization may be used rather than repeating tests. During the study, tumor imaging will be

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performed every 9 weeks (± 7 days) from randomization for the first 52 weeks and then every 12 weeks (± 7 days) based on RECIST v1.1. Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held; they should not be adjusted for possible delays in cycles. Tumor assessments should continue until disease progression is determined by the investigator. Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient experiences disease progression or death, withdraws consent, is lost to follow-up, or until the study terminates, whichever occurs first.

Screening assessments and each subsequent assessment of the tumor must include computed tomography (CT) scans (with oral/intravenous contrast, unless contraindicated) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, 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 is required to be used throughout the study (eg, the same contrast protocol for CT scans or MRI).

- Imaging of the brain (preferably MRI) at baseline is required for all screened patients. Screening evaluations will be performed within 28 days before randomization.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a noncontrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- Bone scans (Technetium-99m [Tc-99m]) or PET should be performed at Screening if clinically indicated. If bone metastases are present at Screening and cannot be seen on CT or MRI scans, Tc-99m or PET bone scans should be repeated when a CR is suspected in target lesion or when progression in bone is suspected.
- CT scans of the neck or extremities should be performed at Screening only if clinically indicated and should be followed throughout the study if there is evidence of metastatic disease in these regions at Screening.
- At the investigator's discretion, other methods of assessment of target lesions and nontarget lesions per RECIST v1.1 may be used.

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

Some patients may benefit from additional immune therapies despite evidence of disease progression. The following criteria must be met in order to continue to treat patients with evidence of disease progression as determined by the investigator:

- Absence of clinical symptoms and signs of disease progression (including clinically significant worsening of laboratory values)

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- ECOG Performance Status ≤ 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, spinal cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer. Patients must be informed that they may be forgoing treatment that has shown benefit by continuing treatment beyond progression.
- The decision to continue study drug(s) beyond initial investigator-assessed progression must be agreed with the sponsor medical monitor.

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

7.7. Pharmacokinetic and Antidrug Antibody Testing

Checkpoint inhibitor drugs may elicit an immune response. Patients with signs of any potential immune response to study drug will be closely monitored (Appendix 7). Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints throughout the study (see Appendix 1). Samples will be collected from all patients, but analyses will be performed in patients receiving ociperlimab + tislelizumab (Arm A) or tislelizumab + placebo (Arm C) only. The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Koren et al 2008; Worobec and Rosenberg 2004a; Worobec and Rosenberg 2004b) to characterize ADA responses to tislelizumab and ociperlimab in support of the clinical development program. This tiered strategy will include an assessment of whether ADA responses correlate with relevant clinical endpoints. Implementation of ADA characterization assays will depend on the safety profile and clinical immunogenicity data.

The following assessments will be performed at a central laboratory:

- ADA assays: serum samples will be tested for the presence of ADAs to tislelizumab and/or ociperlimab using a validated immunoassay
- PK assay: serum samples will be assayed for tislelizumab and/or ociperlimab concentration using a validated immunoassay

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

PK and ADA samples will be collected at the timepoints indicated in Appendix 1.

7.8. Biomarkers

Shipping, storage, and handling of blood, archival tumor, fresh tumor, and leftover tumor tissue for the assessment of biomarkers will be managed through a central laboratory. Tumor samples will be used for developing candidate companion diagnostics (CDx) for this study, including but

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not limited to CDx bridging studies (for China only, refer to Appendix 18 for details of PD-L1 CDx bridging study). Refer to the laboratory manual for details of sample handling.

Patients will be informed whether or not they are eligible for the study based on the central PD-L1 or EGFR (if required) test results (including results of local PD-L1 testing in the US and Japan). Additional biomarker testing will be performed in batches by a central laboratory; therefore, no timeframe is defined for the availability of the results. The sponsor will not inform patients about the results of the additional biomarker tests because the information generated from this research is preliminary and the clinical significance and the scientific validity of the results cannot be determined at this early stage. Taking part in blood collection and optional biopsies is entirely voluntary. Irrespective of the patients' decision (ie, if the patient withdraws optional sample collection consent), it will not affect their participation in the main study or their medical care. If patients withdraw consent, they will decide whether to have any remaining samples destroyed or returned, or allow all previously retained biological samples to be used.

Archival tumor tissues (formalin-fixed paraffin-embedded blocks or approximately 6 to 15 freshly cut unstained slides) need to be sent to the central laboratory for central immunohistochemistry analysis of PD-L1 status using the VENTANA PD-L1 (SP263) CDx Assay (for the US and Japan only, preferably from the same block used for local PD-L1 testing if the latter is used for randomization purposes; Appendix 19). The only difference between the VENTANA PD-L1 (SP263) CDx Assay and the CE marked and commercially available VENTANA PD-L1 (SP263) Assay is that the instructions for use of the latter do not include use for all the therapies used in this study (ie, tislelizumab ± ociperlimab). Otherwise, the two assays are identical in all aspects, including formulation, quality control testing, test procedure, and staining protocol. Note, for US and Japan sites only: If local PD-L1 testing is used for patient randomization purposes, however, later, the central PD-L1 testing result is < 50%, unevaluable or cannot be performed, such patient will remain part of the ITT Population and will not be replaced.

If no archival samples are available, a fresh tumor biopsy at baseline (within 28 days before the screening period, unless the prescreening and screening periods are combined, in which case, it should be performed within 28 days before randomization) is mandatory. If a fresh biopsy is being performed solely for the purpose of central PD-L1 testing, it should be performed according to standard practice in advanced, unresectable, and metastatic NSCLC. For fresh biopsy specimens, acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Tumor tissue should be of good quality and contain viable tumor. Tumor samples from fine-needle aspiration, brushing, cell pellets from pleural effusion, or lavage or that have been decalcified, or fixed in 95% alcohol or higher, AFA or PREFER™ are not acceptable.

Patients who have progressive disease will be asked to provide an optional biopsy at the EOT Visit (Appendix 1) from accessible tumor sites to obtain samples to explore the mechanisms of resistance. If feasible, optional biopsies at the EOT Visit should ideally be taken from the same tumor lesion as the baseline biopsy if one was provided. Written patient consent is required for fresh tumor biopsies.

Other biomarkers, such as the expression of TIGIT, CD226, CD155, CD112, TMB, MSI, immune-related GEP, TILs, and additional PD-L1 related analyses that are related to the

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response or clinical benefit of tislelizumab and ociperlimab, may also be retrospectively evaluated in tumor tissues at baseline and at disease progression. Archival tissue sample for retrospective biomarker testing can be obtained after the prescreening period. (Note, for sites in mainland China: Tissues will be obtained to test the expression of TIGIT, CD226, CD155, CD112, PD-L1, GEP, TMB, gene mutations, MSI, and TILs at baseline and at disease progression).

Blood samples will be taken at baseline (predose on Day 1 of Cycle 1), predose on Day 1 of Cycle 3, and at the EOT Visit after disease progression (10 mL each timepoint) to evaluate TMB, MSI, mutational profiles, and EVs, as well as other biomarkers in blood (Appendix 1). (Note, for sites in mainland China: Blood-based biomarkers, including TMB, MSI, gene mutational profiles, and EVs will be explored in blood samples). Written patient consent is required for blood sample collection.

7.9. Patient-Reported Outcomes

Patient-reported outcomes (PRO) will be collected after randomization starting with Cycle 1 Day 1. Patients will be asked to complete PRO questionnaires before any clinical activities (including blood draws or imaging scans) are performed during applicable on-study dosing visits according to the schedule in Appendix 1. The PROs will include the EORTC-QLQ-C30 (Appendix 11), its lung cancer module QLQ-LC13 (Appendix 12), EuroQol's EQ-5D-5L (Appendix 13), PGI-S (Appendix 14), and PRTSE (Appendix 15). The questionnaires will be provided in the patient's preferred language.

7.10. 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 study treatment infusion/dose unless otherwise noted. Laboratory results are required to be reviewed before dosing.

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

7.11. Unscheduled Visits

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

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

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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 Ociperlimab and Tislelizumab

Tislelizumab and ociperlimab are investigational agents that are currently in clinical development. The following recommendation is based on results from nonclinical and clinical studies with tislelizumab and ociperlimab 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 8.6.12.

Although most imAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested evaluation and management guidelines for suspected imAEs are provided in Appendix 7.

8.1.2. Risks Associated With Pembrolizumab

The most common AEs observed in ≥ 10% patients treated with pembrolizumab are anaemia, hypothyroidism, decreased appetite, headache, cough, dyspnea, diarrhea, abdominal pain, nausea, vomiting, constipation, rash, pruritus, musculoskeletal pain, arthralgia, fatigue, pyrexia, oedema and asthenia. The other significant AEs are infusion-related reactions and immune-mediated AEs including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, and skin adverse reactions (Stevens Johnson syndrome and toxic epidermal necrolysis).

Refer to the manufacturer's Summary of Product Characteristics (SmPC) for additional details.

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies and clinical data with tislelizumab, ociperlimab, and pembrolizumab as well as the nonclinical/clinical data from other PD-L1/PD-1 and TIGIT 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 randomization are excluded from the study (see Section 4.2 for the full list of exclusion criteria).

8.2.2. Safety Monitoring Plan

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

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standard laboratory tests at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs (see Table 3), physical examinations, laboratory measurements (hematology, 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 infections or autoimmune conditions.

At the start of each cycle, study drugs 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 (Section 5.2).

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

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in Section 8.6.

8.3. Adverse Events

8.3.1. Definitions and Reporting

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

Examples of AEs include:

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

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records 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 the NCI-CTCAE v5.0.

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

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

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

8.3.3. Assessment of Causality

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

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

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

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

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

8.3.4. Follow-up of Adverse Events

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

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

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

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

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

8.3.5. Laboratory Test Abnormalities

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

- are associated with clinical signs or symptoms, or
- require active medical intervention, or

- lead to dose interruption or discontinuation, or
- require close observation, more frequent follow-up assessments, or further diagnostic investigation.

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

If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

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

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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 were more severe.
- Requires hospitalization or prolongation of existing hospitalization
  Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
- Results in disability/incapacity
  Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere 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)

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The following are NOT considered to be SAEs:

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

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 product's Reference Safety Information [RSI]) and meets the definition of a serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the Tislelizumab Investigator's Brochure, Ociperlimab Investigator's Brochure, or pembrolizumab prescribing information.

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

8.6.1. Adverse Event Recording Period

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

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study drugs or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of study drugs, regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drugs 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 3. For the follow-up period for AEs, see Section 8.3.4. For the definition of TEAEs, see Section 9.3.2.

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

Event type	Record new or worsening events that occur during this period	
	Begin	End
SAEs [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 4.

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

	Timeframe for sending initial report	Documentation method	Reporting method
All SAEs	Within 24 hours of first knowledge of the SAE [a]	SAE Report	Electronic submission of SAE Form to safety portal [b]

Abbreviations: EDC, electronic data capture; IMP, investigational medicinal product; SAE, serious adverse event.
[a] Report follow-up information that is clinically relevant and pertaining to the SAE as soon as possible (typically, within 7 days), which includes but is not limited to the following: Update to the SAE, new additional SAE, outcome, seriousness criteria, investigator causality, event start date/date of onset, date of death, relationship to each IMP. Follow-up information will also be reported as per the discretion of the investigator if the new or updated information changes the medical assessment of the case.
[b] SAE reports should be submitted to the sponsor safety database electronically from within the EDC. If the electronic submission is not available for any reason, a paper SAE form should be submitted by email or fax.

8.6.2.2. 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

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Report will always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated time frames.

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

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

The sponsor will provide contact information for SAE receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

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

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC. Note, for Japan only: The investigator will report all SAEs to the sponsor and the head of the study center, and then, the head of the study center will inform the IRB/IEC in accordance with site SOP and local regulation.

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

When a study center (in Japan, the head of the 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 (in Japan, the head of the study center) is required to promptly notify his/her IRB or IEC. The investigator should place copies of Safety Reports from the sponsor in the Investigator Site File.

8.6.3. Eliciting Adverse Events

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

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

8.6.4. Disease Progression

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

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8.6.5. Deaths

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

8.6.6. Pregnancies

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

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

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

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

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs, IECs (and, in Japan, the head of the study center), based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following RSI documents:

- Tislelizumab Investigator's Brochure
- Ociperlimab Investigator's Brochure
- Pembrolizumab prescribing information

8.6.8. Assessing and Recording Immune-Mediated Adverse Events

Because treatment with anti-PD-1 or immune checkpoint inhibitors can cause autoimmune disorders, AEs considered by the investigator to be immune-mediated (see Section 8.6.12) should be classified as imAEs and identified as such on the eCRF AE page until 90 days after the last dose of study drug.

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

An extensive list of potential imAEs appears in Table 6 of Section 8.6.12. 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 7.

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8.6.9. Recording Infusion-Related Reactions

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

As a routine precaution, after completing the infusion of study drugs on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for ≥ 120 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 60-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The management of infusion-related reactions, severe hypersensitivity reactions, and imAEs according to the NCI-CTCAE v5.0 criteria are outlined below.

8.6.10. Managing Infusion-Related Reactions

Patients should be closely monitored for infusion-related reactions. Immediate access to an Intensive Care Unit (ICU) 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 drug(s) is provided in Table 5.

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Table 5: Treatment Modifications for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

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

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

Once the study drug infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions and be administered with premedication. If the patient has a second infusion-related reaction (≥ Grade 2) on the slower infusion rate, infusion should be discontinued, and the patient should be withdrawn from study drug treatment.

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, patients should receive oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and an antipyretic (eg, paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion reaction.

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

8.6.11. Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

In the event of a systemic anaphylactic/anaphylactoid reaction the infusion must be immediately stopped, 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 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. The patient should then be placed on monitor immediately, and ICU 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(s) infusion. Alternative treatments for fever (ie, paracetamol) may be given to patients at the discretion of the investigator.

8.6.12. Immune-Mediated Adverse Events

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

A list of potential imAEs is shown below in Table 6. All conditions similar to those listed should be evaluated in patients receiving study drugs to determine whether they are immune-mediated.

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

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Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Table 6: Examples of Immune-Mediated Adverse Events

Body system affected	Events
Skin (mild-common)	pruritus or maculopapular rash; vitiligo
Skin (moderate)	follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet syndrome
Skin (severe-rare)	full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation
Endocrine	thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism, 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, myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure
Neurologic	encephalitis, meningitis, meningoradiculitis, meningoencephalitis

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

Recommendations for managing imAEs are detailed in Appendix 7.

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

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9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

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

9.1. Statistical Analysis

9.1.1. Randomization Methods

As discussed in Section 7.3.2, patients will be randomized using the IRT system for this study by stratified permuted block randomization.

9.1.2. Analysis Sets

The ITT Analysis Set includes all randomized patients. Patients will be analyzed according to their randomized treatment arm. This will be the primary analysis set for efficacy and HRQoL analyses.

The Per-Protocol (PP) Analysis Set includes all randomized patients who received ≥ 1 dose of the assigned study drug and had no critical protocol deviations. Critical protocol deviations will be determined and documented before the database lock for the primary analyses.

The Safety Analysis Set includes all randomized patients who received ≥ 1 dose of study drug. This will be the analysis set for the safety analyses.

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

The Immunogenicity Analysis Set includes all patients who received ≥ 1 dose of any component of study drug and for whom both baseline ADA and at least 1 postbaseline ADA result are available.

9.1.3. Patient Disposition

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

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

9.1.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of the ITT Population will be summarized using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, and time since advanced/metastatic disease diagnosis. Categorical variables include gender, ECOG Performance Status, geographical region, country, race, histological subtype, disease stage, metastatic site, and tobacco use.

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

9.1.5. Prior and Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report (CSR) for this protocol. Prior medications will be defined as medications that stopped before the day of first dose of study drug. Concomitant medications will be defined as medications that 1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or 2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose (as of the 30-day Safety Follow-up). Additional safety follow-up assessment of imAEs and relevant concomitant medications (ie, associated with an imAE or any new anticancer therapy) will be made by telephone or during a visit (see Appendix 1). These contacts will be made at approximately 60 and 90 days after the last dose of study drugs regardless of whether or not the patient starts a new anticancer therapy.

9.2. Efficacy Analyses

OS will be tested at a 1-sided alpha of 0.025. Only when the superiority of OS in the ITT Analysis Set is demonstrated will full alpha of 0.025 (1-sided) be sequentially shifted to the hypothesis testing of the secondary endpoints of PFS and ORR based on the data up to second interim analysis. The hypothesis test will be stopped at PFS if non-significant. Nominal p-values may be computed for other efficacy analysis but should be interpreted with caution.

9.2.1. Primary Efficacy Analysis

<u>OS in ITT Analysis Set</u>:

The null hypothesis (H_0) to be tested is:

H_0: OS in Arm A $\leq$ OS in Arm B

against the alternative hypothesis (H_1):

H_1: OS in Arm A > OS in Arm B

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The primary analysis of OS will be carried out once the targeted number of death events is reached. OS will be compared between ociperlimab + tislelizumab (Arm A) and pembrolizumab + placebo (Arm B) in a stratified log-rank test using pooled stratification factors of regions of enrollment (Asia versus non-Asia) and histology (squamous versus nonsquamous). A significance level of 1-sided alpha of 0.025 will be used in the OS testing.

In the absence of confirmation of death, patients will be censored at the date that the patient is last known to be alive. The median OS and 2-sided 95% CI using the method of Brookmeyer and Crowley will be summarized. The cumulative probability of OS at every 3 months including OS rate at 12 and 24 months, if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Standard error for survival rates will be calculated based on Greenwood's formula. Kaplan-Meier survival probabilities for each arm will be plotted over time.

The treatment effect will be estimated by fitting a Cox regression model to the OS times, including treatment arm as a factor and regions of enrollment and histology as strata. From this model, the hazard ratio (HR) of OS will be estimated and presented with a 2-sided 95% CI.

If patients in the US and Japan are enrolled based on local PD-L1 testing, supplementary analyses of OS may be carried out using stratified Cox regression model among all randomized patients with high PD-L1 expression (PD-L1 positive tumor cells ≥ 50%) as per the central laboratory using VENTANA PD-L1 (SP263) CDx Assay.

9.2.2. Secondary Efficacy Analysis

PFS by investigator per RECIST v1.1 will be estimated using the Kaplan-Meier (KM) method in the ITT Analysis Set. PFS will be censored at the last adequate tumor assessment if one of the following occurs by the time of analysis: absence of event, the event occurred after a new anticancer therapy is given, or the event occurred after two or more missing tumor assessments. For cases with missing baseline tumor assessment, a death occurring within 19 weeks from the reference start date will be considered a PFS event. Clinical or symptomatic progressions without supportive radiologic data will not be considered as PFS events.

The null hypotheses of no difference in PFS between 2 arms will be tested in a stratified log-rank test, stratified by region of enrollment (Asia versus non-Asia) and histology (squamous versus nonsquamous). The median PFS and 2-sided 95% confidence intervals (CI) using the method of Brookmeyer and Crowley will be summarized. The cumulative probability of PFS at every 3 months including PFS rate at 6 and 12 months, if estimable, will be calculated for each treatment arm and presented with 2 sided 95% CIs. Standard error for PFS rates will be calculated based on Greenwood's formula. Kaplan-Meier survival probabilities for each arm will be plotted over time.

Best overall response is defined as the best response per RECIST v1.1 recorded from randomization until data cut, progressive disease, or start of a new anticancer treatment. ORR is the percentage of patients whose best overall response is either CR or PR. The null hypotheses of no difference in ORR per RECIST v1.1 assessed by the investigators between ociperlimab + tislelizumab (Arm A) and pembrolizumab + placebo (Arm B) will be tested in a Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factors in the ITT Analysis Set. Patients with no postbaseline response assessment (for any reason) will be considered

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nonresponders. The 2-sided 95% CIs for the odds ratio in ORR will be calculated, as well as Clopper-Pearson 95% CIs of ORR, for each treatment arm.

DOR as assessed by the investigators will be summarized similarly to PFS in the responders receiving ociperlimab + tislelizumab (Arm A) or pembrolizumab + placebo (Arm B).

HRQoL is assessed via changes in EORTC QLQ-C30's global health status/QoL (GHS) and functional and symptom scale scores and single item scores; index score and symptoms measured by QLQ-LC13 and EQ-5D-5L dimension scale scores and Visual Analogue Scale (VAS). Observed values and changes from baseline will be summarized using descriptive statistics.

A mixed effect model analysis will be performed to assess clinically meaningful changes from baseline in the PRO endpoints (GHS and physical function scales, and symptoms of fatigue, dyspnea, coughing, hemoptysis, pain in chest, pain in arms/shoulders and peripheral neuropathy, and the index score of QLQ-LC13) at key assessment timepoints, ie, Cycles 5 and 7 for Treatment Arms A and B.

TTD will be analyzed using PRO endpoints. TTD between Treatment Arms A and B will be compared using the log-rank test and its Kaplan-Meier probabilities for each arm will be plotted over time.

9.2.3. Exploratory Efficacy Analysis

The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, PR, stable disease, and progressive disease) will be presented for the ociperlimab + tislelizumab (Arm A) and pembrolizumab + placebo (Arm B) treatment arms. DCR and CBR as assessed by the investigators will be analyzed similarly to ORR. Proportion of response categories with unconfirmed CR and PR may be presented as well. TTR will be summarized using descriptive statistics, such as mean, median, and standard deviation. Only patients who have achieved an objective response will be included in the analysis of TTR.

ORR, DCR, and CBR as assessed by investigators with a Clopper-Pearson 95% CI will be summarized in patients receiving tislelizumab (Arm C). The distribution of OS, DOR, and PFS as assessed by investigators in patients receiving tislelizumab will be analyzed based on the Kaplan-Meier method. The median and 95% CI using the method of Brookmeyer and Crowley will be calculated. TTR will be summarized descriptively.

To calculate PFS2, data from patients without disease progression after next line of treatment or death at the time of analysis will be censored at the last time known to be alive. Kaplan-Meier (KM) method as described in the PFS and OS analyses will be used in the analysis of PFS2.

Changes from baseline in scores of PGI-S at key assessment timepoints, ie, Cycles 5 and 7, will be calculated and scores of PRTSE will be collected at Cycles 5 and 7 in all 3 arms.

HRQoL for Arm C will be assessed via changes in EORTC QLQ-C30's global health status/QoL (GHS) and functional and symptom scale scores and single item scores; index score and symptoms measured by QLQ-LC13, and EQ-5D-5L dimension scale scores and VAS. Observed values and changes from baseline will be summarized using descriptive statistics.

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9.3. Safety Analyses

9.3.1. Extent of Exposure

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

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

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

9.3.2. Adverse Events

Verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA, version 22.0 or higher) terms and graded per NCI-CTCAE v5.0. TEAE is defined as an AE that has an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Only those AEs that were treatment emergent will be included in summary tables of TEAE. Immune-mediated AEs will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 90 days from the last dose of study drug, regardless of whether the patient starts a new anticancer therapy. If an imAE occurs outside of the above mentioned TEAE window, it will not be classified as a TEAE. All imAEs will be reported separately. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by System Organ Class and Preferred Term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 within a System Organ Class and Preferred Term, even if the patient experienced more than 1 TEAE within a specific System Organ Class and Preferred Term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to a study drug or with missing assessment of the causal relationship. SAEs, deaths, TEAEs with ≥ Grade 3 severity, 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 and serum chemistry) 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 provided. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; and n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline visit.

Laboratory parameters that are graded by NCI-CTCAE v5.0 will be summarized by NCI-CTCAE Grade. In the summary of laboratory parameters by NCI-CTCAE Grade,

parameters with NCI-CTCAE grading in both high and low directions (eg, glucose, potassium, and sodium) will be summarized separately.

9.3.4. Vital Signs

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

9.3.5. Pulmonary Function Test

Pulmonary function test results will be listed by patient.

9.4. Pharmacokinetic Analysis

Ociperlimab and tislelizumab 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. The results of any additional analyses will be reported separately from the main study report.

9.5. Immunogenicity Analyses

The immunogenicity results from patients treated with ociperlimab + tislelizumab and tislelizumab + placebo 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 allow and reported separately from the main study report.

9.6. Sample Size Consideration

The sample size calculation is driven by the primary efficacy analysis of OS in the comparison between ociperlimab + tislelizumab (Arm A) and pembrolizumab + placebo (Arm B) in the ITT Analysis Set. The number of events needed is based on the assumption of an exponential distribution. The 1-sided overall Type I error in the study is set at 0.025. Table 7 summarizes the statistical assumption and power in the sample size calculation. The initial number of patients planned in the study was 605 in Protocol Amendment Version 1.0 (Version 1.1 in Japan, Version 1.2.1 in Germany, and Version 1.4 in France), which included a randomization ratio of 5:5:1 (275, 275, and 55 patients in Arms A, B, and C, respectively). With the randomization ratio changed to 5:5:2 in Protocol Amendment Version 2.0 (Version 2.1 in Japan, Version 2.2 in Germany, and Version 2.3 in the US), the total number of patients in the study will increase by 55 patients (from 605 to 660). The randomization ratio update was implemented after Protocol Amendment Version 2.0 was finalized and approved at each participating site (ie, Version 2.1 in Japanese sites, Version 2.2 in German sites, and Version 2.3 in the US sites); therefore, it is estimated that approximately 300 patients will be randomized with a randomization ratio of 5:5:1 and approximately 360 patients will be randomized with a randomization ratio of 5:5:2. The final total number of patients in Arms A, B, and C is estimated to be approximately 286, 286, and 88,

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respectively. It is noted that the randomization ratio between Arm A and Arm B will remain unchanged.

Assuming an approximately 5% dropout rate (dropout hazard rate of 0.003) for OS, approximately 572 patients will be enrolled to Arms A and B in order to observe the targeted OS events at the defined time periods as shown in Table 7. The primary analyses will be performed when the target number of events is observed. Two interim analyses are planned after 65% and 80% of the total planned death events have occurred in the 2 treatment arms combined.

Table 7: Hazard Ratio and Median OS Assumptions, Number Of Events, Alpha and Power in the Primary Hypothesis Tests

HR	Median in Arm A (months)	Median in Arm B (months)	Number of events	Alpha	Power
0.70	28.6	20	379	0.025	93%

Abbreviations: HR, hazard ratio; OS, overall survival.

In addition, approximately 88 patients in the tislelizumab + placebo arm (Arm C) will be enrolled to assess antitumor activities of tislelizumab.

9.7. Interim Analyses

Two interim analyses are planned. The first interim analysis for futility will use the Hwang-Shih-DeCani beta spending function with the gamma parameter set at -10. It will be conducted after approximately 245 deaths (65% of total target deaths) have been observed, which will occur approximately 37 months after the first patient is randomized. An administrative alpha=0.0001 will be spent at first interim analysis. The second interim analysis for efficacy will use the Lan-DeMets approach to O'Brien-Fleming spending function using the remaining alpha=0.0249. It will be conducted after approximately 303 deaths (80% of total target deaths) have been observed, which will occur approximately 44 months after the first patient is randomized. The final analysis will be performed after approximately 379 death events have been observed, which will occur approximately 58 months after the first patient is randomized. Results from the two interim analyses will be reviewed by an IDMC.

Efficacy and futility stopping boundaries in p-value and Z score are shown in Table 8. The boundaries will be updated according to the actual numbers of events in the interim and final analyses, using the above pre-specified spending function.

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Table 8: Efficacy and Futility Stopping Boundaries (in p-value and Z score) of Primary Analysis of OS

Analysis	Time (mo)	Number of events	p-Value [a] (Z score) for efficacy	p-Value [a] (Z score) for futility	Approximate HR threshold for efficacy	Approximate HR threshold for futility	Cumulative probability of crossing under H_1
Interim analysis 1 (IA1)	37	245	0.0001 (3.719)	0.5294 (-0.074)	0.619	1.010	0.175
Interim analysis 2 (IA2)	44	303	0.0123 (2.248)		0.771		0.803
Final analysis (FA)	58	379	0.0214 (2.026)		0.811		0.930

Abbreviations: FA, final analysis; H_1, alternate hypothesis; HR, hazard ratio; IA1, first interim analysis; IA2, second interim analysis; mo, month; OS, overall survival.

[a] 1-sided

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10. STUDY COMMITTEES AND COMMUNICATION

10.1. Independent Data Monitoring Committee

Regular safety monitoring (at least every 6 months) and efficacy monitoring will be performed by an IDMC. The first IDMC safety review will occur when 30 patients have been randomized to study treatment and have been on treatment for ≥ 1 month in order to determine if the proposed dosing schedule of tislelizumab and ociperlimab is safe and tolerable. The second safety monitoring and review will be conducted as determined by the IDMC but no later than 6 months after the first evaluation. Thereafter, IDMC will review data approximately every 6 months. The IDMC may recommend study modification, including termination of the study due to safety and/or efficacy concerns. The function and membership of the IDMC will be described in the IDMC charter.

In addition to the planned IDMC review(s), ad hoc reviews may be performed based on new information.

Following IDMC review and discussion, the sponsor will make all final decisions regarding any changes in study conduct. Please see the details in the IDMC charter.

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11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The investigator (and, in Japan, the head of the study center) 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 (ICH) GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency (in Japan, the study monitor must have direct access to all relevant documents in order to verify the data recorded in the eCRFs and other documents for consistency).

The study 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 study monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study 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 (and, in Japan, the head of the study center) is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor or its designee immediately. The investigator (and, in Japan, the head of the study center) agrees to provide access to records, facilities, and personnel to representatives of a regulatory agency or the sponsor for the effective conduct of any inspection or audit.

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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 (CRO'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's study monitors, representatives, and collaborators; and IRB/IEC members to inspect all facilities and records relevant to this study.

12.4. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient drug dispensation records, and returned or destroyed study product. Dispensation records will document quantities received from 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 sponsor's 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.

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

Drug Accountability in Japan Only

The head of the study center has overall responsibility for the investigational drugs. Tasks will be delegated to a qualified designee (eg, the investigational drug manager and a pharmacist are desirable) who is adequately trained in the study protocol. This delegation must be documented in the applicable study delegation of authority form.

An investigational drug will not be dispatched to the study center until the sponsor or designee has received all required documents from the study center in accordance with the applicable regulatory requirements and relevant standard operating procedures. Upon receipt, the study center's investigational drug manager who is assigned by the head of the study center is responsible for ensuring that all investigational drug received at the center is inventoried and accounted for throughout the study. A copy of the shipping documents must be maintained for the investigator's records.

After sufficient amounts of the investigational drug will be shipped to the study center, the investigational drug manager will acknowledge receipt of the investigational drug, documenting shipment content and condition. Accurate records of all investigational dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigational drug manager will dispense the investigational drug only to the study staff included in this study following the procedures set out in the study protocol. The investigational drug will be administered to the patient according to protocol. The investigational drug manager should keep a current record of the inventory and dispensing of all clinical supplies. All dispensed/administered medication will be documented in the patient's source and/or other investigational drug record. The investigational drug manager is also responsible for ensuring the retrieval of all study supplies from subjects.

No investigational product stock or returned inventory from the sponsor may be removed from the study center where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its designee (ie, CRO) will be permitted access to review the supply storage and distribution procedures and records.

At the end of the study, empty/used investigational drug vials or ampules may be destroyed at the center or a local facility. In this case, records identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor. Destruction of the investigational drug must be in accordance with local, state, and national laws.

If the sponsor has not provided written agreement for destruction at the center or a local facility, then, at the end of the study or as instructed by the sponsor, empty/used investigation drug packaging are to be sent to the sponsor or its designee. All unused drug/packaging should be returned to the sponsor (or designee). The investigational drug being returned to the sponsor (or designee) must be counted and verified by the investigational drug manager and the sponsor (or designee).

Based on entries in the center drug accountability forms, it must be possible to reconcile investigational drug delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

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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 ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the patient. The study will also comply with the requirements of the ICH 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 any relevant supporting information must be submitted to and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC. 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 (in Japan, to the head of the study center) annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC (in Japan, the head of the study center submits the summaries of the status to IRB/IEC for their review and approval). Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments (in Japan, investigators are to inform the head of the study center of any protocol amendments for review and approval by the IRB/IEC). 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 (in Japan, the head of the study center). Investigators may receive written investigational new drug (IND) safety reports or other safety-related communications from the sponsor (in Japan, investigators may submit IND safety reports to the head of the study center, who in turn submits them to the IRB/IEC for its review and approval). 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 the patient's participation in the study. For sites in Germany only, signature by a legally authorized representative is not valid; only the patient may sign and date the ICF. 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, if permitted by local regulations, 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 dataset transmitted to any sponsor location.

Patient medical information obtained during this study is confidential and may be disclosed only 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.

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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 US Food and Drug Administration (FDA), the China National Medical Products Administration (NMPA), and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator must ensure 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 the Investigator's Brochures, this protocol, eCRFs, the IND, 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 is executed, and that contract includes confidentiality provisions inconsistent with this section, that contract's provisions shall apply to the extent that 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 the clinical investigators, and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure financial interests and arrangements of the clinical investigators with the sponsor that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

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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 electronic signature of the investigator or designee must be provided in the EDC system to attest to its accuracy, authenticity, and completeness.

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

14.1.3. Data Management/Coding

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

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

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

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

The AE verbatim descriptions (the investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA by Lowest Level Term, Preferred Term, and primary System Organ Class (SOC). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

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14.2. Data Integrity and In-house Blinding

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

14.3. Study Records Retention

The investigator (and, in Japan, the investigational center) 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 (and/or, in Japan, the head of the study center's) study file, and/or 2) patient clinical source documents.

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

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

Following closure of the study, the investigator must maintain all study records in a safe and secure location (in Japan, the investigator and the head of the study center [or designee] must maintain all study records including IRB/IEC records in a safe and secure location according to Japanese-GCP). The records must be maintained to allow easy and timely retrieval when needed (eg, audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure 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 (and, in Japan, the head of the study center [or designee]) of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements, local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator (in Japan, the head of the study center [or designee]) must notify the sponsor of any changes in the archival arrangements, including but not limited to the following: archival at

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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 (in Japan, the head of the study center [or designee]) cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator (in Japan, the head of the study center [or designee]) and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator (in Japan, the head of the study center [or designee]) 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.

Note, for Japan only: The sponsor and/or its designee (CRO) shall also retain all records for required period in accordance with Japanese-GCP. Unless otherwise specified, the retention period will default to 15 years. All documents can be retained for a longer period, as needed.

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

14.4. Protocol Deviations

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations and shall report all protocol deviations to 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 ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

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

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

14.6. Study and Study Center Closure

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

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

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

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

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

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

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14.7. Information Disclosure and Inventions

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

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

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

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

These restrictions do not apply to:

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

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

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15. REFERENCES

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Prescreening	Screening [a]	Treatment cycles				End-of-Treatment Visit [b]	Safety Follow-up [c]	Survival Follow-up [d]
			Cycles 1 to 3 (every 21 days)			Cycle 4 and subsequent cycles (every 21 days)			
Days (window)	**-56 to -28**	**-28 to ~ -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**Within 7 days after permanent treatment discontinuation**	**30 (± 7), 60, 90, and (for pregnancy testing) 120 days after last dose**	**Every 3 months (± 14 days)**
Prescreening informed consent [a]	X								
Main 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		
Physical examination [h]		X	X			X	X		
Chest X-ray (in Japan only) [ff]			X (Cycle 2 only)			As clinically indicated			

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Assessment	**Prescreening**	**Screening [a]**	**Treatment cycles**				**End-of-Treatment Visit [b]**	**Safety Follow-up [c]**	**Survival Follow-up [d]**
			Cycles 1 to 3 (every 21 days)			**Cycle 4 and subsequent cycles (every 21 days)**			
Days (window)	**-56 to -28**	**-28 to ~ -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**Within 7 days after permanent treatment discontinuation**	**30 (± 7), 60, 90, and (for pregnancy testing) 120 days after last dose**	**Every 3 months (± 14 days)**
Sialylated carbohydrate antigen KL-6 (in Japan only) [gg]		X	X			As clinically indicated			
Peripheral capillary oxygen saturation (SpO2) measurement (in Japan only) [gg]		X	X			As clinically indicated			
ECOG Performance Status		X	X			X	X		
12-lead ECG [i]		X	As clinically indicated				X		
Adverse events [j]		X	X	X[k]	X[k]	X	X	X	
Concomitant medications		X	X	X[k]	X[k]	X	X	X	
Hematology[l]		X	X	X	X	X	X		
Serum chemistry [l]		X	X	X	X	X	X		
CK and CK-MB [m]		X	X	X	X	X	X		
Coagulation parameters[l]		X	X			X	X		
Urinalysis [l]		X	As clinically indicated						
Pregnancy test [n]		X	X			X	X	X	

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Assessment	**Prescreening**	**Screening** [a]	**Treatment cycles**				**End-of-Treatment Visit** [b]	**Safety Follow-up** [c]	**Survival Follow-up** [d]
			Cycles 1 to 3 (every 21 days)			**Cycle 4 and subsequent cycles (every 21 days)**			
Days (window)	**-56 to -28**	**-28 to ~ -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**Within 7 days after permanent treatment discontinuation**	**30 (± 7), 60, 90, and (for pregnancy testing) 120 days after last dose**	**Every 3 months (± 14 days)**
Thyroid function [o]		X	X (Cycle 3 only)			X (every 2 cycles)	X		
HBV, HCV, and HIV tests [p]		X	As clinically indicated (HBV/HCV only)						
Pulmonary function tests [q]		X	As clinically indicated						
Pharmacokinetics [r]			X			X	X		
Antidrug antibodies [s]			X			X	X		
Tumor assessment [t]		X	Every 9 weeks (± 7 days) from randomization for the first 52 weeks, then every 12 weeks (± 7 days)						X[t]
Archival tumor tissue [u]	X								
Fresh tumor tissue [v]	X						X		
Collection of *EGFR*/*ALK*/BRAF V600E/*ROS1* status (local PD-L1 testing, if applicable, in the US and Japan only) [w]	X								

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Assessment	Prescreening	Screening [a]	Treatment cycles				End-of-Treatment Visit [b]	Safety Follow-up [c]	Survival Follow-up [d]
			Cycles 1 to 3 (every 21 days)			Cycle 4 and subsequent cycles (every 21 days)			
Days (window)	**-56 to -28**	**-28 to ~ -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**Within 7 days after permanent treatment discontinuation**	**30 (± 7), 60, 90, and (for pregnancy testing) 120 days after last dose**	**Every 3 months (± 14 days)**
Blood collection for biomarker analysis [x]			X				X		
Tislelizumab administration [y]			X			X			
Ociperlimab administration [z]			X			X			
Pembrolizumab administration [aa]			X			X			
Placebo infusion [bb]			X			X			
EORTC QLQ-C30, QLQ-LC13, and EQ-5D-5L [cc]			X			X	X		
PGI-S [dd]			X			X			
PRTSE [ee]						X			
Survival status									X

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; CK, creatine kinase; CK-MB, creatine kinase cardiac muscle isoenzyme; CT, computed tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; ECG, electrocardiogram; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EGFR, epidermal growth factor receptor; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT, End-of-Treatment Visit; EQ5D-5L, 5-Level Euroqol 5 Dimensions; EVs, extracellular vesicles; FEV1, forced expiratory volume; FFPE, formalin-fixed paraffin-embedded; FT3, free triiodothyronine; FT4, free thyroxine; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV,

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human immunodeficiency virus; ICF, informed consent form; IEC, Independent Ethics Committee; imAE, immune-mediated adverse event; IRB, Institutional Review Board; IRT, Interactive Response Technology; KL-6, Krebs von den Lungen-6; MRI, magnetic resonance imaging; MSI, microsatellite instability; NCI-CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; PET, positron emission tomography; PGI-S, patient global impression of severity; PK, pharmacokinetic(s); PRTSE, patient reported treatment-related side-effect burden; QLQ-LC13, Quality of Life Questionnaire Lung Cancer 13; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, Version 1.1; ROS1, ROS proto-oncogene 1; SAE, serious adverse event; SpO2, peripheral capillary oxygen saturation; TIGIT, T cell immunoglobulin and ITIM domain; TMB, tumor mutation burden; TSH, thyroid-stimulating hormone; v, version.

[a] 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 randomization may be used for Screening assessments rather than repeating such tests. Prescreening procedures should be performed within 28 days of the screening period, unless the prescreening and screening periods are combined, in which case, all prescreening and screening procedures should be performed within 28 days of randomization.

[b] The EOT Visit will be conducted within 7 days after the investigator decides to permanently discontinue study treatment (Section 3.5). If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT Visit, tests need not be repeated.

[c] A Safety Follow-up Visit at 30 days (± 7 days) after the last dose of study drug is required to assess AEs and concomitant medications, unless the time window overlaps the time window of the EOT Visit; the Safety Follow-up Visit may be a telephone call or an on-site visit if laboratory assessments are necessary. Additional safety follow-up assessment will be made by telephone or, if a pregnancy test is also required, during a visit and will include assessment of imAEs and concomitant medications if appropriate (ie, if associated with an imAE or a new anticancer therapy). These contacts will be made at 60 days (± 14 days for telephone; ± 3 days for visit) and 90 days (± 14 days for telephone; ± 3 days for visit) after the last dose of study drugs regardless of whether the patient starts a new subsequent anticancer therapy. For women of childbearing potential (see Appendix 9), an additional visit will occur at 120 days (± 3 days) after the last dose of study drugs. If a patient reports a suspected imAE at a safety follow-up telephone call, the investigator should arrange an unscheduled visit if further assessment is indicated. Patients who discontinue study treatment before disease progression will need to undergo tumor assessments as outlined in Section 7.6.

[d] 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 EOT Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or study termination by sponsor. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from survival follow-up.

[e] Patients will be randomized in a 5:5:2 ratio into either the tislelizumab and ociperlimab infusion (Arm A), pembrolizumab and placebo infusion (Arm B), or tislelizumab and placebo infusion (Arm C) via IRT. All patients are required to receive study treatment within 2 business days of randomization.

[f] Includes age or year of birth, sex, 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. Pre-existing AEs at baseline should be recorded as medical history.

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

[h] A complete physical examination is required at Screening while subsequent visits entail limited, symptom-directed physical examinations (as detailed in Section 7.5.2). In Japan, an exception is made for chest auscultation, which is required prior to dosing on Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1.

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

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[j] The AEs and laboratory abnormalities will be graded per NCI-CTCAE v5.0. All AEs will also be evaluated for seriousness. After the main ICF has been signed, but before the first administration of study drug, only SAEs should be recorded. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of all study drug(s) or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or non-serious) should be reported until 90 days after the last dose of study drugs, regardless of whether or not the patient starts a new anticancer therapy. 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.

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

[l] Local or central laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2. If laboratory tests at Screening are not performed within 7 days of Day 1 of Cycle 1, these tests should be repeated and reviewed before randomization. Hematology and serum chemistry (including liver function tests) will be performed weekly for the first 3 cycles, at the beginning of each subsequent cycle, and at the EOT Visit (data collected as specified in Appendix 2). After Cycle 1, results are to be reviewed within 48 hours before study drug administration. If selected laboratory assessment results will not be available prior to dosing despite the site's best efforts, consultation with a medical monitor is required to determine if dosing can safely proceed. Coagulation assays will be performed at Screening, on Day 1 of each cycle, and at the EOT Visit. 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.

[m] All patients will have CK and CK-MB testing at Screening, repeated at all scheduled visits during the first 3 treatment cycles, all predose assessments from Cycle 4 onwards, and at the EOT Visit. If CK-MB fractionation is not available, troponin I and/or troponin T may be tested instead. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[n] Pregnancy tests will be performed for women of childbearing potential, including women who have had a tubal ligation (see Appendix 9). A urine or serum pregnancy test must be performed and documented as negative ≤ 7 days before randomization. Urine pregnancy tests will be performed at each visit before dosing, at the EOT Visit, and at each safety follow-up visit, including 120 days after the last dose of study drugs. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

[o] Analysis of FT3, FT4, and TSH will be performed by a local or central laboratory. Thyroid function tests will be performed at Screening, every 2 cycles starting on Day 1 of Cycle 3 (ie, Day 1 of Cycles 3, 5, and 7, etc.), and at the EOT Visit.

[p] Testing will be performed by a local or central laboratory at Screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and HIV serology (antigen and/or antibodies), unless the patient's HIV status is already known. Viral load assessment (HBV DNA or HCV RNA) will be performed only when HBsAg or HCV antibody is positive, respectively. 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, and 13, etc). Blood samples may be collected on Day 1 of Cycle 1 before dosing of study drug, stored, and may be analyzed if patients develop hepatic AEs. The collection and storage of blood samples for patients with detectable HBV DNA or HCV RNA at Screening will be organized by the central lab if sites do not have local capabilities. Sites that are unable to collect such samples will make every effort to perform a comprehensive diagnostic work up in the event patients with detectable HBV DNA or HCV RNA at Screening develop hepatic AEs.

[q] Pulmonary function testing including spirometry and assessment of oxygenation, either pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity, are to be performed for all patients during the screening period to assist the determination of suitability for the study. Respective test results will be evaluated by the medical monitor during eligibility review. For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, FEV1 < 60% or DLCO (if performed) < 60% of age and sex adjusted predicted performance levels (Pellegrino et al 2005), the medical monitor needs to be consulted to confirm eligibility. Tests may be repeated as clinically indicated while on study.

[r] Procedures for collection of blood samples to evaluate PK are described in the laboratory manual. Predose samples (within 60 minutes before starting infusion) are required to be collected on Day 1 of Cycles 1, 2, 5, 9, and 17. Postdose samples (within approximately 30 minutes after completing study drug infusion) are

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required to be collected on Day 1 of Cycles 1 and 5. An additional PK sample is required to be collected at the EOT Visit. Should a patient present with any ≥ Grade 3 imAE, an additional blood PK sample may be taken. These tests are required when it is allowed by local regulations/IRBs/IECs.

[s] Blood used to test for anti-tislelizumab or anti-ociperlimab antibodies will be collected within 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 5, 9, and 17 and at the EOT Visit. All samples should be collected at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/IECs.

[t] Radiological images captured as standard of care before obtaining written informed consent and ≤ 28 days before randomization 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). Imaging of the brain (preferably MRI) is required for all patients during screening. Bone scan or PET is required if clinically indicated. During the study, tumor imaging will be performed every 9 weeks (± 7 days) from randomization for the first 52 weeks and then every 12 weeks (± 7 days) based on RECIST v1.1. Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held; they should not be adjusted for possible 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 experiences disease progression or death, withdraws consent, is lost to follow-up, or until the study terminates, whichever occurs first. See also Section 7.6.

[u] Patients are required to provide archival tumor tissues during prescreening if available (FFPE blocks or approximately 6 to 15 freshly cut unstained slides) for prospective analysis of PD-L1 status and for retrospective analysis of other biomarkers (Section 7.8). A minimum of 6 additional slides should be provided if central EGFR testing is necessary (Section 3.2 and Section 7.1). (Note, for sites in mainland China: Tissues will be obtained to test the expression of PD-L1, TIGIT, CD226, CD155, CD112, GEP, TMB, gene mutations, MSI, and TILs at baseline and at disease progression).

[v] In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at baseline (within 56 to 28 days before randomization or within 28 days of randomization if prescreening and screening are combined) is required. See Section 7.8 for more information. Patients who have progressive disease will be asked to provide an optional biopsy at the EOT Visit for the assessment of mechanisms of resistance (written informed consent is required before obtaining an optional fresh tumor biopsy).

[w] *EGFR*, *ALK,* BRAF V600, and *ROS1* mutational status, if known, will be collected. Patients with nonsquamous NSCLC and unknown EGFR mutational status will be required to have a tissue-based EGFR test performed either locally or centrally or an EBUS-TBNA–based EGFR test locally at Prescreening. Note, for the US and Japan only: Local PD-L1 testing may be used for patient randomization purposes, in which case, the local PD-L1 testing results will be collected in the eCRF. For all sites, local PD-L1 testing results, if available for patients who are randomized based on central PD-L1 testing results, may be captured in the eCRF if patients consent to this information being collected.

[x] Blood samples will be taken at baseline (predose on Day 1 of Cycle 1), predose on Day 1 of Cycle 3, and at the EOT Visit after disease progression (10 mL each timepoint) to evaluate TMB, MSI, mutational profiles, and EVs, as well as other biomarkers in blood. Written patient consent is required for blood sample collection. (Note, for sites in mainland China: Blood-based biomarkers, including TMB, MSI, gene mutational profiles, and EVs will be explored in the blood samples.)

[y] Tislelizumab will be given intravenously once every 3 weeks. On Day 1 of Cycles 1 and 2, tislelizumab will be delivered for ≥ 55 minutes. If well tolerated, subsequent infusions can be administered for ≥ 25 minutes. The first dose will be given on Cycle 1 Day 1 and subsequent dosing will continue on scheduled 21-day intervals. Note: Tislelizumab must not be concurrently administered with any other drug. Patients must be monitored after study treatment infusions are complete as shown in Table 2.

[z] Ociperlimab will be given intravenously once every 3 weeks. On Day 1 of Cycles 1 and 2, ociperlimab will be delivered for ≥ 55 minutes. If well tolerated, subsequent infusions can be administered for ≥ 25 minutes. The first dose will be given on Cycle 1 Day 1 and subsequent dosing will continue on scheduled 21-day intervals. Ociperlimab infusion must always occur after the infusion of tislelizumab has been completed. Patients must be monitored after study treatment infusions are complete as shown in Table 2.

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[aa] Pembrolizumab will be given intravenously once every 3 weeks. On Day 1 of Cycles 1 and 2, pembrolizumab will be delivered for ≥ 55 minutes. If well tolerated, subsequent infusions can be administered for ≥ 25 minutes. The first dose will be given on Cycle 1 Day 1 and subsequent dosing will continue on scheduled 21-day intervals. Patients must be monitored after study treatment infusions are complete as shown in Table 2.

[bb] Placebo infusions will be given intravenously once every 3 weeks in Arms B and C. On Day 1 of Cycles 1 and 2, placebo infusions will be delivered for ≥ 55 minutes. If well tolerated, subsequent infusions can be administered for ≥ 25 minutes. The first dose will be given on Cycle 1 Day 1 and subsequent dosing will continue on scheduled 21-day intervals. Placebo infusions must always occur after the infusions of pembrolizumab or tislelizumab have been completed. Patients must be monitored after study treatment infusions are complete as shown in Table 2.

[cc] To be completed before any clinical activities during applicable on-study dosing site visits. EORTC QLQ-C30, QLQ-LC13, and EQ-5D-5L will be completed at baseline (Day 1 of Cycle 1), at every other cycle through Cycle 13, then every 4 cycles thereafter, and at the EOT Visit.

[dd] To be completed before any clinical activities during applicable on-study dosing visits. PGI-S will be completed at baseline (Cycle 1 Day 1), Cycle 5 Day 1, and Cycle 7 Day 1.

[ee] To be completed before any clinical activities during applicable on-study dosing visits. PRTSE will be completed at Cycle 5 Day 1 and Cycle 7 Day 1.

[ff] In Japan only, chest x-rays will only be required predose on Cycle 2 Day 1. After Cycle 3 Day 1, chest x-rays will be performed if clinically indicated.

[gg] In Japan only, sialylated carbohydrate antigen KL-6 and peripheral capillary oxygen saturation (SpO2) measurements are required at Screening and prior to dosing on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1. After Cycle 3 Day 1, tests will be performed if clinically indicated. If the screening KL-6 testing was performed ≤ 7 days before the planned first dose (Cycle 1 Day 1) and the results have been reviewed, then a Cycle 1 Day 1 KL-6 is not required to be performed. As for Cycle 2 Day 1 and Cycle 3 Day 1, KL-6 results may be performed during the Cycle 1 Day 15 and Cycle 2 Day 15 visits respectively if the Cycle 2 and Cycle 3 KL-6 results are not expected to be available prior to dosing on these visits.

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APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

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

Abbreviations: CK-MB, creatine kinase cardiac muscle isoenzyme.

[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] Calcium values will be corrected for patients with hypoalbuminemia. Calcium correction should be performed according to the following formula: Corrected Calcium [in mmol/L] = Total Calcium [in mmol/L] + (0.02 x (40-Albumin [in g/L]).

[c] Cardiac enzyme testing has been added to monitor for potential event of immune-related 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**.**

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

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

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

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

Source: Eisenhauer et al 2009.

Definitions

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

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

Measurable Disease

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

- 10 mm by computed tomography (CT) and magnetic resonance imaging (MRI) (no less than double the slice thickness and a minimum of 10 mm). Assumes a scan slice thickness no greater than 5 mm.
- 10 mm caliper measurement by clinical 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 scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease

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

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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 nonmeasurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if 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 organs, but in addition should be those that lend themselves to reproducible repeated measurements.

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

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

Nontarget Lesions

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

Guidelines for Evaluation of Measurable Disease

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

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

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.
- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date, and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in

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the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

Response Criteria

Evaluation of Target Lesions

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

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- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report form may be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
- Target lesions that become "too small to measure." While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure."
  When this occurs, it is important that a value be recorded on the electronic case report form (eCRF). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially nonreproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that measurement should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Evaluation of Nontarget Lesions

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

- CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits

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- PD: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: The appearance of one or more new lesions is also considered progression.)
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.
- When the patient has only nonmeasurable disease: This circumstance arises in some phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept applies here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).
- Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

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

A lesion identified on a follow-up trial in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain scan

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- Timepoint Response
- It is assumed that at each protocol specified time point, a response assessment occurs. The following table provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline:

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

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When patients have nonmeasurable (therefore nontarget) disease only, the following table is to be used:

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	SD (Non-CR/non-PD)
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study drug treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the 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 best overall response is determined once all the data for the patient is known.

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

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

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

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In trials where confirmation of response is required, repeated "NE" (not evaluable) time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

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

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

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

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

Confirmation of Measurement/Duration of Response

Confirmation

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

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

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Duration of Overall Response

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

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

Duration of Stable Disease

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

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

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

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APPENDIX 5. PREEXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

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

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

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

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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.

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APPENDIX 7. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

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

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

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

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

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

Immune-Mediated Toxicity	Diagnostic Evaluation Guideline
Thyroid Disorders	Scheduled and repeated thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss, and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath, or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including DLCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.

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

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

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

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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 is required.
- Immune-mediated AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice, and contact the study medical monitor.
- For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study medical monitor.
- Steroid dosages in the table below are for oral or intravenous methylprednisolone. 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.
- Study drugs must be permanently discontinued for any onset of Grade 4 or recurrent Grade 3 imAEs.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management (All Arms)
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 both study drugs in cases with systemic symptoms.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management (All Arms)
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with comorbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1. Alternative text for France only: For Grade 3: Hold both study drugs; resume both study drugs when resolved/improved to Grade 0-1. For recurrent Grade 3: Discontinue both study drugs. For Grade 4: Discontinue both study drugs.
Hypophysitis	**1-2** Mild-moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4.	For Grade 1: Continue study treatment. For Grade 2: Hold study treatment until controlled by hormone replacement.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management (All Arms)
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse intravenous methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinologist's advice.	Hold both study drugs. Consider resuming once controlled with hormone replacement and improved to ≤ Grade 2, after corticosteroid taper (if indicated). Otherwise, discontinue treatment. Alternative text for France only: For Grade 3: Hold both study drugs; resume when resolved/improved to Grade 0-1. 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 both study drugs until appearance improves and cause is determined.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management (All Arms)
	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 both study drugs. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue both study drugs if symptoms persist with corticosteroid treatment or for recurrent Grade 2 pneumonitis (For Japan only, discontinue both study drugs if symptoms persist with corticosteroid treatment or if the event recurs upon reintroduction of study treatment).
	3-4 Severe or life-threatening symptoms: breathless at rest	Admit to a hospital and initiate treatment with intravenous methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for *Pneumocystis* infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue both study drugs.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management (All Arms)
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 both study drugs; resume both study drugs when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening symptoms, or Grade 3 or 4 encephalitis, or Guillain-Barré syndrome	Initiate treatment with oral prednisolone or intravenous methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue both study drugs.
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 (nonenteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks. Consider endoscopy if symptoms are recurring.	Hold both study drugs; resume both study drugs when resolved/improved to baseline grade.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management (All Arms)
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA Class III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Hold both drugs; retreatment with both study drugs may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor. Added text for France only: For recurrent Grade 3: Discontinue both study drugs.
	4 Life-threatening symptoms		Discontinue both study drugs.
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.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management (All Arms)
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis	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: intravenous methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold both study drugs. Re-treat with both study drugs when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor. Added text for France only: For recurrent Grade 3: Discontinue both study drugs.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment) or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis. Added text for France only: including Stevens-Johnson syndrome (all grades), and toxic epidermal necrolysis.	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue both study drugs.
Hepatitis	**1** ALT or AST > ULN to 3 x 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 both study drugs if LFTs are worsening until improvement is seen.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management (All Arms)
	2 ALT or AST 3-5 x ULN	Recheck LFTs every 48-72 hours. For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days, then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold both study drugs; treatment with both study drugs may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST 5-20 x ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate intravenous methylprednisolone 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. Alternative text for France only: If ALT or AST ≤ 8 x ULN or total bilirubin ≤ 5 x ULN: Hold study treatment until improved to baseline grade; reintroduce only after discussion with the study medical monitor. If ALT or AST > 8 x ULN or total bilirubin > 5 x ULN: Discontinue study treatment. For recurrent Grade 3: Discontinue study treatment.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management (All Arms)
	4 ALT or AST > 20 x ULN	Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue both study drugs.
	Worsening LFTs despite steroids: • If on oral prednisolone, change to pulsed intravenous methylprednisolone. • If on intravenous methylprednisolone, add mycophenolate mofetil (MMF) 500 to 1000 mg twice a day. • If worsens on MMF, consider addition of tacrolimus. Duration and dose of steroid required will depend on severity of event.		
Nephritis	**1** Creatinine 1.5 x baseline or > ULN to 1.5 x ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5-3 x baseline or > 1.5-3 x ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate 1-2 mg/kg/day prednisolone or equivalent and taper over at least 4 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.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management (All Arms)
	3 Creatinine > 3 x baseline or > 3-6 x ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. Initiate intravenous methylprednisolone 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. Added text for France only: For recurrent Grade 3: Discontinue study treatment.
	4 Creatinine > 6 x ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold both study drugs until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1. Added text for France only: For recurrent Grade 3: Discontinue study treatment.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management (All Arms)
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1. Added text for France only (split Grade 3 and 4): Discontinue study treatment.
Ocular Toxicity	**1** Asymptomatic eye examination/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold both study drugs t 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 ≥ 4 weeks.	Hold both study drugs until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor. Added text for France only: For recurrent Grade 3: Discontinue study treatment.
	4 Blindness (at least 20/200) in the affected eyes	Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over ≥ 4 weeks.	Discontinue both study drugs
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management (All Arms)
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2 and taper over ≥ 4 weeks.	Hold both study drug; reintroduce both study drugs only after discussion with the study medical monitor. Added text for France only: For recurrent Grade 3: Discontinue study treatment.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue both study drugs.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment, manage as a Grade 3 event.	Continue treatment or, if symptoms continue to worsen, hold both study drugs 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 ≥ 4 weeks.	Hold both study drugs unless improved to Grade 0-1; reintroduce both study drugs only after discussion with the study medical monitor. Added text for France only: For recurrent Grade 3: Discontinue study treatment.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management (All Arms)
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improve to Grade 2 and taper over ≥ 4 weeks.	Hold both study drugs until improved to Grade 0-1. Added text for France only: For recurrent Grade 3: Discontinue study treatment.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider intravenous corticosteroids if not contraindicated by infection.	Discontinue both study drugs.
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 ≥ 4 weeks.	Hold both study drugs until improved to Grade 0-1.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management (All Arms)
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus intravenous methylprednisolone 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 ≥ 4 weeks.	For Grade 3: Hold study treatment until improved to Grade 0-1. Discontinue upon any evidence of myocardial involvement. Added text for France only: For recurrent Grade 3: Discontinue both study drugs. For Grade 4: Discontinue both study drugs.
Myocarditis [a]	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing and including ECG, cardiac echo/MUGA, and/or other interventions per institutional guidelines; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2.	Hold both study drugs. If a diagnosis of myocarditis is confirmed and considered immune-mediated, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart study drugs unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or intravenous methylprednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of	
	3 Severe symptoms with mild exertion		Hold study treatment. If a diagnosis of myocarditis is

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management (All Arms)
	4 Life-threatening	cardiac failure according to local guidelines. If no immediate response, change to pulsed doses of methylprednisolone 1 g/day and add MMF, infliximab, or anti-thymocyte globulin.	confirmed and considered immune related, permanently discontinue study treatment. Alternative text for France and Germany only: Discontinue study treatment.
Other immune-mediated adverse events	**≤ 2**	Clinical management per local guideline based on adverse event type and severity.	Continue study treatment.
	3		Hold study treatment until improved to Grade 0-1. For recurrent Grade 3: Discontinue study treatment.
	4		Discontinue study treatment.

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

[a] If clinically significant cardiac enzyme abnormalities are detected during laboratory assessment and serial cardiac enzyme assessments pose logistical hardship for the patient, then patient hospitalization should strongly be considered until immune-mediated myocarditis has been ruled out.

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

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

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

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

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

where:

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

κ is 0.7 for 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

Cockcroft and Gault Equation

Creatinine Clearance (CrCl) = [((140-age) x weight)/(72 x Scr)] x 0.85 if female (Cockcroft and Gault 1976).

Note: CrCl is expressed in mL/min, age is expressed in years, weight is expressed in kilograms, and S_{cr} is expressed in mg/dL.

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APPENDIX 9. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

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

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

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

Contraceptive Methods Allowed in Japan:

- The following methods are approved or permitted in Japan:
  - Intrauterine devices (IUD, all types) or intrauterine hormone releasing systems (IUS)

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  - Orally combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation
- Other acceptable contraception methods include:
  - Bilateral tubal occlusion
  - Vasectomized partner
  - Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment)
    Note: Sexual abstinence may only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle.

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 (ie, fertile) following menarche and until becoming postmenopausal, unless permanently sterile.

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

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

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

Adapted from Clinical Trials Facilitation Group (CTFG) 2020.

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APPENDIX 10. LIST OF PROHIBITED CHINESE HERBAL AND PATENT MEDICINES

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

Drug Name (Chinese)	**Drug Name (English)**
Rg3 参一胶囊	Ginsenoside-Rg3 capsule
养正消积胶囊	Yangzheng Xiaoji capsule
化癥回生口服液	Huazheng Huisheng oral liquid
十全大补汤	Juzentaihoto
华蟾素注射液	Cinobufacini/Huachansu injections
华蟾素片/**胶囊**	Cinobufacini/Huachansu tablet/capsule
博尔宁**胶囊**	Boerning capsule
去甲斑蝥素片	Norcantharidin tablet
参丹散结胶囊	Shendan Sanjie capsule
参芪扶正注射液	Shengqi Fuzheng injections
参莲胶囊/颗粒	Shen Lian capsule/granules
吗特灵注射液	Ma Te Ling injection
回生口服液	Hui Sheng oral liquid
复方斑蝥胶囊	Fufang Banmao capsule
复方红豆杉胶囊	Fufang Hongdoushan capsule
复方苦参注射液	Fufang Kushen injections
天仙胶囊	Tian Xian capsule
奇宁注射液	Qining injections
威麦宁胶囊	Weimaining capsule
安尔欣注射液	Anerxin/Ginseng polysaccharide injections
安康欣胶囊	Ankangxin capsule
安替可胶囊	Antike capsule
岩舒注射液	Yanshu injections
平消片/胶囊	Ping Xiao tablet/capsule
康力欣胶囊	Kanglixin capsule

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Drug Name (Chinese)	Drug Name (English)
康艾注射液	Kang'ai injections
康莱特注射液	Kanglaite injections
康莱特软胶囊	Kanglaite soft capsules
慈丹胶囊	CIDAN capsule
槐耳颗粒	Huaer granules
海生素注射液	Haishengsu injections
消癌平丸/片/胶囊/颗粒	Xiaoaiping pill/tablet/capsule/granules
消癌平注射液	Xiaoaiping injections
牛黄醒消丸	Niuhuang Xingxiao pill
猪苓多糖注射液	Polyporus polysaccharide injections
白花蛇舌草注射液	Hedyotis Dissusa wild injections
紫龙金片	Zi Long Jin tablet
肝复乐片/胶囊	Ganfule tablet/GFL capsule
肿节风片	Zhongjiefeng tablet
胃复春片	Weifuchun tablet
艾迪注射液	Ai Di injections
芪珍胶囊	Qizhen capsule
莪术油注射液	Zedoary turmeric oil injections
金复康口服液	Kanglixin oral liquid
金蒲胶囊	Jinpu capsule
金龙胶囊	Jinlong capsules
香菇多糖	Lentinan
鸦胆子油乳注射液	Yadanzi/Brucea javanica Youru injections
鸦胆子油软胶囊/口服乳液	Yadanziyou soft capsule/oral emulsion

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APPENDIX 11. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE CANCER QUESTIONNAIRE QLQ-C30

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

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

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

Please go on to the next page

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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

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Specimen

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APPENDIX 12. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE QUESTIONNAIRE LUNG CANCER QLQ-LC13

EORTC QLQ - LC13

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

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

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APPENDIX 13. THE 5-LEVEL VERSION OF EUROPEAN QUALITY OF LIFE 5-DIMENSIONAL QUESTIONNAIRE

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

MOBILITY

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

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 ❑

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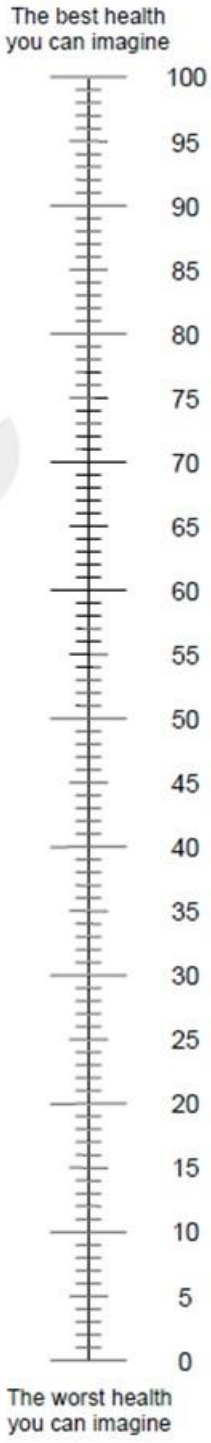
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the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

YOUR HEALTH TODAY = ☐



Sample

APPENDIX 14. PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S)

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During the past week, how severe were your lung cancer symptoms (for example, coughing, pain in the chest and pain in the arms and shoulders, numbness and tingling in your fingers, coughing blood, etc.).

Please choose only 1 answer for each question.

- Not at all
- Mildly
- Moderately
- Very
- Extremely

Scoring Criteria: Lower scores = Less symptom severity

APPENDIX 15. PATIENT REPORTED TREATMENT-RELATED SIDE-EFFECT BURDEN (PRTSE)

Were you bothered by side effects of your treatment?

- Not at all bothered
- Mildly bothered
- Moderately bothered
- Very bothered
- Extremely bothered

Scoring Criteria: Lower scores = Less burden

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APPENDIX 16. SAFETY RUN-IN SUBSTUDY INVESTIGATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PRELIMINARY EFFICACY OF OCIPERLIMAB, AN ANTI-TIGIT ANTIBODY, IN COMBINATION WITH TISLELIZUMAB IN JAPANESE PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS

SAFETY RUN-IN SUBSTUDY SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.

Investigational Products: Ociperlimab (also known as BGB-A1217) and tislelizumab (also known as BGB-A317)

Title of Study: Safety Run-in Substudy Investigating the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of Ociperlimab, an Anti-TIGIT Antibody, in Combination With Tislelizumab in Japanese Patients With Locally Advanced or Metastatic Solid Tumors

Protocol Identifier: BGB-A317-A1217-302 (also known as AdvanTIG-302) safety run-in substudy

Phase of Development: 3

Number of Patients: Minimum of 6

Study Centers: Approximately 3 to 6 centers in Japan

Study Objective:

Primary:

- To investigate the safety and tolerability of ociperlimab in combination with tislelizumab in Japanese patients
- To characterize the pharmacokinetics (PK) of ociperlimab in combination with tislelizumab in Japanese patients

Secondary:

- To assess the host immunogenicity to ociperlimab in combination with tislelizumab in Japanese patients.
- To assess the preliminary antitumor activity of ociperlimab in combination with tislelizumab in Japanese patients with locally advanced or metastatic solid tumors

Exploratory:

- To assess the preliminary overall survival benefit of ociperlimab in combination with tislelizumab in Japanese patients

Study Endpoints:

Primary:

- The incidence and severity of adverse events (AEs) according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) of ociperlimab in combination with tislelizumab in Japanese patients

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- Serum concentrations at specified timepoints and PK parameters of ociperlimab in Japanese patients

Secondary:

- Immunogenic responses to ociperlimab and tislelizumab, evaluated through the detection of antidrug antibodies (ADAs)
- Overall response rate (ORR), progression-free survival (PFS), and duration of response (DOR) will be assessed by investigators according to the Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

Exploratory:

- Overall survival (OS)

Study Design:

This is a safety run-in substudy to be conducted in Japanese patients prior to allowing Japanese patients to enroll in the primary global AdvanTIG-302 study. One cohort of Japanese patients will be enrolled to receive ociperlimab in combination with tislelizumab to evaluate the safety of these drugs in Japanese patients.

Patients will be required to sign an informed consent before enrolling in the safety run-in substudy. A minimum of 6 patients will be enrolled.

Study treatments will be given as follows:

- Tislelizumab 200 mg intravenously followed by ociperlimab 900 mg intravenously once every 3 weeks

All study treatments will be administered until intolerable toxicity, withdrawal of informed consent, or the timepoint at which, in the opinion of the investigator, the patient is no longer benefiting from study therapy.

Safety Assessments and Dose-Limiting Toxicities:

Safety Assessments:

Patients will be evaluated for any AEs, serious adverse events (SAEs), and dose-limiting toxicities (DLTs; see below). All toxicities will be graded according to the NCI-CTCAE v5.0. After informed consent has been signed but prior to the administration of study drug, only SAEs should be reported. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last dose of ociperlimab and tislelizumab. Immune-mediated AEs (imAEs; serious or nonserious) should be reported until 90 days after the last dose of study drugs. 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.

Dose-Limiting Toxicities:

A DLT is defined as 1 of the following toxicities occurring during the DLT-assessment window (first 42 study days or 2 cycles) and considered by the investigator to be related to ociperlimab and/or tislelizumab.

Hematologic:

- Grade 4 neutropenia lasting > 7 days
- ≥ Grade 3 febrile neutropenia
- Grade 3 thrombocytopenia with clinically significant bleeding and/or requiring transfusion
- Grade 4 thrombocytopenia lasting > 7 days and/or requiring transfusion
- ≥ Grade 4 anemia and/or requiring transfusion

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Nonhematologic:

- ≥ Grade 4 toxicity
- Grade 3 toxicity that is clinically significant and does not resolve to baseline or Grade 1 within 7 days of initiating optimal supportive care

Note: The following AEs will not be considered DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 rash
- Grade 3 infusion-related AE that is transient (resolving within 6 hours of onset)
- Grade 3 nausea, vomiting, or diarrhea lasting for ≤ 72 hours with adequate antiemetic and/or other supportive care
- Grade 3 fatigue lasting for ≤ 7 days
- ≥ Grade 3 electrolyte abnormality that lasts for ≤ 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions

Patients will be considered not evaluable for DLTs if they 1) withdraw from the study prior to the completion of the DLT-assessment window unless the reason for withdrawal is a DLT or other toxicity, or 2) did not receive ≥ 80% of each scheduled study drug administration during the DLT-assessment window unless the reason for not receiving 80% or more of the planned dosing is a DLT or other toxicity, and/or 3) received supportive care during the DLT-assessment window that confounds the evaluation of DLTs (not including supportive care described as part of the DLT definition). Patients who are not DLT evaluable will be replaced; however, all available safety data from such patients will be provided to the Independent Data Monitoring Committee (IDMC) for its review.

Clinically important or persistent AEs that are not part of the DLT criteria may also be considered a DLT following review by the sponsor in consultation with the investigators and/or an IDMC.

To ensure patient safety during the safety run-in, patients will be hospitalized during the first cycle of therapy (Days 1 to 21). An interval of at least 24 hours will be observed between the dosing of the first and second patients participating in the safety run-in substudy. Patients will be monitored per institutional standards during hospitalization, and AEs and concomitant medications will be recorded throughout this period. Patients will be assessed with medical history and physical examination (including vital signs) prior to discharge to assess for any emerging or worsening AEs. If such AEs are identified, the patient will be managed according to standard medical practice, including ongoing hospitalization if indicated. If there are no significant safety concerns upon Day 21, they can be seen weekly in an outpatient setting for safety and other study level assessments as defined in the protocol schedule of assessments.

Initial enrollment into the safety run-in substudy will include up to 3 evaluable patients. If none of the first 3 evaluable patients experiences a DLT during the DLT assessment period (first 42 study days or 2 cycles), enrollment of 3 additional evaluable patients will proceed. Close monitoring of safety data by the sponsor's medical monitor, clinical research associate, and representative from Pharmacovigilance/Drug Safety will occur throughout the safety run-in substudy. If a DLT is experienced at any time, the sponsor's medical monitor and representative from Pharmacovigilance/Drug Safety will evaluate all available safety data, including AEs and laboratory assessments, and discuss with the respective investigator, as necessary, as well as consult with Steering Committee members when appropriate. An adhoc IDMC meeting will be convened in the event of DLT occurrence and all available safety-relevant data (ie, AEs, SAEs, dose modifications, and potential DLTs) will be made available for IDMC review. Enrollment of additional patients and dosing of existing patients will pause until the IDMC issues a recommendation.

If ≥ 1 DLT is observed in the first 3 evaluable patients, the IDMC will review the totality of the safety data and may recommend the enrollment of 3 additional patients, if there are no major safety concerns,

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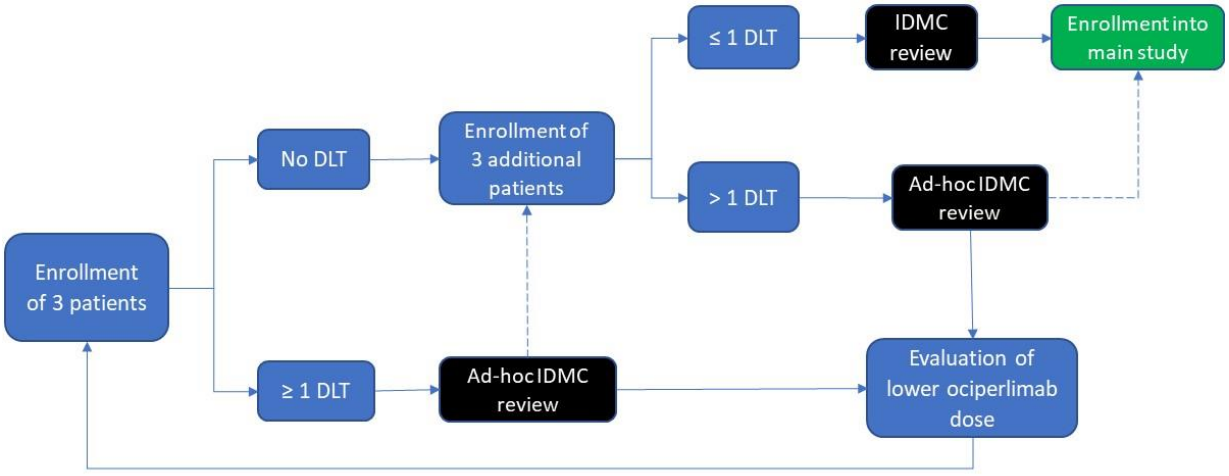
or that a lower ociperlimab dose be assessed for toxicity in the same manner as described above. If ≥ 2 DLTs are observed in 6 evaluable patients, the IDMC will review the totality of the safety data and may recommend the enrollment of 3 additional patients or that a lower ociperlimab dose be assessed for toxicity in the same manner as described above. If less than one-third of evaluable patients experience a DLT (eg, ≤ 1 DLT among 6 evaluable patients), the IDMC will review the totality of the safety data and may recommend that enrollment of Japanese patients into the global study proceeds.

The safety run-in substudy DLT evaluation process is summarized in the figure below:



Abbreviations: DLT, dose-limiting toxicity; IDMC, Independent Data Monitoring Committee

Study Population:

Inclusion Criteria:

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

1. Signed informed consent form (ICF) and is able to comply with study requirements
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 documented locally advanced or metastatic solid tumor for which standard-of-care treatment in Japan is not available or not tolerated
4. ECOG Performance Status ≤ 1
5. Adequate organ function as indicated by the following laboratory values during screening:
   a. Patients must not have required blood transfusion or growth factor support ≤ 14 days before sample collection at screening for the following:
      – Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
      – Platelets ≥ 75 x 10^9/L
      – Hemoglobin ≥ 90 g/L
   b. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated Glomerular Filtration Rate ≥ 60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation
   c. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilberts syndrome)

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d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN or < 5 x ULN if hepatic metastases present or for hepatocellular carcinoma (HCC) patients.
e. HCC patients are required to have a Child-Pugh A liver function classification.

6. Females 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, and must have a negative urine or serum pregnancy test ≤ 7 days before C1D1. See Appendix 9.
7. Nonsterile males must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of study drug.
   a. A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
   b. Males with known "low sperm counts" (consistent with "subfertility") are not to be considered sterile for purposes of this study.

Exclusion Criteria

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

1. Eligible to receive a standard-of-care therapy in Japan
2. Has received more than 2 prior systemic therapies for metastatic solid tumors
3. Discontinued prior therapy with an anti-PD-1, anti-PD-L1, anti-programmed cell death ligand 2 (PD-L2), anti-T cell immunoglobulin and ITIM domain (TIGIT), or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathway due to serious or ≥ Grade 3 (per NCI-CTCAE v5.0 criteria) immune-related toxicity.
4. Active leptomeningeal disease or uncontrolled, untreated brain metastasis.
   - Patients with a history of treated and, at the time of screening, stable central nervous system (CNS) metastases are eligible, provided they meet all the following:
     – Brain imaging at screening shows no evidence of interim progression, clinically stable for at least 2 weeks and have no evidence of new brain metastases
     – No ongoing requirement for corticosteroids as therapy for CNS disease; off steroids 3 days prior to C1D1; anticonvulsants at a stable dose are allowed
     – No stereotactic radiation or whole-brain radiation within 14 days prior to C1D1
5. Active autoimmune diseases or history of autoimmune diseases that may relapse.

   Note: Patients with the following diseases are not excluded and may proceed to further screening:
   a. Controlled Type I diabetes
   b. Hypothyroidism (provided it is managed with hormone replacement therapy only)
   c. Controlled celiac disease
   d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia)
   e. Any other disease that is not expected to recur in the absence of external triggering factors
6. Any active malignancy ≤ 2 years before the first dose of study drug(s) except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated with curative intent (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast)
7. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone [in Japan, prednisolone] or equivalent) or other immunosuppressive medication ≤ 14 days before C1D1

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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 [in Japan, prednisolone] 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)

8. 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 C1D1
9. History of interstitial lung disease, non-infectious pneumonitis or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc.
10. Infection (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal or antiviral therapy within 14 days prior to C1D1

    Note: Antiviral therapy is permitted for patients with hepatocellular carcinoma or 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 (in Japan, defined as patients who are HBsAg-positive but asymptomatic), 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 C1D1.
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 C1D1.
13. Known history of HIV infection
14. Any major surgical procedure ≤ 28 days before C1D1 or anticipation of need for major surgical procedure during the course of the study. Patients must have recovered adequately from the toxicity and/or complications from the intervention before C1D1.
15. Immunodeficiency, 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 C1D1.
    b. Pulmonary embolism ≤ 28 days before C1D1.
    c. Any history of acute myocardial infarction ≤ 6 months before C1D1.
    d. Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 6) ≤ 6 months before C1D1.
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before C1D1.
    f. Any history of cerebrovascular accident ≤ 6 months before C1D1.

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g. Uncontrolled hypertension that cannot be managed by standard antihypertension medications ≤ 28 days before C1D1.

h. Any episode of syncope or seizure ≤ 28 days before C1D1.

17. A history of severe hypersensitivity reactions to other monoclonal antibodies or a history of hypersensitivity to the ingredients of tislelizumab or ociperlimab.
18. Was administered a live vaccine ≤ 28 days before C1D1

    Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed. A non-live COVID-19 vaccine may be administered if recommended per local practice.
19. Toxicities from prior therapy that have not recovered to baseline, ≤ Grade 1, or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
20. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug or that will affect the explanation of drug toxicity or AEs, or result in insufficient or impaired compliance with study conduct.
21. Concurrent participation in another therapeutic clinical study
    - 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.
22. Women who are pregnant or are breastfeeding.
    Note: If pregnancy is suspected during physical examination or interview, patient is not eligible regardless of whether or not a negative urine or serum pregnancy test is subsequently obtained before C1D1.
    Breastfeeding women who agree to stop breastfeeding prior to C1D1 are allowed to enroll and they shall not resume breastfeeding until ≥120 days after the last dose of study drugs.

Investigational Product, Dose, and Mode of Administration:

Ociperlimab

Ociperlimab is a monoclonal antibody formulated for intravenous injection in a single-use vial (20 mL glass vial, USP Type I) containing a total of 200 mg antibody in 10 mL (or 300 mg antibody in 15 mL) of buffered isotonic solution as available. Ociperlimab 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 should be stored at the conditions specified on the label. Shaking should be avoided.

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

Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous injection in a single-use vial (20R glass, United States Pharmacopeia [USP] type I), containing a total of 100 mg of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in a single-use glass vial with a rubber stopper and capped by an aluminum flip-off seal cap. Each vial is packaged into a single carton box.

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

The study drug must be kept at the temperature condition as specified on the label.

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

Dose, and Mode of Administration:

Ociperlimab 900 mg will be administered on Day 1 of each 21-day cycle (once every 3 weeks).

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

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

The initial infusions of study drugs (Day 1 of Cycle 1 and Cycle 2) will be delivered for ≥ 55 minutes; if this is well tolerated, then the subsequent infusions may be administered for ≥ 25 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug.

As a routine precaution, after infusion of study treatment is complete on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for ≥ 120 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 60-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

Guidelines for treatment interruption or discontinuation and for the management of infusion-related reactions are provided in Section 8.6.10 of the main protocol. Guidelines for treatment interruption or discontinuation and for the management of imAEs are provided in Section 8.6.12 of the main protocol and in Appendix 7.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Statistical Methods:

Analysis Sets:

- Safety: The DLT-Evaluable Analysis Set includes all treated patients if they 1) did not withdraw from the study prior to the completion of the DLT-assessment window unless the reason for withdrawal is a DLT or other toxicity, 2) received ≥ 80% of each scheduled study drug administration during the DLT-assessment window unless the reason for not receiving ≥ 80% of the planned dosing is a DLT or other toxicity, and 3) did not receive supportive care during the DLT-assessment window that confounds the evaluation of DLTs (not including supportive care described as part of the DLT definition). This will be the primary analysis set for safety analysis.
- PK: The PK Analysis Set includes all patients who received ≥ 1dose of study drugs and have ≥ 1 derivable PK parameter.

Safety Analyses

In the case of ad-hoc IDMC meetings and to expedite decision making, only listings of relevant patients' information will be provided for IDMC review. For regular IDMC meetings, the totality of the safety data available for the safety run-in patients will be provided to the IDMC as described below.

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

Verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA, version 22.0 or higher) terms and graded per NCI-CTCAE v5.0. A TEAE is defined as an AE that has an onset date or a worsening in severity from baseline (pretreatment) on or after the first

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dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Only those AEs that were treatment emergent will be included in summary tables. Immune-mediated AEs will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 90 days from the last dose of study drug, regardless of whether the patient starts a new anticancer therapy. If an imAE occurs outside of the above mentioned TEAE window, it will not be classified as treatment-emergent adverse event. All imAE will be reported separately. All AEs, treatment emergent or otherwise, will be presented in patient data listings. Overviews of SAEs; deaths; TEAEs with ≥ Grade 3; treatment-related TEAEs; TEAEs that led to treatment discontinuation; dose interruption or dose delay; and imAEs will be summarized and associated listings will be provided. While every effort will be made to perform sponsor medical review of imAEs according to investigators prior to IDMC review, this may not be possible if ad-hoc IDMC meetings need to be convened.

Clinical laboratory data with values outside of the normal ranges will be identified. Select laboratory data by grade and changes in vital signs may be provided by listings considered the limited number of patients in the safety run-in. Summary tables may be provided as needed.

Pharmacokinetic Analyses

Noncompartmental analysis will be carried out using ociperlimab serum concentrations. The PK analyses will include patients with sufficient data to enable estimation of key parameters, and the parameters such as peak serum concentration (C_{max}), trough serum concentration (C_{min}), time to peak concentration (T_{max}), and area under the concentration-time curve (AUC) (as appropriate for data collected) may be derived and summarized by visit/cycle at which these concentrations are collected with descriptive statistics such as mean, standard deviation, and coefficient of variation, etc.

Individual and/or mean serum ociperlimab and tislelizumab concentration versus time data will be tabulated and plotted as appropriate. Additional PK analyses may be conducted as appropriate.

Immunogenicity Analyses

Samples to assess anti-ociperlimab 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.

Efficacy Analyses

Efficacy per RECIST v1.1 (ie, ORR, PFS, and DOR) will be evaluated to explore the preliminary anticancer activity of ociperlimab in combination with tislelizumab in Japanese patients.

The ORR is defined as the proportion of patients who had a confirmed complete response (CR) or partial response (PR) as assessed by the investigator using RECIST v1.1.

The DOR is defined as the time from the first determination of a confirmed objective response by the investigator per RECIST v1.1 until the first documentation of disease progression or death, whichever occurs first.

The PFS is defined as the time from the date of first dose of study drug to the date of first documentation of disease progression as assessed by the investigator using RECIST v1.1 or death, whichever occurs first.

The ORR and its 95% confidence interval will be summarized in the DLT-Evaluable Analysis Set. PFS and DOR of each individual patient will be calculated and listed. A waterfall plot of maximum tumor shrinkage per patient will be presented.

Exploratory analysis

OS is defined as the time from the date of first dose of study drug until the date of death due to any cause. OS for each individual patient will be calculated and listed.

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1. INTRODUCTION

Before initiating this Phase 3 study in Japan, a safety run-in substudy investigating the safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of ociperlimab in combination with tislelizumab in Japanese patients with locally advanced or metastatic solid tumors is planned.

The background on the monoclonal antibodies ociperlimab and tislelizumab is provided in the main study protocol in Section 1.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary:

- To investigate the safety and tolerability of ociperlimab in combination with tislelizumab in Japanese patients
- To characterize the pharmacokinetics (PK) of ociperlimab in combination with tislelizumab in Japanese patients

Secondary:

- To assess the host immunogenicity to ociperlimab in combination with tislelizumab in Japanese patients
- To assess the preliminary antitumor activity of ociperlimab in combination with tislelizumab in Japanese patients with locally advanced or metastatic solid tumors

Exploratory:

- To assess the preliminary overall survival benefit of ociperlimab in combination with tislelizumab in Japanese patients

2.2. Endpoints

Primary:

- The incidence and severity of adverse events (AEs) according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) of ociperlimab in combination with tislelizumab in Japanese patients
- Serum concentrations at specified timepoints and PK parameters of ociperlimab in Japanese patients

Secondary:

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

- Overall response rate (ORR), progression-free survival (PFS), and duration of response (DOR) will be assessed by investigators according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

Exploratory:

- Overall survival (OS)

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3. STUDY DESIGN

3.1. Summary of Study Design

This is an open-label, single-arm, multicenter, non-randomized, safety run-in substudy to be conducted in Japanese patients with locally advanced or metastatic solid tumors prior to allowing Japanese patients to enroll in the primary global AdvanTIG-302 study. One cohort of Japanese patients will be enrolled to receive ociperlimab in combination with tislelizumab to evaluate the safety of these drugs in Japanese patients.

Patients will be required to sign an informed consent before enrolling in the safety run-in substudy. A minimum of 6 patients will be enrolled to assess dose-limiting toxicities (DLTs) and to characterize the PK of ociperlimab in combination with tislelizumab in Japanese patients. Additional patients may be enrolled if more than 1 dose level is explored.

Study treatments will be given as follows:

- Tislelizumab 200 mg intravenously followed by ociperlimab 900 mg intravenously once every 3 weeks

All study treatments will be administered until intolerable toxicity, withdrawal of informed consent, or the timepoint at which, in the opinion of the investigator, the patient is no longer benefiting from study therapy.

To ensure patient safety during the safety run-in, patients will be hospitalized during the first cycle of therapy (Days 1 to 21). An interval of at least 24 hours will be observed between the dosing of the first and second patients participating in the safety run-in substudy.

3.2. Schedule of Study Assessments

A schedule of study assessments is presented in Table 9. A schedule of PK and immunogenicity sampling is presented in Table 10.

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Table 9: Japan Safety Run-in Substudy Schedule of Assessments

Assessment	Screening [a]	Treatment cycles				End-of-Treatment Visit [b]	Safety Follow-up [c]	Survival Follow-up [d]
		Cycles 1 to 3 (every 21 days)			Cycle 4 and subsequent cycles (every 21 days)			
Days (window)	**-28 to ~ -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**Within 7 days after permanent treatment discontinuation**	**30 (± 7), 60 (± 14), and 90 (± 14) days (and 120 days for pregnancy testing) after last dose**	**Every 3 months (± 14 days)**
Main informed consent [a]	X							
Inclusion/exclusion criteria	X							
Enrollment [e]	X							
Demographics/medical history/prior medications [f]	X							
Vital signs/ height and weight [g]	X	X			X	X		
Physical examination [h]	X	X			X	X		
Chest X-ray [w]		X (Cycle 2 only)			As clinically indicated			
Sialylated carbohydrate antigen KL-6 [w]	X	X			As clinically indicated			
Peripheral capillary oxygen saturation (SpO2) measurement [w]	X	X			As clinically indicated			
ECOG Performance Status	X	X			X	X		
12-lead ECG [i]	X	As clinically indicated				X		

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Assessment	**Screening** [a]	**Treatment cycles**				**End-of-Treatment Visit** [b]	**Safety Follow-up** [c]	**Survival Follow-up** [d]
		Cycles 1 to 3 (every 21 days)			**Cycle 4 and subsequent cycles (every 21 days)**			
Days (window)	**-28 to ~ -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**Within 7 days after permanent treatment discontinuation**	**30 (± 7), 60 (± 14), and 90 (± 14) days (and 120 days for pregnancy testing) after last dose**	**Every 3 months (± 14 days)**
Adverse events [j]	X	X	X [k]	X [k]	X	X	X	
Concomitant medications	X	X	X [k]	X [k]	X	X	X	
Hematology [l]	X	X	X	X	X	X		
Serum chemistry [l]	X	X	X	X	X	X		
CK and CK-MB [m]	X	X	X	X	X	X		
Coagulation parameters [l]	X	X			X	X		
Urinalysis [l]	X	As clinically indicated						
Pregnancy test [n]	X	X			X	X	X	
Thyroid function [o]	X	X (Cycle 3 only)			X (every 2 cycles)	X		
HBV/HCV tests [p]	X	As clinically indicated						
Pulmonary function tests [q]	X [q]	As clinically indicated						
Pharmacokinetics [r]		See Table 10				X		
Antidrug antibodies [s]		See Table 10				X		
Tumor assessment [t]	X	Every 9 weeks (± 7 days) from C1D1 for the first 52 weeks, then every 12 weeks (± 7 days)						X [t]

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Assessment	Screening [a]	Treatment cycles				End-of-Treatment Visit [b]	Safety Follow-up [c]	Survival Follow-up [d]
		Cycles 1 to 3 (every 21 days)			Cycle 4 and subsequent cycles (every 21 days)			
Days (window)	**-28 to ~ -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**Within 7 days after permanent treatment discontinuation**	**30 (± 7), 60 (± 14), and 90 (± 14) days (and 120 days for pregnancy testing) after last dose**	**Every 3 months (± 14 days)**
Tislelizumab administration [u]		X			X			
Ociperlimab administration [v]		X			X			
Survival status								X

Abbreviations: ADA, antidrug antibody; AE, adverse event; CK, creatine kinase; CK-MB, creatine kinase cardiac muscle isoenzyme; DLCO, diffusing capacity of the lungs for carbon monoxide; ECG, electrocardiogram; EOT, End-of-Treatment Visit; FEV1, forced expiratory volume; FT3, free triiodothyronine; FT4, free thyroxine; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; ICF, informed consent form; IEC, Independent Ethics Committee; imAE, immune-mediated adverse event; IRB, Institutional Review Board; KL-6, Krebs von den Lungen-6; NCI-CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0; NSCLC, non-small cell lung cancer; PK, pharmacokinetic(s); RECIST v1.1, Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE, serious adverse event; SpO2, peripheral capillary oxygen saturation; TSH, thyroid-stimulating hormone; v, version.

[a] 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 drug may be used for Screening assessments rather than repeating such tests.

[b] The EOT Visit will be conducted within 7 days after the investigator decides to permanently discontinue study treatment (Section 3.5 of the main protocol). If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT Visit, tests need not be repeated.

[c] A Safety Follow-up Visit at 30 days (± 7 days) after the last dose of study drug is required to assess AEs and concomitant medications, unless the time window overlaps the time window of the EOT Visit; the Safety Follow-up Visit may be a telephone call or an on-site visit if laboratory assessments are necessary. Two additional telephone calls with patients will occur in the safety follow-up period to assess imAEs and concomitant medications if appropriate (ie, if associated with an imAE or a new anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of study drugs regardless of whether the patient starts a new subsequent anticancer therapy. If a patient reports a suspected imAE at a safety follow-up telephone call, the investigator should arrange an unscheduled visit if further assessment is indicated. Patients who discontinue study treatment before disease progression will need to undergo tumor assessments as outlined in Section 7.6 of the main protocol.

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[d] 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 EOT Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from survival follow-up.

[e] All patients are required to receive study treatment within 2 business days of enrollment.

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

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

[h] A complete physical examination is required at Screening while subsequent visits entail limited, symptom-directed physical examinations (as detailed in Section 7.5.2 of the main protocol), except for chest auscultation, which is required prior to dosing on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1 for NSCLC patients only.

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

[j] The AEs and laboratory abnormalities will be graded per NCI-CTCAE v5.0. All AEs will also be evaluated for seriousness. After the main ICF has been signed, but before the first administration of study drug, only SAEs should be recorded. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after the last dose of all study drug(s) or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or non-serious) should be reported until 90 days after the last dose of study drugs, regardless of whether or not the patient starts a new anticancer therapy. 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 study treatment.

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

[l] Local laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2. If laboratory tests at screening are not performed within 7 days of Day 1 of Cycle 1, these tests should be repeated and reviewed before the first dose of study drug. Hematology and serum chemistry (including liver function tests) will be performed weekly for the first 3 cycles, at the beginning of each subsequent cycle, and at the EOT Visit (data collected as specified in Appendix 2). After Cycle 1, results are to be reviewed within 48 hours before study drug administration. Coagulation assays will be performed at screening, on Day 1 of each cycle, and at the EOT Visit. Urinalysis is to be conducted during the treatment period only if clinically warranted. Refer to Section 8.3.5 of the main protocol for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[m] All patients will have CK and CK-MB testing at Screening, repeated at all scheduled visits during the first 3 treatment cycles, all predose assessments from Cycle 4 onwards, and at the EOT Visit. If CK-MB fractionation is not available, troponin I and/or troponin T may be tested instead. Refer to Section 8.3.5 of the main protocol for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[n] Pregnancy tests will be performed for women of childbearing potential, including women who have had a tubal ligation). A urine or serum pregnancy test must be performed and documented as negative ≤ 7 days before the first dose of study drug. Urine pregnancy tests will be performed at each visit before dosing, at the EOT Visit, and at each safety follow-up visit, including 120 days after the last dose of study drugs. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

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[o] Analysis of FT3, FT4, and TSH will be performed by a local or central laboratory. Thyroid function tests will be performed at Screening, every 2 cycles starting on Day 1 of Cycle 3 (ie, Day 1 of Cycles 3,5, and 7, etc.), and at the EOT Visit.

[p] Testing will be performed by a local laboratory at Screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody). Viral load assessment (HBV DNA or HCV RNA) will be performed only when HBsAg or HCV antibody is positive, respectively. 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, and 13, etc). Blood samples will be collected on Day 1 of Cycle 1 before dosing of study drug, stored, and may be analyzed if patients develop hepatic AEs. The collection and storage of blood samples for patients with detectable HBV DNA or HCV RNA at Screening will be organized by the central laboratory if sites do not have local capabilities. Sites that are unable to collect such samples will make every effort to perform a comprehensive diagnostic work up in the event of patients with detectable HBV DNA or HCV RNA at Screening develop hepatic AEs.

[q] Patients who are suspected of having or known to have serious/severe respiratory conditions, or exhibit significant respiratory symptoms unrelated to the underlying cancer, or with a history of thoracic radiotherapy will undergo pulmonary function testing 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. Respective test results need to be submitted to the sponsor. For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, FEV1 < 60% or DLCO (if performed) < 60% of age and sex adjusted predicted performance levels (Pellegrino et al 2005), the medical monitor needs to be consulted to confirm eligibility. Tests may be repeated as clinically indicated while on study.

[r] Procedures for collection of blood samples to evaluate PK are described in the laboratory manual. PK sampling schedule for both ociperlimab and tislelizumab in this safety substudy is provided in Table 10. These tests are required when it is allowed by local regulations/IRBs/IECs.

[s] ADA sampling schedule for both ociperlimab and tislelizumab in this safety substudy is provided in Table 10. All samples should be collected at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/IECs.

[t] Radiological images captured as standard of care before obtaining written informed consent and ≤ 28 days before the first dose of study drug 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. During the study, tumor imaging will be performed every 9 weeks (± 7 days) from the first dose of study drug for the first 52 weeks and then every 12 weeks (± 7 days) based on RECIST v1.1. Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held; they should not be adjusted for possible delays in cycles. Tumor assessment should continue until disease progression is determined by the investigator. Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient experiences disease progression or death, withdraws consent, is lost to follow-up, or until the study terminates, whichever occurs first. See also Section 7.6 of the main protocol for additional details.

[u] Tislelizumab will be given intravenously once every 3 weeks. On Day 1 of Cycles 1 and 2, tislelizumab will be delivered for ≥ 55 minutes. If well tolerated, subsequent infusions can be administered for ≥ 25 minutes. The first dose will be given on Cycle 1 Day 1 and subsequent dosing will continue on the scheduled 21-day intervals. Note: Tislelizumab must not be concurrently administered with any other drug. Patients must be monitored after study treatment infusions are complete as shown in Table 2.

[v] Ociperlimab will be given intravenously once every 3 weeks. On Day 1 of Cycles 1 and 2, ociperlimab will be delivered for ≥ 55 minutes. If well tolerated, subsequent infusions can be administered for ≥ 25 minutes. The first dose will be given on Cycle 1 Day 1 and subsequent dosing will continue on the scheduled 21-day intervals. Ociperlimab infusion must always occur after the infusion of tislelizumab has been completed. Patients must be monitored after study treatment infusions are complete as shown in Table 2.

[w] Sialylated carbohydrate antigen KL-6 and peripheral capillary oxygen saturation (SpO2) measurements are required at Screening and prior to dosing on Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1 for NSCLC patients only. Chest x-rays will only be required predose on Cycle 2 Day 1 for NSCLC patients only. After Cycle 3 Day 1, assessments should be performed if clinically indicated.

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Table 10: Japan Safety Run-in Substudy Schedule of Pharmacokinetic and Immunogenicity Sampling

Study Week	Study Visit	Time	PK	ADA
1	Cycle 1, Day 1	Predose (-60 min to predose)	Ociperlimab and tislelizumab	Ociperlimab and tislelizumab
		30 (±10) min after end of ociperlimab infusion	Ociperlimab and tislelizumab	
	Cycle 1, Day 2	24 (± 6) h after end of ociperlimab infusion on Day 1	Ociperlimab	
	Cycle 1, Day 4	72 (± 12) h after end of ociperlimab infusion on Day 1	Ociperlimab	
2	Cycle 1, Day 8 (± 1 day)	Any time during visit	Ociperlimab	
3	Cycle 1, Day 15 (± 1 day)	Any time during visit	Ociperlimab	
4	Cycle 2, Day 1	Predose (-60 min to predose)	Ociperlimab and tislelizumab	Ociperlimab and tislelizumab
		30 (±10) min after end of ociperlimab infusion	Ociperlimab	
13	Cycle 5, Day 1	Predose (-60 min to predose)	Ociperlimab and tislelizumab	Ociperlimab and tislelizumab
		30 (±10) min after end of ociperlimab infusion	Ociperlimab and tislelizumab	
14	Cycle 5, Day 8 (± 1 day)	Any time during visit	Ociperlimab	
15	Cycle 5, Day 15 (± 1 day)	Any time during visit	Ociperlimab	
16	Cycle 6, Day 1	Predose (-60 min to predose)	Ociperlimab	Ociperlimab
		30 (±10) min after end of ociperlimab infusion	Ociperlimab	
25	Cycle 9, Day 1	Predose (-60 min to predose)	Ociperlimab and tislelizumab	Ociperlimab and tislelizumab
37	Cycle 13, Day 1	Predose (-60 min to predose)	Ociperlimab	Ociperlimab
49	Cycle 17, Day 1	Predose (-60 min to predose)	Ociperlimab and tislelizumab	Ociperlimab and tislelizumab

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Study Week	Study Visit	Time	PK	ADA
73	Cycle 25, Day 1	Predose (-60 min to predose)	Ociperlimab	Ociperlimab
End of treatment		Any time during visit	Ociperlimab and tislelizumab	Ociperlimab and tislelizumab

Abbreviations: ADA, antidrug antibody; PK, pharmacokinetics.
Note: Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK and ADA should be from a different catheter on opposite arm.

3.3. Duration of Study

Total duration of study participation will vary by patient. Each study phase beyond the DLT assessment period is further discussed in the main protocol in Section 3.4 through Section 3.6.

3.4. Safety Assessments

Patients will be evaluated for any AEs, serious adverse events (SAEs), and DLTs (Section 3.4.1). All toxicities will be graded according to the NCI-CTCAE v5.0. After informed consent has been signed but prior to the administration of study drug, only SAEs should be reported. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last dose of ociperlimab and tislelizumab. Immune-mediated AEs (imAEs; serious or nonserious) should be reported until 90 days after the last dose of study drugs. 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.

3.4.1. Dose-Limiting Toxicities

A DLT is defined as 1 of the following toxicities occurring during the DLT-assessment window (first 42 study days or 2 cycles) and considered by the investigator to be related to ociperlimab and/or tislelizumab.

Hematologic:

- Grade 4 neutropenia lasting > 7 days
- ≥ Grade 3 febrile neutropenia
- Grade 3 thrombocytopenia with clinically significant bleeding and/or requiring transfusion
- Grade 4 thrombocytopenia lasting > 7 days and/or requiring transfusion
- ≥ Grade 4 anemia and/or requiring transfusion

Non-hematologic:

- ≥ Grade 4 toxicity
- Grade 3 toxicity that is clinically significant and does not resolve to baseline or Grade 1 within 7 days of initiating optimal supportive care

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Note: The following AEs will not be considered DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 rash
- Grade 3 infusion-related AE that is transient (resolving within 6 hours of onset)
- Grade 3 nausea, vomiting, or diarrhea lasting for ≤ 72 hours with adequate antiemetic and/or other supportive care
- Grade 3 fatigue lasting for ≤ 7 days
- ≥ Grade 3 electrolyte abnormality that lasts for ≤ 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions.

Patients will be considered not evaluable for DLTs if they 1) withdraw from the study prior to the completion of the DLT-assessment window unless the reason for withdrawal is a DLT or other toxicity, or 2) did not receive ≥ 80% of each scheduled study drug administration during the DLT-assessment window unless the reason for not receiving 80% or more of the planned dosing is a DLT or other toxicity, and/or 3) received supportive care during the DLT-assessment window that confounds the evaluation of DLTs (not including supportive care described as part of the DLT definition). Patients who are not DLT evaluable will be replaced; however, all available safety data from such patients will be provided to the Independent Data Monitoring Committee (IDMC) for its review.

Clinically important or persistent AEs that are not part of the DLT criteria may also be considered a DLT following review by the sponsor in consultation with the investigators and/or an IDMC.

To ensure patient safety during the safety run-in, patients will be hospitalized during the first cycle of therapy (Days 1 to 21). An interval of at least 24 hours will be observed between the dosing of the first and second patients participating in the safety run-in substudy. Patients will be monitored per institutional standards during hospitalization, and AEs and concomitant medications will be recorded throughout this period. Patients will be assessed with medical history and physical examination (including vital signs) prior to discharge to assess for any emerging or worsening AEs. If such AEs are identified, the patient will be managed according to standard medical practice, including ongoing hospitalization if indicated. If there are no significant safety concerns upon Day 21, they can be seen weekly in an outpatient setting for safety and other study level assessments as defined in the protocol schedule of assessments.

Initial enrollment into the safety run-in substudy will include up to 3 evaluable patients. If none of the first 3 evaluable patients experiences a DLT during the DLT assessment period (first 42 study days or 2 cycles), enrollment of 3 additional evaluable patients will proceed. Close monitoring of safety data by the sponsor's medical monitor, clinical research associate, and representative from Pharmacovigilance/Drug Safety will occur throughout the safety run-in substudy. If a DLT is experienced at any time, the sponsor's medical monitor and representative from Pharmacovigilance/Drug Safety will evaluate all available safety data, including AEs and laboratory assessments, and discuss with the respective investigator, as necessary, as well as consult with Steering Committee members when appropriate. An ad-hoc IDMC meeting will be

convened in the event of DLT occurrence and all available safety-relevant data (ie, AEs, SAEs, dose modifications, and potential DLTs) will be made available for IDMC review. Enrollment of additional patients and dosing of existing patients will pause until the IDMC issues a recommendation.

If ≥ 1 DLT is observed in the first 3 evaluable patients, the IDMC will review the totality of the safety data and may recommend the enrollment of 3 additional patients, if there are no major safety concerns, or that a lower ociperlimab dose be assessed for toxicity in the same manner as described above. If ≥ 2 DLTs are observed in the 6 evaluable patients, the IDMC will review the totality of the safety data and may recommend the enrollment of 3 additional patients or that a lower ociperlimab dose be assessed for toxicity in the same manner as described above. If less than one-third of evaluable patients experience a DLT (eg, ≤ 1 DLT among 6 evaluable patients), the IDMC will review the totality of the safety data and may recommend that enrollment of Japanese patients into the global study proceeds.

The safety run-in substudy DLT evaluation process is summarized in Figure 3.

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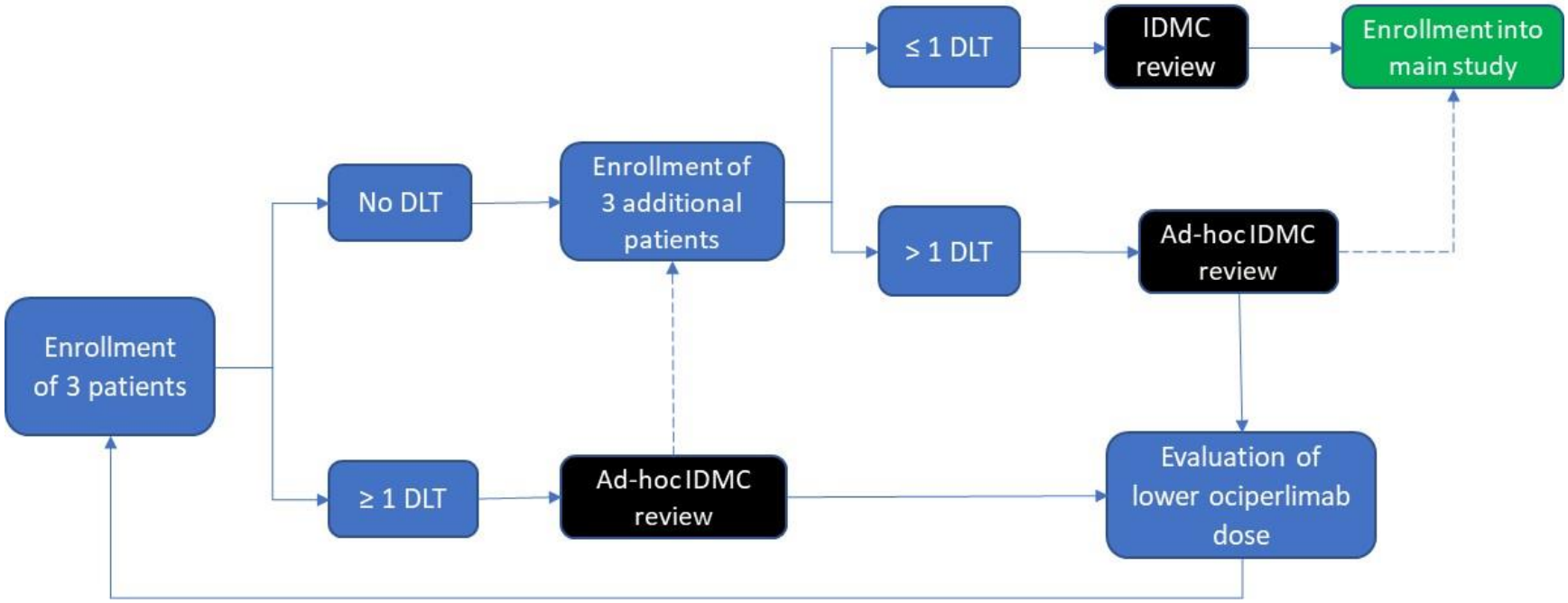
Figure 3: Japan Safety Run-in Substudy Evaluation of Dose-Limiting Toxicities



Abbreviations: DLT, dose-limiting toxicity; IDMC, Independent Data Monitoring Committee.

3.5. Study Rationale

Before initiating the AdvanTIG-302 study in Japan, this substudy in Japanese patients will provide additional safety information allowing the enrollment of patients into the larger Phase 3 study in Japan. Please see Section 1.5.2 of the main protocol for the rationale for the selection of ociperlimab dose in combination with tislelizumab.

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4. STUDY POPULATION

4.1. Inclusion Criteria

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

1. Signed informed consent form (ICF) and is able to comply with study requirements
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 documented locally advanced or metastatic solid tumor for which standard-of-care treatment in Japan is not available or not tolerated
4. ECOG Performance Status ≤ 1
5. Adequate organ function as indicated by the following laboratory values during screening:
   a. Patients must not have required blood transfusion or growth factor support ≤ 14 days before sample collection at screening for the following:
      – Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
      – Platelets ≥ 75 x 10^9/L
      – Hemoglobin ≥ 90 g/L
   b. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated Glomerular Filtration Rate ≥ 60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation.
   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 or for hepatocellular carcinoma (HCC) patients.
   e. HCC patients are required to have a Child-Pugh A liver function classification.
6. Females 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, and must have a negative urine or serum pregnancy test ≤ 7 days before C1D1. See Appendix 9.
7. Nonsterile males must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of study drug.
   a. A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
   b. Males with known “low sperm counts” (consistent with “subfertility”) are not to be considered sterile for purposes of this study.

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4.2. Exclusion Criteria

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

1. Eligible to receive a standard-of-care therapy in Japan.
2. Has received more than 2 prior systemic therapies for metastatic solid tumors.
3. Discontinued prior therapy with an anti-PD-1, anti-PD-L1, anti-programmed cell death ligand 2 (PD-L2), anti-T cell immunoglobulin and ITIM domain (TIGIT), or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathway due to serious or ≥ Grade 3 (per NCI-CTCAE v5.0 criteria) immune-related toxicity.
4. Active leptomeningeal disease or uncontrolled, untreated brain metastasis.
   - Patients with a history of treated and, at the time of screening, stable central nervous system (CNS) metastases are eligible, provided they meet all the following:
     - Brain imaging at screening shows no evidence of interim progression, clinically stable for at least 2 weeks and have no evidence of new brain metastases
     - No ongoing requirement for corticosteroids as therapy for CNS disease; off steroids 3 days prior to C1D1; anticonvulsants at a stable dose are allowed
     - No stereotactic radiation or whole-brain radiation within 14 days prior to C1D1
5. Active autoimmune diseases or history of autoimmune diseases that may relapse.

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

   a. Controlled Type I diabetes
   b. Hypothyroidism (provided it is managed with hormone replacement therapy only)
   c. Controlled celiac disease
   d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia)
   e. Any other disease that is not expected to recur in the absence of external triggering factors
6. Any active malignancy ≤ 2 years before the first dose of study drug(s) except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated with curative intent (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast)
7. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone [in Japan, prednisolone] or equivalent) or other immunosuppressive medication ≤ 14 days before C1D1

   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 [in Japan, prednisolone] or equivalent)
   b. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption

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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

8. 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 C1D1
9. History of interstitial lung disease, non-infectious pneumonitis or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc.
10. Infection (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal or antiviral therapy within 14 days prior to C1D1.

    Note: Antiviral therapy is permitted for patients with hepatocellular carcinoma or 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 (in Japan, defined as patients who are HBsAg-positive but asymptomatic), 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 C1D1.
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 C1D1.
13. Known history of HIV infection.
14. Any major surgical procedure ≤ 28 days before C1D1 or anticipation of need for major surgical procedure during the course of the study. Patients must have recovered adequately from the toxicity and/or complications from the intervention before C1D1.
15. Immunodeficiency, 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 C1D1.
    b. Pulmonary embolism ≤ 28 days before C1D1.
    c. Any history of acute myocardial infarction ≤ 6 months before C1D1.
    d. Any history of heart failure meeting New York Heart Association (NYHA) Classification III or IV (Appendix 6) ≤ 6 months before C1D1.
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before C1D1.
    f. Any history of cerebrovascular accident ≤ 6 months before C1D1.
    g. Uncontrolled hypertension that cannot be managed by standard antihypertension medications ≤ 28 days before C1D1.

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h. Any episode of syncope or seizure ≤ 28 days before C1D1.

17. A history of severe hypersensitivity reactions to other monoclonal antibodies or a history of hypersensitivity to tislelizumab or ociperlimab or their ingredients.
18. Was administered a live vaccine ≤ 28 days before C1D1.

    Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed. A non-live COVID-19 vaccine may be administered if recommended per local practice.
19. Toxicities from prior therapy that have not recovered to baseline, ≤ Grade 1, or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
20. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug or that will affect the explanation of drug toxicity or AEs, or result in insufficient or impaired compliance with study conduct.
21. Concurrent participation in another therapeutic clinical study

    - 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.
22. Women who are pregnant or are breastfeeding.
    Note: If pregnancy is suspected during physical examination or interview, patient is not eligible regardless of whether or not a negative urine or serum pregnancy test is subsequently obtained before C1D1.
    Breastfeeding women who agree to stop breastfeeding prior to C1D1 are allowed to enroll and they shall not resume breastfeeding until ≥120 days after the last dose of study drugs.

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5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

Refer to Section 5.1 of the main protocol for detailed information on the formulation, packaging, and handling of ociperlimab and tislelizumab.

5.2. Dosage, Administration, and Compliance

Refer to Section 5.2 of the main protocol for detailed information on the dosage, administration, and compliance of ociperlimab and tislelizumab.

5.3. Overdose or Incorrect Administration

Refer to Section 5.3 of the main protocol for detailed information.

5.4. Investigational Medicinal Product Accountability

Refer to Section 5.4 of the main protocol for information.

5.5. Dose Delay or Interruption

Refer to Section 5.5 of the main protocol for information.

5.6. Blinding

Not applicable to the safety run-in substudy.

6. PRIOR AND CONCOMITANT THERAPY

Please refer to Section 6 of the main protocol for detailed information.

7. STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures will be similar to those in the main protocol (Section 7) except for those described in Section 3.2 and Section 3.4.1 of this appendix and with the exceptions that patients will not be randomized for the substudy and there are no other treatment arms. In addition, PK assessments have been included in this substudy for thorough characterization of PK after a single dose and at steady state in Japanese patients and are provided in further detail in Table 10 of this substudy protocol. Patients will be closely monitored for safety and tolerability throughout the study and patients will be hospitalized during the first cycle of therapy (Days 1 to 21). An interval of at least 24 hours should be observed between the dosing of the first and second patients participating in the safety run-in substudy. All assessments must be performed and documented in the medical record and electronic case report form (eCRF) for each patient.

Tumor response will be assessed by investigators based on RECIST v1.1. See Table 9 and Section 7.6 of the main protocol for additional information.

8. SAFETY MONITORING AND REPORTING

Safety monitoring and reporting procedures will follow those in the main protocol (Section 8). An addition to this substudy is the definition of DLTs as described in Section 3.4.1 of this appendix. All toxicities or AEs will be graded according to NCI-CTCAE v5.0.

Independent Data Monitoring Committee

An IDMC (described in Section 10.1 of the main protocol) will evaluate the safety and tolerability of ociperlimab in combination with tislelizumab in Japanese patients and may recommend that a lower ociperlimab dose be evaluated, that additional patients be enrolled into the safety run-in, or that enrollment of Japanese patients into the main study proceeds (Figure 3). The totality of the safety data available from the safety run-in substudy patients will be provided to the IDMC for its review. After the DLT assessment period, safety assessments and review will continue according to the main protocol.

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9. STATISTICAL METHODS AND ANALYSIS PLAN

9.1. Analysis Sets

The DLT-Evaluable Analysis Set includes all treated patients if they 1) did not withdraw from the study prior to the completion of the DLT-assessment window unless the reason for withdrawal is a DLT or other toxicity, 2) received ≥ 80% of each scheduled study drug administration during the DLT-assessment window unless the reason for not receiving ≥ 80% of the planned dosing is a DLT or other toxicity, and 3) did not receive supportive care during the DLT-assessment window that confounds the evaluation of DLTs (not including supportive care described as part of the DLT definition). This will be the primary analysis set for safety analysis.

The PK Analysis Set includes all patients who received ≥ 1 dose of study drugs and have ≥ 1 derivable PK parameter.

9.2. Patient Disposition

Refer to Section 9.1.3 of the main protocol for detailed information.

9.3. Demographic and Other Baseline Characteristics

Refer to Section 9.1.4 of the main protocol for detailed information.

9.4. Prior and Concomitant Therapies

Administration of hematopoietic stimulating factors (eg, granulocyte colony stimulating factor [G-CSF]) is prohibited during the DLT evaluation period. Refer to Section 9.1.5 of the main protocol for other detailed information.

9.5. Safety Analyses

As described in the main protocol (Section 9.3), safety will be assessed by monitoring and recording of all AEs graded according to NCI-CTCAE v5.0. Laboratory values (eg, hematology, clinical chemistry), vital signs, electrocardiograms (ECGs), and physical examinations will also be used in determining safety. Descriptive statistics will be used to analyze all safety data in the DLT-Evaluable Analysis Set. Section 3.4.1 of this substudy includes DLT definitions as well as specific information on the role of the IDMC in the assessment of DLTs. While every effort will be made to perform sponsor medical review of imAEs according to investigators prior to IDMC review, this may not be possible if ad-hoc IDMC meetings need to be convened.

9.6. Pharmacokinetic Analyses

Noncompartmental analysis will be carried out using ociperlimab serum concentrations. The PK analyses will include patients with sufficient data to enable estimation of key parameters, and the parameters such as peak serum concentration (C_{max}), trough serum concentration (C_{min}), time to peak concentration (T_{max}), and area under the concentration-time curve (AUC) (as appropriate for data collected) may be derived and summarized by visit/cycle at which these concentrations are collected with descriptive statistics such as mean, standard deviation, and coefficient of variation, etc.

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Individual and/or mean serum ociperlimab and tislelizumab concentration versus time data will be tabulated and plotted as appropriate. Additional PK analyses may be conducted as appropriate.

9.7. Immunogenicity Analyses

Samples to assess anti-ociperlimab 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.

9.8. Efficacy Analyses

Efficacy per RECIST v1.1 (ie, ORR, PFS, and DOR) will be evaluated to explore the preliminary anticancer activity of ociperlimab in combination with tislelizumab in Japanese patients.

The ORR is defined as the proportion of patients who had confirmed complete response (CR) or partial response (PR) assessed by the investigator using RECIST v1.1.

The DOR is defined as the time from the first determination of a confirmed objective response by the investigator per RECIST v1.1 until the first documentation of disease progression or death, whichever occurs first.

The PFS is defined as the time from the date of first dose of study drug to the date of first documentation of disease progression assessed by the investigator using RECIST v1.1 or death, whichever occurs first.

The ORR and its 95% confidence interval will be summarized in the DLT-Evaluable Analysis Set. PFS and DOR of each individual patient will be calculated and listed. A waterfall plot of maximum tumor shrinkage per patient will be presented.

Exploratory analysis

OS is defined as the time from the date of first dose of study drug until the date of death due to any cause. OS for each individual patient will be calculated and listed.

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10. STUDY COMMITTEES AND COMMUNICATION

Refer to Section 10.1 of the main protocol for information on the IDMC. The IDMC will also review DLTs in this substudy as described in Section 3.4.1.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Refer to Section 11 of the main protocol for detailed information.

12. QUALITY ASSURANCE AND QUALITY CONTROL

Refer to Section 12 of the main protocol for detailed information.

13. ETHICS/PROTECTION OF HUMAN PATIENTS

Refer to Section 13 of the main protocol for detailed information.

14. DATA HANDLING AND RECORD KEEPING

Refer to Section 14 of the main protocol for detailed information.

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APPENDIX 17. CAUTION FOR USE CONCERNING VACUUM BLOOD-COLLECTION TUBES (APPLICABLE IN JAPAN ONLY)

1. The temperature of the blood collection tubes prior to blood draw must be equivalent to room temperature (the inner pressure may change, which could cause the blood in the blood collection tube to flow back into the body along with the contaminants).
2. Do not move, or release the pressure applied on the arm of the patient before removing the blood-collection needle (moving the position of, or releasing the pressure applied on the arm may cause rapid decrease in the venous blood pressure, which could cause the blood in the blood-collection tube to flow back into the body along with the contaminants).
3. After the blood starts flowing into the collection tube, do not apply force on the tube that could push it into the blood-collection holder (the inner pressure may change, which could cause the blood in the blood collection tube to flow back into the body along with the contaminants).
4. Do not remove the tourniquet after the completion of blood draw unless otherwise the blood collection needle is removed first (changes in the pressure due to removal of the tourniquet could cause the blood in the blood-collection tube to flow back into the body along with the contaminants).
5. The holder is for single patient use only and should be disposed of after each use (the holder may be contaminated with the blood, which could cause cross infection).
6. Do not draw blood from extracorporeal circuit or central vein (changes in the pressure could cause the blood in the blood-collection tube to flow back into the body along with the contaminants).
7. Do not re-use evacuated blood collection tube.

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APPENDIX 18. OVERVIEW OF PD-L1 CDX BRIDGING STUDY IN CHINA OF BEIGENE PHASE 3 STUDY BGB-A317-A1217-302

In the BGB-A317-A1217-302 study, a bridging study will be conducted to validate one candidate companion diagnostics (CDx) kit in China. The candidate CDx kit is PD-L1 antibody kit (IHC) (hereinafter referred to as "Bridging CDx") (type: E1L3N-L2, packing specification: 6 mL/vial) manufactured by Amoy Diagnostics Co., Ltd. It mainly includes anti-PD-L1 rabbit monoclonal antibodies (1 μg/mL), Antibody Dilution Buffer (containing disodium hydrogen phosphate dodecahydrate, potassium dihydrogen phosphate, 1% bovine serum albumin [BSA], surfactant Triton X-100, preservative Proclin 300, food coloring leaf green). Its supporting instrument is Fully Automated IHC and ISH Staining System (model: BOND-MAX, NMPA Device 20140277) and main supporting reagents are Bond Dewax Solution (NMPA Device 20140293), Bond Epitope Retrieval Solution 2 (NMPA Device 20150327), Bond Wash Solution 10X Concentrate (NMPA Device 20150492), Bond Polymer Refine Detection (NMPA Device 20150558), and Anti-IgG reagents (IHC) (Xiamen Device 20210266). This kit is intended for the in-vitro qualitative detection of the expression of PD-L1 protein in 10% neutral buffer formalin-fixed paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue slides, and to be an aid in identifying NSCLC patients who are eligible for treatment with tislelizumab (tislelizumab injection) in combination with ociperlimab, also to serve as a companion diagnostic of tislelizumab in combination with ociperlimab. Specific sample requirements and test procedures are detailed in the Bridging CDx package insert.

The bridging test samples are derived from the remaining samples of the drug clinical trial subjects who have completed the tests for enrollment using the Clinical Trial Assay (hereinafter referred to as CTA).

The bridging test will be performed at Shanghai Xiawei Biotechnology Co. Laboratory (hereinafter referred to as Shanghai Xiawei). After transporting the blinded samples to Shanghai Xiawei, the test will be performed there and the results will be interpreted in a blinded manner according to the requirements of the Bridging CDx package insert (including test procedures, use of supporting reagents and instruments, etc). After the test, the sponsor will analyze the unblinded data, the demographic baseline data of relevant population and assess the consistency between the Bridging CDx test results and CTA results (including the positive percent agreement, negative percent agreement, overall percent agreement, and their corresponding 95% confidence intervals). Moreover, the correlation between Bridging CDx test results and drug response will be assessed in accordance with the drug clinical trial endpoints (including the primary endpoint: overall survival [OS], and key secondary endpoints: progression-free survival [PFS] and objective response rate [ORR] per investigator using RECIST v1.1), so as to comprehensively evaluate whether Bridging CDx is suitable for the companion diagnostic of the drug in China.

APPENDIX 19. DIAGNOSTIC PROTOCOL FOR VENTANA PD-L1 (SP263) CDX ASSAY IN BEIGENE PHASE 3 STUDY BGB-A317-A1217-302

The diagnostic device testing protocol follows this page.

Approved Date 12/22/2023

Diagnostic Protocol for VENTANA PD-L1 (SP263) CDx Assay in BeiGene Phase 3 Study BGB-A317-A1217-302

Diagnostics Protocol RD005805

Protocol Document No. D162788

Version: Amendment 6

Approved Date 12/22/2023

Study BGB-A317-A1217-302 Sponsor:

(including the performance evaluation of VENTANA PD-L1 (SP263) CDx Assay)

BeiGene, Ltd.

Study BGB-A317-A1217-302 Full Title:

A Phase 3, Randomized, Double-Blind Study of Ociperlimab, an Anti-TIGIT Antibody, in Combination with Tislelizumab Compared to Pembrolizumab in Patients with Previously Untreated, PD-L1-Selected, and Locally Advanced, Unresectable, or Metastatic Non-Small Cell Lung Cancer

Diagnostic Protocol for VENTANA PD-L1 (SP263) CDx Assay in BeiGene Phase 3 Study BGB-A317-A1217-302

Diagnostics Protocol RD005805

Protocol Document No. D162788

Version: Amendment 6

Approved Date 12/22/2023

DIAGNOSTIC PROTOCOL APPROVALS

The following individuals (or their respective designees) have approved this diagnostic protocol via electronic signatures within the 21 CFR Part 11-compliant document management system maintained by Ventana Medical Systems, Inc. (Roche Tissue Diagnostics; RTD).

Name and title of the persons authorized to sign the protocol:

Role	Name, Title	Signature	Date
Clinical Operations Representative	[redacted], Global Study Lead	e-signature	e-date
Biometrics Lead	[redacted], Biometrics Director	e-signature	e-date
Development Representative	[redacted], PHCS Senior Manager	e-signature	e-date
Regulatory Representative	[redacted], Senior Regulatory Affairs Manager	e-signature	e-date
Medical Expert	[redacted], Staff Pathologist II	e-signature	e-date
Clinical Quality Representative	[redacted], Clinical Quality Assurance Lead	e-signature	e-date
Clinical Development Lead	[redacted], Clinical Development Lead	e-signature	e-date
Medical Writer	[redacted], Clinical Development Lead	e-signature	e-date

Diagnostic Protocol for VENTANA PD-L1 (SP263) CDx Assay in BeiGene Phase 3 Study BGB-A317-A1217-302

Diagnostics Protocol RD005805

Protocol Document No. D162788

Version: Amendment 6

Approved Date 12/22/2023

PROTOCOL SIGNATURE PAGE

ADHERENCE TO THE PROTOCOL AND APPLICABLE REGULATIONS:

I have read and understand this diagnostic (Dx) protocol provided by the investigational in vitro diagnostic (IVD) device manufacturer, Ventana Medical Systems, Inc. (Roche Tissue Diagnostics; RTD). I agree to conduct the investigational diagnostic testing-related study activities in accordance with this Dx protocol, Good Clinical Practice (GCP) guidelines, standard laboratory practices, local laws, and applicable country-specific regulations.

USE OF INVESTIGATIONAL PRODUCT:

I understand that the investigational IVD device may be used only for the purposes explicitly described in this Dx protocol. The Dx testing site must document receipt, use, and disposition of all investigational products received and used during the course of the Dx testing as directed by RTD. Furthermore, I understand that the staining procedure used during the conduct of this Dx protocol is considered investigational and will not be available for use after the study is complete.

COOPERATION IN AUDITS:

I agree to make all original source documents and regulatory documents pertaining to this Dx protocol available to RTD or its authorized agents, and applicable regulatory authorities. I agree to cooperate fully with the conduct of protocol-related audits.

CONFIDENTIALITY:

I agree to handle all Dx protocol-related information and documentation received from RTD and its authorized agents under the terms of the Statement of Work.

Investigator Name (Print)	Investigator Signature	Date (dd-Mmm-yyyy)

Diagnostic Protocol for VENTANA PD-L1 (SP263) CDx Assay in BeiGene Phase 3 Study BGB-A317-A1217-302

Diagnostics Protocol RD005805

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The information contained in this protocol is the property of Ventana Medical Systems, Inc. (Roche Tissue Diagnostics; RTD). This information is confidential and is to be used only in connection with matters authorized by RTD; no part of this Dx protocol is to be disclosed or distributed to others without prior written permission from RTD.

The conduct of this Dx protocol will be in accordance with applicable sponsor and Investigator responsibilities as described in Title 21 of the US Federal Code of Regulations (CFR) parts 803, 809 and 812, ISO 20916:2019, GCP guidelines, Declaration of Helsinki, In Vitro Diagnostic Regulation (IVDR) EU 2017/746, and applicable local regulations.

This protocol is conducted using the investigational product VENTANA PD-L1 (SP263) CDx Assay and the product labeling includes the following:

CAUTION: Investigational Device. Limited by Federal (or United States) law to Investigational Use.

The investigational device for the performance study conforms to the requirements of the EU Regulation 2017/746 of the European Parliament and of the Council on In Vitro Diagnostic Medical Devices (IVDR) apart from those to be evaluated.

Diagnostic Protocol for VENTANA PD-L1 (SP263) CDx Assay in BeiGene Phase 3 Study BGB-A317-A1217-302

Diagnostics Protocol RD005805

Protocol Document No. D162788

Version: Amendment 6

Approved Date 12/22/2023

REVISION HISTORY

Version	Changes and Rationale	Effective Date
Amendment 6 (PDPDA1011167)	• To align with versions 2.0, 4.1, and 5.0 of the BeiGene Phase 3 Study BGB-A317-A1217-302 protocol amendments, the Dx protocol was updated as follows: ○ Updated randomized study population target from 605 to 660 patients to align with version 2.0 of the BeiGene Study BGB-A317-A1217-302 Rx Protocol ○ Updated the study population randomization ratio from 5:5:1 to 5:5:2 (patients in Arms A, B, and C, respectively) to align with version 2.0 of the BeiGene Study BGB-A317-A1217-302 Rx Protocol ○ Updated pharmaceutical study tumor specimen exclusion criteria to include BRAF V600E mutations and ROS1 mutations to align with version 2.0 of the BeiGene Study BGB-A317-A1217-302 Rx Protocol ○ Updated specimen inclusion criteria to include specimens sent to the Dx testing site for confirmatory testing from Japan patients that were enrolled and randomized using results from a local PD-L1 test that is approved by the Ministry of Health, Labour and Welfare to align with version 4.1 of the BeiGene Study BGB-A317-A1217-302 Rx Protocol. ○ Updated study duration from 50 to 58 months to align with version 5.0 of the BeiGene Study BGB-A317-A1217-302 Rx Protocol ○ Updated the study primary efficacy endpoints to remove Progression Free Survival to align with version 5.0 of the BeiGene Study BGB-A317-A1217-302 Rx Protocol • Updated Section 13 to align safety language with IVDR • Minor typographical error corrections were made throughout the document	20-Dec-2023
Amendment 5 (PDPDA 1004316)	• Dx protocol was updated to align the definition of Serious Adverse Event (SAE) with Regulation (EU) 2017/746 (IVDR) Article Number 2(61).	19-Dec-2022

Approved Date 12/22/2023

	• BeiGene Study BGB-A317-A1217-302 title is updated to align with BeiGene Phase 3 Study BGB-A317-A1217-302 protocol amendment 3.0. • Name of therapeutic updated to be consistent with Beigene protocol amendment 3.0	
Amendment 4 (C118426)	To align with 'ver 2.3 US' of the BeiGene Phase 3 Study BGB-A317-A1217-302 protocol, the Dx protocol was updated as follows: • Dx Protocol was updated to describe the use of local PD-L1 test results from a certified laboratory using an FDA-approved assay (limited to 22C3, SP263, 28-8) for patient enrollment in the United States (US). • In Section 7.2.1 "Primary Endpoints": the Intent to Treat (ITT) Analysis Set was updated to include all randomized patients, which are selected using either the investigational VENTANA PD-L1 (SP263) CDx Assay or the local PD-L1 test result in the US. • In Section 8.2.3.1 specimen inclusion criteria were updated to include specimens sent to the Dx testing site for confirmatory testing from US patients that were enrolled and randomized using a local PD-L1 test result. • Added Section 13.2.3 "DD Reporting Requirements" to align with the internal processes. • Added Section 13.2.4 "AE Causality Assessment Procedure" to align with the EU regulations.	27-Jun-2022
Amendment 3 (C113775)	• Dx Protocol was updated to clarify that BeiGene is the Sponsor of the performance evaluation of VENTANA PD-L1 (SP263) CDx Assay. • Added additional background information to give context for the rationale for the diagnostic protocol. • The primary efficacy endpoints applicable to the performance evaluation of VENTANA PD-L1 (SP263) CDx Assay were explicitly incorporated into the Dx protocol and referenced from the BeiGene Study BGB-A317-A1217-302 protocol. • Details on the planned statistical analyses were added along with references to the applicable sections of the BeiGene Study BGB-A317-A1217-302 protocol. • Added RTD's confirmation on its adherence to currently effective local regulations including MPG §22c with respect to revisions of the Dx protocol.	12-Jan-2022

Diagnostic Protocol for VENTANA PD-L1 (SP263) CDx Assay in BeiGene Phase 3 Study BGB-A317-A1217-302

Diagnostics Protocol RD005805

Protocol Document No. D162788

Version: Amendment 6

Approved Date 12/22/2023

Amendment 2 (C110999)	• Dx protocol updated to clarify that BeiGene is the Sponsor of the performance evaluation and that the role of this Dx protocol is to support the Dx testing under BeiGene Study BGB-A317-A1217-302 with VENTANA PD-L1 (SP263) CDx Assay. • Updates made to the Dx protocol objectives and endpoints to clarify that the outcome analyses to be used as a basis for the performance evaluation of the investigational IVD device will be performed by BeiGene and that this Dx protocol's primary endpoints are dependent on the endpoints defined under the pharmaceutical study. • The serious adverse event reporting requirements specific to BfArM agency were reinstated following feedback from BfArM. • Clarified that the methods and risks associated with the sample collection are the responsibility of the enrollment sites under BeiGene Study BGB-A317-A1217-302, and that information on these methods can be found in the pharmaceutical lab manual for BeiGene Study BGB-A317-A1217-302. • Other updates included clerical edits throughout the document.	24-Sep-2021
Amendment 1 (C106617)	• In response to the BfArM, Germany, the intended use statement for VENTANA PD-L1 (SP263) CDx Assay was revised. • Removed instructions specific to Germany for the handling of serious adverse event reporting, because Dx testing will not be conducted in Germany. • The definitions for the Adverse Event (AE), Device Deficiency (DD), and Adverse Device Effect (ADE) were revised or added per ISO 20916 standard. • AE reporting, study risk assessments, and ethics committee approval requirements, and responsibilities were updated in alignment with ISO 20916 standard. • Added clarity on the responsibilities between Dx testing sponsor and associated pharmaceutical study sponsor. • Updated the recommended storage temperature for the unstained slides. • Other updates included minor clerical edits throughout the document.	13-May-2021
Initial (C100623)	Initial release	16-Nov-2020

Approved Date 12/22/2023

AMENDMENT 6 SUMMARY

Rationale for Amendment 6

The purpose of this protocol amendment is to align the Dx Protocol with versions 2.0, 4.1, and 5.0 of the BeiGene Study BGB-A317-A1217-302 Rx Protocol amendments with updates that are relevant to the Dx Protocol.

Summary of Changes for Amendment 6

Changes to the protocol are summarized below:

Sections Changed	Description of Change
Diagnostic Protocol Approvals	Updated Dx protocol approvers
§2.3 BeiGene Study BGB-A317-A1217-302 pharmaceutical study design and §12.1 Sample Size and Justification	Updated study population target from 605 to 660 patients to align with version 2.0 of the BeiGene Study BGB-A317-A1217-302 Rx Protocol
§2.3 BeiGene Study BGB-A317-A1217-302 pharmaceutical study design	Updated the study population randomization ratio from 5:5:1 to 5:5:2 (patients in Arms A, B, and C, respectively) to align with version 2.0 of the BeiGene Study BGB-A317-A1217-302 Rx Protocol
§2.3 BeiGene Study BGB-A317-A1217-302 pharmaceutical study design and §3.6 Rationale	Updated pharmaceutical study tumor specimen exclusion criteria to include BRAF V600E mutations and ROS1 mutations to align with version 2.0 of the BeiGene Study BGB-A317-A1217-302 Rx Protocol
Throughout the document	Updated specimen inclusion criteria to include specimens sent to the Dx testing site for confirmatory testing from Japan patients that were enrolled and randomized using results from a local PD-L1 test that is approved by the Ministry of Health, Labour and Welfare to align with version 4.1 of the BeiGene Study BGB-A317-A1217-302 Rx Protocol.
Synopsis and §2.4	Updated study duration from 50 to 58 months to align with version 5.0 of the BeiGene Study BGB-A317-A1217-302 Rx Protocol
§7.2.1 Primary Endpoint	Updated the study primary efficacy endpoints to remove Progression Free Survival to align with version 5.0 of the BeiGene Study BGB-A317-A1217-302 Rx Protocol
§13 Adverse Event Reporting and Handling	Updated section to align with IVDR

Throughout the document	Made minor typographical error corrections

AMENDMENT 5 SUMMARY

Rationale for Amendment 5

To align the definition of Serious Adverse Event (SAE) with Regulation (EU) 2017/746 (IVDR) Article Number 2(61).

Summary of Changes for Amendment 5

Changes to the protocol are summarized below:

Sections Changed	Description of Change
Throughout	Drug name updated to be consistent with Beigene protocol amendment 3.0
§13.1.4.Serious Adverse Event (SAE)	Updated SAE definition to align with the IVDR Article number 2(61)
Cover Page and DIAGNOSTIC PROTOCOL SYNOPSIS	Updated BeiGene Study BGB-A317-A1217-302 title to align with BeiGene Phase 3 Study BGB-A317-A1217-302 protocol amendment 3.0.

Approved Date 12/22/2023

Approved Date 12/22/2023

AMENDMENT 4 SUMMARY

Rationale for Amendment 4

To align with 'ver 2.3 US' of the BeiGene Phase 3 Study BGB-A317-A1217-302 protocol, the Dx protocol was updated as follows:

- Dx Protocol was updated to describe the use of local PD-L1 test results from a certified laboratory using an FDA-approved assay (limited to 22C3, SP263, 28-8) for patient enrollment in the United States (US).
- In Section 7.2.1 "Primary Endpoints": the ITT Analysis Set was updated to include all randomized patients, which are selected using either the investigational VENTANA PD-L1 (SP263) CDx Assay or the local PD-L1 test result in the US.
- In Section 8.2.3.1 the specimen inclusion criteria were updated to include specimens sent to the Dx testing site for confirmatory testing from US patients that were enrolled and randomized using a local PD-L1 test result.
- Added Section 13.2.3 "DD Reporting Requirements" to align with the internal processes.
- Added Section 13.2.4 "AE Causality Assessment Procedure" to align with EU regulations.

Summary of Changes for Amendment 4

Changes to the protocol are summarized below:

Sections Changed	Description of Change
Diagnostic Protocol Approvals	Updated Dx protocol approvers
DIAGNOSTIC PROTOCOL SYNOPSIS	Updated language to match the body of the Dx protocol.
§1.ABBREVIATIONS AND DEFINITIONS	Updated the list to include United States (US).
§2.3.BeiGene Study BGB-A317-A1217-302	Added local PD-L1 testing using an FDA-approved assay (limited to 22C3, SP263, 28-8) at a certified laboratory for patient enrollment in the US. Added details on confirmatory testing of tumor samples collected for local PD-L1 testing in the central Dx testing sites before patient randomization process.

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	Updated Table 1 to include device deficiency reporting in "Responsibilities per RTD Dx Protocol RD005805" column.
§7.1.Design Overview	Added details on the local PD-L1 testing for patient randomization purposes in the US. Added details on confirmatory testing of tumor samples collected for local PD-L1 testing in the central Dx testing sites before patient randomization process.
§7.2.1.Primary Endpoint	Added US patients randomized based on local PD-L1 testing, in the Intent to Treat (ITT) population.
§8.2.3.1.Inclusion Criteria	Inclusion Criteria are extended to include specimens collected from US patients for local PD-L1 testing sent to the Dx testing site for confirmatory testing.
§13.2.3.DD Reporting Requirements	Added "Device Deficiency (DD) Reporting Requirements" section to align with internal processes.
§13.2.4.AE Causality Assessment Procedure	Added "Adverse Events (AE) Causality Assessment Procedure" section to align with EU regulations.

Approved Date 12/22/2023

AMENDMENT 3 SUMMARY

Rationale for Amendment 3

- Dx Protocol was updated to clarify that BeiGene is the sponsor of the performance evaluation of VENTANA PD-L1 (SP263) CDx Assay.
- Added additional background information to give context for the rationale for the diagnostic protocol.
- The primary efficacy endpoints applicable to the performance evaluation of VENTANA PD-L1 (SP263) CDx Assay were explicitly incorporated into the Dx protocol and referenced from the BeiGene Study BGB-A317-A1217-302 protocol.
- Details on the planned statistical analyses were added along with references to the applicable sections of the BeiGene Study BGB-A317-A1217-302 protocol.
- Added RTD's confirmation on its adherence to currently effective local regulations including MPG §22c with respect to revisions of the Dx protocol.

Summary of Changes for Amendment 3

Changes to the protocol are summarized below:

Sections Changed	Description of Change
Title Page	Clarified that BeiGene is the sponsor of the performance evaluation of VENTANA PD-L1 (SP263) CDx Assay.
Diagnostic Protocol Approvals	Updated list of Dx protocol approvers.
DIAGNOSTIC PROTOCOL SYNOPSIS	Included BeiGene Ltd. as the sponsor of the Performance Evaluation. Updated language to match the body of the Dx protocol.
§1. ABBREVIATIONS AND DEFINITIONS	Updated list of abbreviations to add PFS and OS.
§3.6. Rationale	Added additional background information to give context to the rationale for the use of VENTANA PD-L1 (SP263) CDx Assay in BeiGene Study BGB-A317-A1217-302.
§7.1. Design Overview	Added language to clarify that the performance of the CDx investigational IVD is evaluated in the same clinical trial as the investigational treatment and that the performance is considered acceptable if the endpoints of the pharmaceutical trial in the population identified by the IVD are met.

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§7.2. Endpoints and Acceptance Criteria	Added specificity to the primary endpoints by clarifying the endpoints associated with BeiGene Study BGB-A317-A1217-302 that would be used to assess the performance of VENTANA PD-L1 (SP263) CDx Assay.
§12.1. Sample Size and Justification	Specified where the information for sample size and justification for the BieGene study can be located in the BeiGene Study BGB-A317-A1217-302 protocol.
§12.2. Planned Analyses	Added details on the planned statistical analyses for the determination of the performance of VENTANA PD-L1 (SP263) CDx Assay.
§14.6. Revisions to the Dx Testing Protocol	Updated to clarify that amendments to the Dx protocol will be conducted according to applicable local regulations including MPG §22c. Applicable content under MPG §22c was added to the section.
Throughout Document	Clerical edits made for clarity.

Approved Date 12/22/2023

AMENDMENT 2 SUMMARY

Rationale for Amendment 2

- Dx protocol updated to clarify that BeiGene is the sponsor of the performance evaluation and that the role of this Dx protocol is to support the Dx testing under BeiGene Study BGB-A317-A1217-302 with VENTANA PD-L1 (SP263) CDx Assay.
- Updates made to the Dx protocol objectives and endpoints to clarify that the outcome analyses to be used as a basis for the performance evaluation of the investigational IVD device will be performed by BeiGene and that this Dx protocol's primary endpoints are dependent on the endpoints defined under the pharmaceutical study.
- The serious adverse event reporting requirements specific to BfArM agency were reinstated following feedback from BfArM.
- Clarified that the methods and risks associated with the sample collection are the responsibility of the enrollment sites under BeiGene Study BGB-A317-A1217-302, and that information on these methods can be found in the pharmaceutical lab manual for BeiGene Study BGB-A317-A1217-302.
- Other updates included clerical edits throughout the document.

Summary of Changes for Amendment 2

Changes to the protocol are summarized below:

Sections Changed	Description of Change
Title Pages	Clarified that the sponsor of the Study is BeiGene, and changed the title of the protocol as it is intended to support BeiGene Study BGB-A317-A1217-302. Statement added that this Dx protocol is in accordance with ISO 20916 and other applicable standards.
Diagnostic Protocol Approvals	Updated to current approver information.
DIAGNOSTIC PROTOCOL SYNOPSIS	Updated sections to match content within the body of the Dx protocol.
§1. ABBREVIATIONS AND DEFINITIONS	Added abbreviations for companion diagnostic (CDx), diagnostic (Dx), BfArM, IVD device, and intention-to-treat (ITT).
§2.2 Dx Protocol Contact Information	Updated Dx protocol contact information.
§2.3. BeiGene Study BGB-A317-A1217-302	Clarified the relationship between this Dx protocol and BeiGene Study BGB-A317-A1217-302.

Approved Date 12/22/2023

	Added **Table 1** delineating the responsibilities between BeiGene Study BGB-A317-1217-302 and RTD's Dx protocol.
§2.4. Start Date and Duration of the Investigational IVD Device Testing	Clarified that applicable authorizations and favorable opinions for this Dx protocol are needed before testing.
§3.5. Analytical Performance for the VENTANA PD-L1 (SP263) CDx Assay	Clarified that the summary of analytical performance can be found in the associated Investigator's Brochure.
§3.6. Rationale	Removed statement on responsibilities as this statement was added to pg. 4 and expanded.
§5. DIAGNOSTIC TESTING PROTOCOL OBJECTIVES	Clarified that the objective of this Dx protocol is to support BeiGene Study BGB-A317-A1217-302 and that the results from BeiGene Study BGB-A317-A1217-302 would serve as the performance evaluation of the investigation IVD device.
§7.1. Design Overview	Clarified the design of this Dx protocol is in support of BeiGene Study BGB-A317-A1217-302. Updated **Figure 1** to point to Section 10.4.2.4.2. for instructions on repeat staining.
§7.2.1 Endpoints And Acceptance Criteria	Clarified that the efficacy analyses that will be used in the performance evaluation of the investigational IVD device will be performed by BeiGene and will depend on the outcome results of BeiGene Study BGB-A317-A1217-302.
§8.2.1. Source and Number of Specimens	Clarified that the sample collection methods and risks are the responsibility of the enrollment sites for BeiGene Study BGB-A317-A1217-302.
§10.5.4.1. PD-L1 Expression in Tumor Cells	Clarified the details on the estimation of the PD-L1 expression level.
§12.2. Planned Analyses	Clarified that BeiGene will perform efficacy analyses related to patients identified by the investigational IVD device, and that these results will be used as the basis for the performance evaluation of the investigational IVD device.
§13.1.4. Serious Adverse Event (SAE)	Reinstated language for the definition of SAE in accordance with MPSV.
§13.2.2. Serious Adverse Events Reporting Requirements	Reinstated SAE reporting requirements and Error! Reference source not found. following BfArM feedback.
§14.1. Diagnostic Testing Protocol Risk Assessment	Added language surrounding risks associated with biopsies under BeiGene Study BGB-A317-A1217-302 as described in the appendix (benefit-risk assessment) of the associated investigator's brochure.

Approved Date 12/22/2023

	Added language to align with the associated investigator's brochure on risk associated with false results and in the use of the investigational IVD device by Dx testing site personnel.
§14.1.7. Risk Benefit Conclusion	Added a risk benefit conclusion to Dx protocol risk assessment. Removed language on insurance as it is not applicable to the Dx protocol.
§14.6. Revisions to the Dx Testing Protocol	Updated to provide clarity around the amendment process.
§14.8. Early Termination	Added reporting requirement following early termination to be in alignment the Medical Devices Act.
Throughout Document	Updated language to clarify that this Dx protocol supports BeiGene Study BGB-A317-A1217-302. Aligned on the terminology used for the investigational IVD device. Clerical edits made for clarity.

Approved Date 12/22/2023

AMENDMENT 1 SUMMARY

Rationale for Amendment 1

- The intended use statement for the VENTANA PD-L1 (SP263) CDx Assay was revised in response to the feedback received from the Federal Institute for Drugs and Medical Devices (BfArM), Germany and to better align with what will be evaluated in this specific study.
- The serious adverse event reporting requirements to the BfArM agency were removed. because 1) the Dx testing for NSCLC specimens will not be conducted in Germany, and 2) adverse events associated with patients will be handled according to the efficacy study protocol BGB-A317-A1217-302.
- The definitions for the Adverse Event (AE), Device Deficiency (DD), and Adverse Device Effect (ADE) were updated or added to better align with ISO 20916 standard.
- AE reporting, study risk assessments, and ethics committee approval requirements and responsibilities were updated in alignment with ISO 20916 standard.
- Added clarity on the responsibilities between the Dx testing sponsor and the associated pharmaceutical study sponsor.
- Updated the recommended storage temperature for the unstained slides based on new analytical data available from RTD's Research and Development team.
- Other updates included clerical edits throughout the document.

Summary of Changes for Amendment 1

Changes to the protocol are summarized below:

Sections Changed	Description of Change
Throughout the Document	• Added clarity on the study responsibilities between the Dx testing sponsor and associated pharmaceutical study sponsor. • Clarified that the diagnostic testing using the investigational CDx device (VENTANA PD-L1 [SP263] CDx Assay) will be executed per this protocol, and the study activities associated with the diagnostic testing are sponsored by RTD. • Minor clerical edits were made throughout the document for clarity.
Sponsor Approvals	Updated with current representatives at RTD.
Protocol Signature Page	Clarified that the signature page applies to the diagnostic testing protocol.

Approved Date 12/22/2023

Sections Changed	Description of Change
Synopsis	• The intended use statement for the VENTANA PD-L1 (SP263) CDx Assay was revised. • The study classification was updated as "Companion Diagnostic (CDx)".
§1 Abbreviations and Definitions	Updated the list of abbreviations
§2.2 CDx Device Sponsor Contact Information	Minor clerical edits, and added author name for the protocol Amendment 1.
§2.3 Associated Pharmaceutical Trial: Relationship between Pharmaceutical Study and Companion Diagnostic Protocol:	Added text to clarify the overall objectives of the CDx device protocol and associated pharmaceutical study protocol.
§2.4 Duration of the Investigational CDx Device Testing	Updated title of Section §2.4 to reflect testing period for the investigational CDx device, and made minor clerical edits in the paragraph for clarity.
§3.6 Rationale	Updated title of Section §3.6 and minor edits were made in the paragraph for clarity.
§4. Investigational Product Proposed Intended Use	The final sentence in the intended use statement for the VENTANA PD-L1 (SP263) CDx Assay was revised to better align with what is being evaluated in this specific study: <u>Currently reads:</u> It is indicated as an aid in identifying patients eligible for treatment with PD-L1 or PD-1 targeted therapy. <u>Revised to read:</u> VENTANA PD-L1 (SP263) CDx Assay is indicated as an aid in identifying NSCLC patients who may benefit from treatment with PD-1 targeted therapy in combination regimens."
§5. Diagnostic Testing Protocol Objectives	Updated the heading title for Section §5, and a minor edit was made in the paragraph for clarity.
§6. Investigation CDx Device	Updated the heading title.
§7.1 Design Overview	Removed details associated with the drug study and focused this section on activities related to this Dx protocol.
Figure 1	Updated the Figure. 1 title.
§9. Materials	In this section, updated the heading and table 1 title, and made minor edits for clarity in sections §9.2 and §9.3.
§10 Procedures	• Updated the heading for Section §10.

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Sections Changed	Description of Change
	• The sponsor name for the diagnostic testing protocol was added in Section §10.1. • Minor edits in Section §10.2.
§10.3.1 Case Slides	In the first paragraph, the recommended storage temperature for the unstained slides was updated from "30°C ± 5°C or 5°C ± 3°C" to "room temperature".
§10.6 Close-Out	Updated the heading title for Section §10.6, and a minor edit was made in the paragraph for clarity.
§11.1 Data Collection and Handling	The following text was added in the first paragraph, "Demographic data and specimen characteristic data associated with the specimens among the intent to diagnose population, including screen failures, is desired and when available will be provided to RTD via data transfer."
§13. Adverse Event Reporting and Handling	The following revisions were made in Section §13. • The definitions (§13.1) for the Adverse Event (AE), Device Deficiency (DD), and Adverse Device Effect (ADE) were updated or added per ISO 20916 standard. • In Section §13.2.1, it was clarified that no AEs are anticipated at the Dx study sites among users of the VENTANA PD-L1 (SP263) CDx Assay (includes Benchmark ULTRA instrument operators and pathologist readers interpreting the assay). Added a statement that RTD will report to the drug study sponsor any events in which RTD has become aware that the accuracy of one or more reported results were compromised. • The serious adverse event reporting requirements to BfArM agency (§13.2.2) was removed in this section.
§14. Ethics and Compliance	• In sections §14.1.1, §14.1.2, §14.1.3, and §14.1.4, clarified text related to risks associated with false results from the investigational CDx device assay. Also, clarified text to describe the responsibility of Dx protocol versus drug study, and made minor edits for clarity. • Removed the following Germany specific texts (*italics* text)), 1. In Section §14.1.6, "*and these investigational; testing sites receiving samples from BeiGene Study BGB-A317-A1217-302 enrolling sites located in Germany will adhere to the provisions of the German Federal Data Protection Act*" 2. In Section §14.1.7, "*For patients from German enrolling sites, RTD will provide patient insurance according to §20 of the German Medical Device Act*

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Sections Changed	Description of Change
	through an insurer authorized to conduct business in Germany". 3. In Section §14.2, "*When applicable, the diagnostic testing site receiving specimens from BeiGene Study BGB-A317-A1217-302 clinical enrollment sites in Germany must comply with the sections of the German Medical Device Act and the Ordinance on Clinical Trials with Medical Devices (MPKPV) that apply to performance evaluation studies with in vitro diagnostic devices. The site may not begin testing specimens from German sites until BfArM grants approval for the diagnostic performance evaluation and a German ethics committee grants approval for Study BGB-A317-A1217-302, if required by the Lead German EC responsible to approve Study BGB-A317-A1217-302. BeiGene and RTD will comply with the sections of the German MPKPV that apply to performance evaluation studies with in vitro diagnostic devices in the conduct of this study"*. • Added the following texts (*italics* text), 1. In Section §14.1.6, "*to minimize the risk of false results from the VENTANA PD-L1 (SP263) CDx Assay, the assay has been analytically validated, appropriate controls are included as part of the staining procedure, and all pathologists evaluating patient slide for the CDx study will be medical professionals trained in the interpretation of the assay-stained slides. The pathologists will be required to demonstrate competence in assay interpretation before evaluating any patient slides for the study*". 2. In section §14.2, the last bullet point, "*studies in EU must adhere to specific regulations, including those from National Health Authorities from EU member states, etc*". 3. In Section §14.2, "*In countries where national health authorities require approvals or notifications related to the use of an investigational diagnostic in a pharmaceutical clinical trial, diagnostic testing site(s) may not begin testing specimens received from clinical enrollment sites until requisite permissions have been obtained. The pharmaceutical study sponsor is responsible to ensure the requisite permissions have been obtained prior to submitting tumor samples to diagnostic testing sites*." 4. In Section, §14.6, the second paragraph, "*Where applicable, major changes may be reportable to health authorities (eg, FDA)*". The heading title was updated for the §14.6 section.

Sections Changed	Description of Change
	• In Section §14.8, added clarifying text on how to handle study termination. • In Section 14.10.2, the part number for the product method sheet/package insert was updated.

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DIAGNOSTIC PROTOCOL SYNOPSIS

This protocol describes the procedures for the investigational diagnostic testing occurring as part of BeiGene Study BGB-A317-A1217-302.

PHARMACEUTICAL STUDY/DIAGNOSTIC PERFORMANCE EVALUATION SPONSOR	
Sponsor	BeiGene, Ltd.
DIAGNOSTIC (Dx) PROTOCOL TITLE	
Full Title	Diagnostic Protocol for VENTANA PD-L1 (SP263) CDx Assay in BeiGene Phase 3 Study BGB A317-A1217-302
Short Title	PD-L1 (SP263) NSCLC CDx Study for BeiGene Phase 3 Study BGB-A317-A1217-302
Dx PROTOCOL CONTACT INFORMATION	
Company Name and Address	Ventana Medical Systems, Inc. (Roche Tissue Diagnostics; RTD) 1910 E. Innovation Park Drive Tucson, AZ 85755
Responsible Contact Person(s)	An updated list of RTD staff contact information will be maintained throughout the study in the study file. The definitive list will be provided in the report from RTD.
INVESTIGATIONAL IN VITRO DIAGNOSTIC (IVD) DEVICE INFORMATION	
IVD Device Name	VENTANA PD-L1 (SP263) CDx Assay
Instrument & Software	VENTANA BenchMark ULTRA instrument running Ventana System Software (VSS) version 12.3 or higher
Proposed Intended Use Statement	VENTANA PD-L1 (SP263) CDx Assay is intended to be a qualitative immunohistochemical assay using anti-PD-L1 monoclonal antibody (SP263) for the assessment of programmed death ligand 1 (PD-L1) protein in formalin-fixed, paraffin-embedded (FFPE) NSCLC tissue stained with OptiView DAB IHC Detection Kit on a BenchMark ULTRA instrument. VENTANA PD-L1 (SP263) CDx Assay is indicated as an aid in identifying NSCLC patients who may benefit from treatment with PD-1 targeted therapy in combination regimens.
Dx PROTOCOL INFORMATION	
Classification	Companion Diagnostic (CDx)
Primary Objective	The primary objective of this Dx protocol is to support BeiGene Study BGB-A317-A1217-302 by identifying the PD-L1 expression level of tumor specimens for patient enrollment. Results from BeiGene Study BGB-A317-A1217-302 will serve as the performance evaluation for VENTANA PD-L1 (SP263) CDx Assay in terms of its ability to identify patients who are likely to benefit from ociperlimab in combination with tislelizumab in patients with previously untreated, PD-L1-selected, and locally advanced, unresectable, or metastatic NSCLC.

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Design Summary	In the standard drug-companion diagnostic (CDx) co-development model, the clinical utility of an investigational treatment and an investigational IVD are evaluated in the same clinical trial, and the performance of the investigational IVD is considered acceptable if the clinical trial efficacy endpoint(s) in the population identified by the IVD are met. Following this model, a combined study approach will be used, which will include protocols for the investigational treatment (BGB-A317-A1217-302) and the investigational IVD (D162788). As part of the co-development paradigm including both an investigational therapy and an investigational IVD, RTD, as the IVD device manufacturer, will be responsible for certain aspects of the investigational IVD medical device's [VENTANA PD-L1 (SP263) CDx Assay] use within BeiGene Study BGB-A317-A1217-302. As such, this Dx protocol supports BeiGene Study BGB-A317-A1217-302 by describing the procedures for how the patient tumor samples collected as part of BeiGene Study BGB-A317-A1217-302 should be tested with VENTANA PD-L1 (SP263) CDx Assay at the Dx testing sites. No hypothesis testing will be performed under this Dx protocol, as outcome data from BeiGene Study BGB-A317-A1217-302 will be used to evaluate the clinical performance of VENTANA PD-L1 (SP263) CDx Assay as an IVD device for ociperlimab in combination with tislelizumab in patients with previously untreated, PD-L1-selected, locally advanced, unresectable, or metastatic NSCLC. The investigational VENTANA PD-L1 (SP263) CDx Assay will be used to assess the PD-L1 expression level in NSCLC tumor specimens collected from patients who are being screened to determine eligibility to participate in BeiGene Study BGB-A317-A1217-302. It is anticipated that tumor specimens from approximately 2400 patients undergoing screening to participate in Study BGB-A317-A1217-302, will be stained with VENTANA PD-L1 (SP263) CDx Assay at central Dx testing sites. Stained slides from each case submitted for testing will be interpreted by qualified pathologists who will assign a PD-L1 expression level at the 50% tumor cell (TC) threshold (< 50% vs. ≥ 50%). A PD-L1 expression level ≥ 50% TC will be one of several factors used to determine eligibility for enrolling patients into BeiGene Study BGB-A317-A1217-302. In the United States (US) and Japan only, a local PD-L1 test result from an FDA-approved or Ministry of Health, Labour and Welfare-approved assay, respectively (limited to 22C3, SP263, 28-8) used at a certified laboratory according to manufacturer's instructions may be used for patient enrollment and randomization. Tumor specimens from US and Japan patients enrolled with a local PD-L1 result will also be stained centrally with VENTANA PD-L1 (SP263) CDx Assay. Performance of VENTANA PD-L1 (SP263) CDx Assay will be evaluated in BeiGene Study A317-A1217-302 as described in this Dx protocol.
Target Population for BeiGene Study BGB-A317-A1217-302	The target patient population is described in detail in the BeiGene Study BGB-A317-A1217-302 protocol, including a list of eligibility criteria.
Planned Number of Specimens	Specimens from approximately 2400 patients are expected to be tested with VENTANA PD-L1 (SP263) CDx Assay.

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Main Inclusion/Exclusion Criteria for Specimens	To be included in this Dx protocol, a specimen must meet all of the following criteria: 1. It must be a newly acquired tumor biopsy or an archival tumor specimen submitted for either patient enrollment screening or confirmatory testing for US and Japan patients enrolled with a local test result for BeiGene Study BGB-A317-A1217-302 2. It must be an FFPE NSCLC specimen processed in accordance with standard practice; 3. It must contain sufficient tumor tissue for interpretation (at the discretion of the reviewing pathologist); and 4. If an FFPE tissue block is unavailable, unstained FFPE slides prepared from these specimens can be submitted A specimen will be excluded if any of the following criteria are met: 1. It is a fine needle aspirate or cytology specimen. 2. It consists of tissue that has been decalcified; 3. It is fixed in 95% alcohol or higher, AFA or PREFER™; 4. Cut slides from tissue blocks were prepared over 12 months prior to staining.
Investigational IVD Device Testing Start And Duration	It is anticipated that testing under this Dx protocol will begin as soon as reasonably possible after all applicable authorizations and favorable opinions have been issued for this Dx protocol. Thus, the anticipated Dx testing start will be late 2020. The Dx testing will continue until all specimens are tested by VENTANA PD-L1 (SP263) CDx Assay for BeiGene Study BGB-A317-A1217-302 enrollment or central confirmation (US and Japan only). The estimated duration of BeiGene Study BGB-A317-A1217-302 is 58 months.
Medical Expert/Medical Monitor	[redacted] Staff Pathologist II Tel: Tel: [redacted] Email [redacted]
Investigators	An updated list of Principal Investigators, Dx testing sites, and institutions will be maintained throughout the conduct of the Dx protocol in RTD's study file. The definitive list will be provided in the final report from RTD.
PHARMACEUTICAL CLINICAL TRIAL INFORMATION	
Study Sponsor	BeiGene, Ltd. c/o BeiGene USA, Inc. 2955 Campus Drive, Suite 200 San Mateo, California 94403 USA *United States Tel: +1 (781) 801-1800* *Europe Tel:+41-61-685-1900* *Legal Representative in the EU:* *BeiGene Ireland Limited* 10 Earlsfort Terrace Dublin 2, D02 T380 Ireland

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Study Number	BGB-A317-A1217-302
Study Title	A Phase 3, Randomized, Double-Blind Study of Ociperlimab, an Anti-TIGIT Antibody, in Combination With Tislelizumab Compared to Pembrolizumab in Patients With Previously Untreated, PD-L1-Selected, and Locally Advanced, Unresectable, or Metastatic Non-Small Cell Lung Cancer
Investigational Therapy	tislelizumab (BGB-A317) and ociperlimab (BGB-A1217)
Investigational Therapy Indication	Locally advanced, unresectable, or metastatic NSCLC
Role of the Diagnostic Protocol in BeiGene Study BGB-A317-A1217-302	RTD's Dx protocol, RD005805, will use NSCLC specimens from patients undergoing screening to determine eligibility for BeiGene Study BGB-A317-A1217-302. Samples will be tested with VENTANA PD-L1 (SP263) CDx Assay to determine their PD-L1 expression level (< 50% vs. ≥ 50% TC staining). Only patients with PD-L1 expression level ≥ 50% TC (referred to as high level of PD-L1 in BeiGene Study BGB-A317-A1217-302) will be enrolled into BeiGene Study BGB-A317. In the US and Japan only, a local PD-L1 test result from an FDA-approved or Ministry of Health, Labour and Welfare-approved assay, respectively (limited to 22C3, SP263, 28-8) used at a certified laboratory according to manufacturer's instructions may be used for patient enrollment and randomization. Tumor specimens from US and Japan patients enrolled with a local PD-L1 result will also be stained centrally with VENTANA PD-L1 (SP263) CDx Assay. BeiGene Study BGB-A317-A1217-302 aims to evaluate the efficacy and safety of ociperlimab plus tislelizumab combination therapy. The efficacy results from BeiGene Study BGB-A317-A1217-302 will also provide the basis to evaluate the performance of VENTANA PD-L1 (SP263) CDx Assay as an IVD device for the investigational combination therapy, in the target patient population described above.

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1. ABBREVIATIONS AND DEFINITIONS

Term	Definition
Ab	Antibody
ADE	adverse device effect
AE	adverse event
ALK	anaplastic lymphoma kinase
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
case slide	slide with test specimen
CDx	companion diagnostic
CFR	Code of Federal Regulations
CR	complete response
CRA	clinical research associate
CRF	case report form
DAB	Diaminobenzidine
DD	device deficiency
Dx	diagnostic
EC	Ethics Committee
EGFR	epidermal growth factor receptor
FDA	US Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
H&E	hematoxylin and eosin
H&E slide	case slide stained with H&E
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IVD device	in vitro diagnostic medical device
IHC	Immunohistochemistry
IRB	Institutional Review Board
ITT	intention-to-treat
IUO	Investigational Use Only
Neg Ctrl Ig	VENTANA Rabbit Monoclonal Negative Control Ig
NRC slide	case slide stained with Neg Ctrl Ig
NSCLC	Non-small Cell Lung Cancer
OS	overall survival

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Term	Definition
PD-1	program cell death protein 1
PD-L1	programmed death ligand 1
PD-L1 (SP263) Ab	VENTANA PD-L1 (SP263) rabbit monoclonal primary antibody
PD-L1 case slide	case slide stained with VENTANA PD-L1 (SP263) CDx Assay
RTD	Roche Tissue Diagnostics
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SDS	safety data sheet
TC	tumor cell
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TMF	Trial Master File
US	United States
Ventana	Ventana Medical Systems, Inc. (Roche Tissue Diagnostics)
VSS	Ventana System Software

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2. GENERAL INFORMATION

2.1. Investigator(s) and Dx Testing Site(s)

A list of Investigators(s) and participating diagnostic (Dx) testing sites will be maintained separately from this Dx protocol. The list will be available throughout the study in the trial master file (TMF) at Roche Tissue Diagnostics (RTD) and the definitive list will be provided in the final report from RTD.

Note: The "Dx testing sites" referred to in this Dx protocol are the laboratories where specimens are being tested with the investigational IVD device.

2.2. Dx Protocol Contact Information

Company Name and Address	**Authorized Representative in Europe**
Ventana Medical Systems, Inc. (Roche Tissue Diagnostics; RTD) 1910 E. Innovation Park Drive Tucson, AZ 85755	Roche Diagnostics GmbH Sandhoferstrasse 116, DE-68305 Mannheim Tel.:+49 621 759 0
Monitor	**Medical Expert/Monitor**
[redacted] CRA, Clinical Operations Tel: [redacted] Email: [redacted]	[redacted] Staff Pathologist II Tel: [redacted] Email: [redacted]
Primary Contact and Adverse Event Reporting	
[redacted] Global Study Lead, Clinical Operations Tel: [redacted] Email: [redacted]	

2.3. BeiGene Study BGB-A317-A1217-302

RTD's Dx protocol, RD005805, is being conducted in support of the following pharmaceutical study:

Sponsor: BeiGene, Ltd.

Protocol Number: BGB-A317-A1217-302 (AdvanTIG-302)

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Title: A Phase 3, Randomized, Double-Blind Study of Ociperlimab, an Anti-TIGIT Antibody, in Combination with Tislelizumab Compared to Pembrolizumab in Patients with Previously Untreated, PD-L1-Selected, and Locally Advanced, Unresectable, or Metastatic Non-Small Cell Lung Cancer.

Pharmaceutical Study Design:

BeiGene Phase 3 Study BGB-A317-A1217-302 is a randomized, double-blind, multicenter, Phase 3 study designed to evaluate the efficacy and safety of ociperlimab in combination with tislelizumab compared to pembrolizumab in patients with PD-L1-selected NSCLC who have locally advanced or recurrent disease that is unresectable or not amenable to radiotherapy, with or without chemoradiotherapy, or previously untreated metastatic disease, and whose tumors do not harbor epidermal growth factor receptor (EGFR)-sensitizing mutations, anaplastic lymphoma kinase (ALK) translocations, BRAF V600E mutations, or ROS1 mutations. The efficacy and safety of tislelizumab alone will be explored in a small cohort of the same patient population.

The study will screen approximately 2400 patients and randomize approximately 660 eligible patients in a 5:5:2 ratio to receive ociperlimab + tislelizumab (Arm A), pembrolizumab + placebo (Arm B), or tislelizumab + placebo (Arm C).

Relationship between Pharmaceutical Study and RTD Dx Protocol:

RTD's Dx protocol, RD005805, will use NSCLC specimens from patients undergoing screening to determine eligibility for BeiGene Study BGB-A317-A1217-302. Samples will be tested with VENTANA PD-L1 (SP263) CDx Assay to determine their PD-L1 expression level (< 50% vs. ≥ 50% for tumor cell [TC] staining). Only patients with PD-L1 expression level ≥ 50% TC (referred to as high level of PD-L1 in BeiGene Study BGB-A317-A1217-302) will be enrolled into BeiGene Study BGB-A317-A1217-302. In the US and Japan only, a local PD-L1 test result from an FDA-approved or Ministry of Health, Labour and Welfare-approved assay (limited to 22C3, SP263, 28-8) used at a certified laboratory according to manufacturer's instructions may be used for patient enrollment and randomization. Tumor specimens from US and Japan patients enrolled with a local PD-L1 result will also be stained centrally with VENTANA PD-L1 (SP263) CDx Assay. If a local PD-L1 result is used for patient enrollment, confirmation of receipt of a tumor sample by the central lab is required before patient randomization. BeiGene Study BGB-A317-A1217-302 aims to evaluate the efficacy and safety of ociperlimab plus tislelizumab combination therapy. The efficacy results from BeiGene Study BGB-A317-A1217-302 will also provide the basis to evaluate the performance of VENTANA PD-L1 (SP263) CDx Assay as an IVD device for the investigational combination therapy, in the target patient population described above.

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BeiGene Study BGB-A317-A1217-302 and this Dx protocol (RD005805) name different investigators and define distinct responsibilities. The assignment of key responsibilities are presented in **Table 1**.

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Table 1. Activities Occurring per Pharmaceutical Study versus Dx Protocol

Responsibilities per BeiGene Study BGB-A317-A1217-302	Responsibilities per RTD Dx Protocol RD005805
- Consent of patients, including an informed consent form informing patients about the use of their specimen, the investigational IVD device, and the associated risks of participation in the study - Procure tumor specimens (archival or on study biopsy) to be tested with the investigational IVD device - Submit the specimen to Dx testing sites (ie, central testing laboratories) →	
	- Dx testing sites receive tumor specimens from screening sites - Dx testing sites prepare slides from tumor specimens - Dx testing sites execute IHC staining per Dx protocol - Laboratory pathologists interpret stained slides for PD-L1 expression per Dx protocol - Dx testing sites report the PD-L1 expression level for screened patient on the respective CRF - Dx testing sites report adverse events and device deficiencies related to Dx protocol conduct
- Manage patient enrollment decisions based on the Dx test results from Dx testing sites - Report adverse events related to patients enrolled in BeiGene Study BGB-A317-A1217-302 - Analyses of efficacy data - Report on efficacy of **investigational therapy** →	
	- RTD conducts analyses of staining acceptability - RTD receives efficacy results from BeiGene Study BGB-A317-A1217-302 relevant to performance of investigational IVD device - RTD reports on performance of **investigational IVD device**

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2.4. Start Date and Duration of the Investigational IVD Device Testing

Testing of specimens under this Dx protocol will begin as soon as reasonably possible after all applicable authorizations and favorable opinions have been issued for this Dx protocol. Thus, the anticipated Dx testing will start in late 2020. The Dx testing will continue until all specimens are tested by VENTANA PD-L1 (SP263) CDx Assay for BeiGene Study BGB-A317-A1217-302 enrollment or central confirmation (US and Japan only). The estimated duration of the BeiGene Study BGB-A317-A1217-302 is 58 months.

3. INTRODUCTION

Contains modified excerpts from the protocol for BeiGene Study BGB-A317-A1217-302.

3.1. Non-Small-Cell Lung Cancer

Lung cancer is the most common cancer, with approximately 2.1 million new diagnoses and 1.8 million deaths worldwide in 2018, which corresponds to the highest incidence among cancers and the most common cancer-related mortality[1]. The disease is more common in men than women, representing 16.8% of all cancers in men and 8.8% of all cancers in women. In China, lung cancer is the leading cause of cancer-related death in both men and women, with an estimated 610,200 deaths and an estimated 733,300 new cases in 2015[2]. NSCLC originates from the epithelial cells of the lung and accounts for 80% to 85% of all lung cancers. There are three main histological subtypes of NSCLC, adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, which constitute 40%, 25%, and 10% of lung cancers, respectively[3].

3.2. Anti-PD-1/PD-L1 and Immunotherapies

PD-L1 (B7-H1, CD274) is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. In normal tissue, PD-L1 is expressed on T cells, B cells, dendritic cells, macrophages, mesenchymal stem cells, bone marrow-derived mast cells, as well as various nonhematopoietic cells.[4] Its normal function is to regulate the balance between T-cell activation and tolerance through interaction with its 2 receptors, programmed cell death protein-1 (PD-1; also known as CD279) and CD80 (B7-1). PD-1 and PD-L1 offer inhibitory signals that regulate both central and peripheral tolerance in multiple ways, which includes reduction in cytokine production and suppression of T-cell proliferation.[4] In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T

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cells, preventing them from killing target tumor cells, and protecting the tumor from immune elimination.[5]

Anti-PD-1 therapy has emerged as an effective treatment for those patients with tumors expressing varying degrees of PD-L1[6]. Anti-PD-1 and anti-PD-L1 therapies target the programmed death receptor pathway of T lymphocytes, and this checkpoint has been found to be activated in cancer allowing tumors to evade the host immune system.

3.3. Ociperlimab (BGB-A1217)

Ociperlimab is a humanized immunoglobulin G (IgG) one monoclonal antibody against T-cell immunoglobulin and ITIM domain (TIGIT) under clinical development for the treatment of human malignancies.

Ociperlimab binds to the extracellular domain of human TIGIT with high specificity and affinity (equilibrium dissociation constant [KD] = 0.135 nM), as demonstrated by target-binding assays and SPR characterization. Ociperlimab has shown antitumor activity 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, ociperlimab in combination with anti–mouse PD-1 significantly inhibited tumor growth compared with either therapy alone.

Ociperlimab has constant region of a wild-type human immunoglobulin G1 (IgG1) to enable the Fc-mediated effector functions. Ociperlimab has demonstrated competent binding to C1q and all FcγRs and induces antibody-dependent cellular cytotoxicity against a TIGIT-overexpressing cell line, but no antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity against primary T cells in the cell-based assays.

3.4. Tislelizumab (BGB-A317)

Tislelizumab is a humanized, immunoglobulin G4 (IgG4)-variant monoclonal antibody against PD-1 under clinical development for the treatment of several human malignancies.

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity and affinity (dissociation constant [KD] = 0.15 nM). It competitively blocks binding of both programmed cell death protein ligand-1 (PD-L1) and PD-L2, thus inhibiting PD-1-mediated negative signaling in T cells. In in vitro cell-based assays, tislelizumab was observed to dose-dependently enhance the functional activity of human T cells and pre-activated, primary peripheral blood mononuclear cells. Tislelizumab has demonstrated in-vivo antitumor activity in several allogeneic xenograft models, in which peripheral blood mononuclear cells

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were co-injected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

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 [7, 8]. Tislelizumab was specifically engineered to abrogate these potential mechanisms of T-cell clearance and potential resistance to anti-PD-1 therapy.

3.5. Analytical Performance for the VENTANA PD-L1 (SP263) CDx Assay

The analytical performance of the VENTANA PD-L1 (SP263) CDx Assay as an IVD device has been validated for its use in the clinical study. Summary results of the analytical performance studies are provided in the VENTANA PD-L1 (SP263) CDx Assay Investigator's Brochure (D172202) accompanying this Dx protocol.

3.6. Rationale

This diagnostic protocol is intended to support BeiGene Study BGB-A317-A1217-302 clinical trial in validating the performance of the VENTANA PD-L1 (SP263) CDx Assay as a IVD device for ociperlimab plus tislelizumab compared with pembrolizumab in patients with PD-L1-selected NSCLC who have locally advanced or recurrent disease that is unresectable or not amenable to radiotherapy, with or without chemoradiotherapy, or previously untreated metastatic disease, and whose tumors do not harbor EGFR-sensitizing mutations, ALK translocations, BRAF V600E mutations, or ROS1 mutations. The rationale for choice of study design is provided in the BeiGene Study BGB-A317-A1217-302 protocol.

PD-L1 expression in tumor and tumor-associated immune cells has been shown to correlate with clinical efficacy of anti-PD-1 or anti-PD-L1 treatment in multiple studies[9-14]. PD-L1 has been established as a predictive biomarker of response to these immunotherapies in first-line NSCLC, the indication in BeiGene Study BGB-A317-A1217-302. Pembrolizumab (anti PD-1 agent) monotherapy, the control arm in BeiGene Study BGB-A317-A1217-302, is considered standard of care for the first-line treatment of patients with metastatic NSCLC whose tumors express a high level of PD-L1 (TPS ≥ 50%) and bear no genomic aberrations in the EGFR and ALK genes.

The role of PD-L1 in predicting response to treatments combining anti-TIGIT and anti-PD-L1 or anti-PD-1 agents in patients with NSCLC is still under investigation, but clinical data suggests that PD-L1 could also be a predictive biomarker of response for this type of combination treatment. Furthermore, the global standard of care treatment (outside of the

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US) for patients with first-line NSCLC with PD-L1 expression < 50% is not pembrolizumab monotherapy (control arm in BeiGene Study BGB-A317-A1217-302), therefore, inclusion of such patients would also pose ethical and feasibility concerns. For example, in the CITYSCAPE study, NSCLC patients with tumors with PD-L1 TPS ≥ 50% derived significant benefit from atezolizumab (anti-PD-L1) plus tiragolumab (anti-TIGIT) compared to atezolizumab alone (ORR of 66% versus 24%), while no difference in ORR was observed between the 2 arms (16% versus 18%) for patients with 1% to 49% PD-L1 expression [15].

From a patient benefit/risk perspective, the evidence described above supports an enrichment (selection) strategy based on PD-L1 expression to select the population more likely to respond to the investigational treatment. To that end, the PD-L1 expression level determined by VENTANA PD-L1 (SP263) CDx Assay will be used to select patients into BeiGene Study BGB-A317-A1217-302, to support the pharmaceutical trial design and simultaneously evaluate the performance of the assay as a companion diagnostic. Because patients with tumors with a PD-L1 expression level < 50% will not be enrolled in the trial, the performance evaluation will be limited to determining whether patients selected with the assay derive benefit from the investigational treatment, and not whether the assay predicts response to treatment [16, 17].

4. INVESTIGATIONAL IVD DEVICE PROPOSED INTENDED USE

VENTANA PD-L1 (SP263) CDx Assay is intended to be a qualitative immunohistochemical assay using anti-PD-L1 monoclonal antibody (SP263) for the assessment of programmed death ligand 1 (PD-L1) protein in formalin-fixed, paraffin-embedded (FFPE) NSCLC tissue stained with OptiView DAB IHC Detection Kit on a BenchMark ULTRA instrument.

VENTANA PD-L1 (SP263) CDx Assay is indicated as an aid in identifying NSCLC patients who may benefit from treatment with PD-1 targeted therapy in combination regimens.

5. DIAGNOSTIC TESTING PROTOCOL OBJECTIVES

The primary objective of this Dx protocol is to support BeiGene Study BGB-A317-A1217-302 by identifying the PD-L1 expression level of tumor specimens for patient enrollment. Results from BeiGene Study BGB-A317-A1217-302 will serve as the performance evaluation for VENTANA PD-L1 (SP263) CDx Assay in terms of its ability to identify patients who are likely to benefit from ociperlimab in combination with tislelizumab in

patients with previously untreated, PD-L1-selected, and locally advanced, unresectable, or metastatic NSCLC.

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6. INVESTIGATIONAL IVD DEVICE DESCRIPTION

6.1. VENTANA PD-L1 (SP263) CDx Assay

The formulated antibody reagent for VENTANA PD-L1 (SP263) CDx Assay is a rabbit monoclonal primary antibody produced against programmed death ligand-1 (PD-L1) B7 homolog 1 (B7-H1, CD274). It recognizes a transmembrane bound glycoprotein that has a molecular mass of 45–55 kDa. This antibody produces membranous and/or cytoplasmic staining.

VENTANA PD-L1 (SP263) CDx Assay requires three slides per case. One slide stained with hematoxylin and eosin (H&E) to confirm adequacy of the tissue (H&E slide), one slide is strained with PD-L1 (SP263) Ab (PD-L1 case slide), and one slide is stained with Rabbit Monoclonal Negative Control Ig (Neg Ctrl Ig) to assess background staining and serve as the negative reagent control for the assay (NRC slide).

6.2. Staining Instrument and Software

6.2.1. VENTANA BenchMark ULTRA Instrument

The VENTANA BenchMark ULTRA instrument automatically stains histological or cytological specimens on microscope slides with specific immunohistochemical (IHC) or *in situ* hybridization reagents for *in vitro* diagnostic use. It fully automates the processes of baking, deparaffinization, cell conditioning, and staining. The VENTANA BenchMark ULTRA instrument can hold up to 30 slides at one time.

6.2.2. VENTANA System Software

VENTANA BenchMark ULTRA instruments used in this study will be controlled and monitored using Ventana System Software (VSS) version 12.3 or higher. The staining procedures specific for the VENTANA PD-L1 (SP263) CDx Assay (U VENTANA PD-L1 [SP263] Assay IUO v1.00.0000), are designed and developed to operate within the VSS environment.

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7. Dx PROTOCOL DESIGN

7.1. Design Overview

In the standard drug-companion diagnostic (CDx) co-development model, the clinical utility of an investigational treatment and an investigational IVD are evaluated in the same clinical trial, and the performance of the investigational IVD is considered acceptable if the clinical trial efficacy endpoint(s) in the population identified by the IVD are met. Following this model, a combined study approach will be used, which will include protocols for the investigational treatment (BGB-A317-A1217-302) and the investigational IVD (D162788).

As part of the co-development paradigm including both an investigational therapy and an investigational IVD, RTD, as the IVD device manufacturer, will be responsible for certain aspects of the investigational IVD device's [VENTANA PD-L1 (SP263) CDx Assay] use within BeiGene Study BGB-A317-A1217-302. As such, this Dx protocol supports BeiGene Study BGB-A317-A1217-302 by describing the procedures for how the patient tumor samples collected as part of BeiGene Study BGB-A317-A1217-302 should be tested with VENTANA PD-L1 (SP263) CDx Assay at the Dx testing sites.

No hypothesis testing will be performed under this Dx protocol, as outcome data from BeiGene Study BGB-A317-A1217-302 will be used to evaluate the clinical performance of VENTANA PD-L1 (SP263) CDx Assay as an IVD device for ociperlimab in combination with tislelizumab in patients with previously untreated, PD-L1-selected, locally advanced, unresectable, or metastatic NSCLC.

The investigational VENTANA PD-L1 (SP263) CDx Assay will be used to assess the PD-L1 expression level in NSCLC tumor specimens collected from patients who are being screened to determine eligibility to participate in BeiGene Study BGB-A317-A1217-302. It is anticipated that tumor specimens from approximately 2400 patients undergoing screening to participate in Study BGB-A317-A1217-302, will be stained with VENTANA PD-L1 (SP263) CDx Assay at central Dx testing sites. Stained slides from each case submitted for testing will be interpreted by qualified pathologists who will assign a PD-L1 expression level at the 50% tumor cell (TC) threshold (< 50% vs. ≥ 50%, to be used for patient enrollment).

A PD-L1 expression level at the ≥ 50% TC will be one of several factors used to determine eligibility for enrolling patients into BeiGene Study BGB-A317-A1217-302. In the US and Japan only, a local PD-L1 test result from an FDA-approved or Ministry of Health, Labour and Welfare-approved assay, respectively (limited to 22C3, SP263, 28-8) used at a certified laboratory according to manufacturer's instructions may be used for patient enrollment and randomization. Tumor specimens from US and Japan patients enrolled with a local PD-L1 result will also be stained centrally with VENTANA PD-L1 (SP263) CDx Assay. If a local

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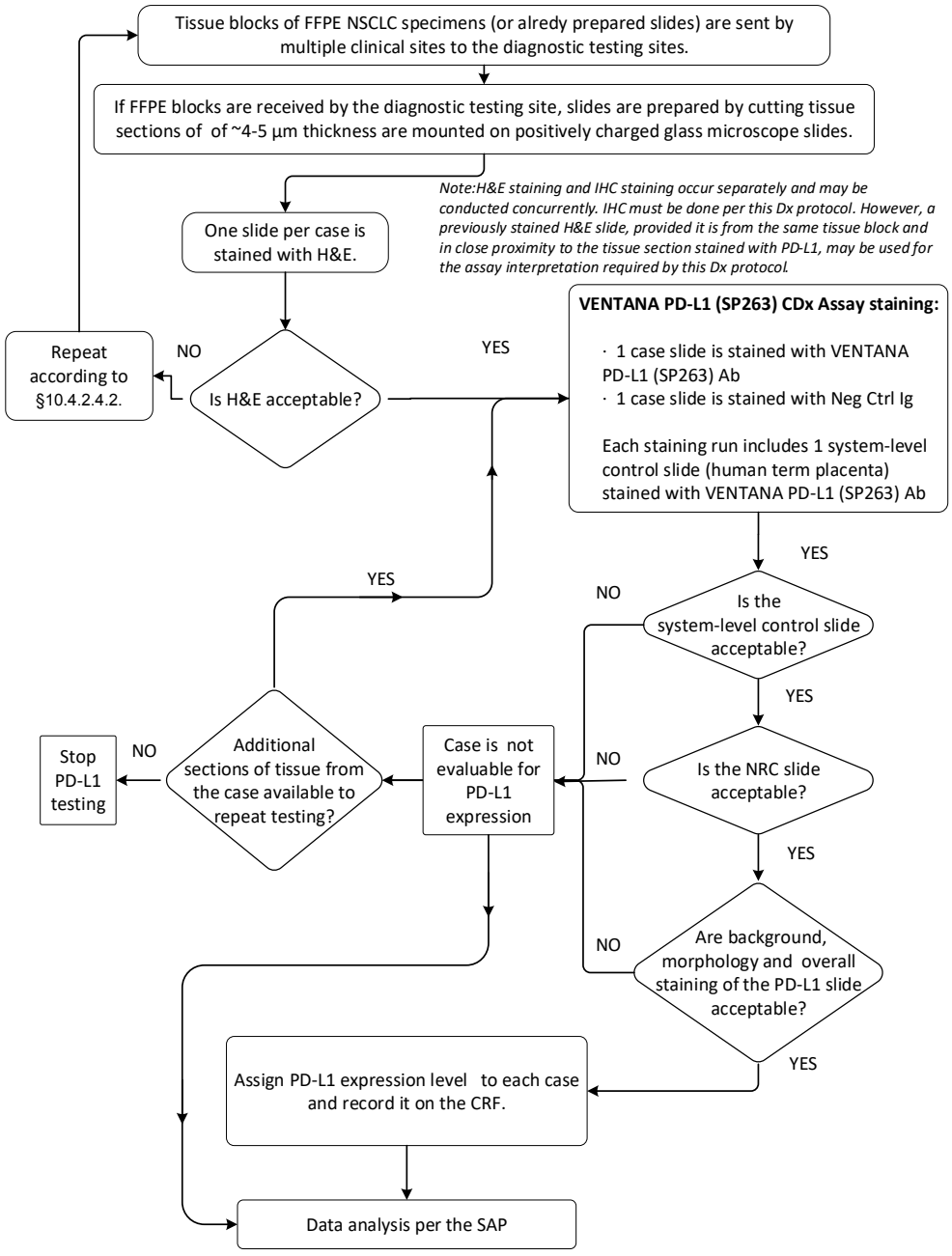
PD-L1 result is used for patient enrollment, confirmation of receipt of a tumor sample by the central lab is required before patient randomization. Performance of VENTANA PD-L1 (SP263) CDx Assay will be evaluated in BeiGene Study A317-A1217-302 as described in **§7.2**.

Figure 1: Diagnostic Testing Workflow



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7.2. Endpoints and Acceptance Criteria

Performance of RTD's investigational IVD device will be measured by:

(i) evaluating its ability to identify patients who are likely to benefit from ociperlimab in combination with tislelizumab in patients with previously untreated, PD-L1-selected, and locally advanced, unresectable, or metastatic NSCLC, and

(ii) by evaluating how often the investigational IVD device is able to yield a valid PD-L1 (SP263) expression level result (i.e., staining acceptability rates). To evaluate the investigational IVD device's performance, the following endpoints are defined for this protocol:

7.2.1. Primary Endpoint

The primary efficacy endpoint described in the BeiGene Study BGB-A317-A1217-302 protocol addresses the clinical benefit of ociperlimab in combination with tislelizumab in patients with previously untreated, PD-L1-selected, and locally advanced, unresectable, or metastatic NSCLC, and whose tumors PD-L1 expression level has been determined by VENTANA PD-L1 (SP263) CDx Assay (or in the US and Japan only by a local PD-L1 result) as described in Section 2.2.1 of the BeiGene Study BGB-A317-A1217-302 protocol:

- Overall survival (OS) between Arm A (ociperlimab in combination with tislelizumab) and Arm B (pembrolizumab followed by placebo) in the ITT Analysis Set[1].

The efficacy analyses, to be conducted by BeiGene for BeiGene Study BGB-A317-A1217-302 to evaluate the efficacy of their investigational therapy in the PD-L1 selected ITT population, will also provide the basis for the clinical performance evaluation of VENTANA PD-L1 (SP263) CDx Assay as an IVD device to identify patients who will benefit from ociperlimab in combination with tislelizumab. The results of the efficacy analyses, will be provided by BeiGene, and will be summarized in the final report associated with this Dx protocol.

7.2.2. Primary Acceptance Criteria

Performance of VENTANA PD-L1 (SP263) CDx Assay will be considered acceptable if the results of BeiGene Study BGB-A317-A1217-302 support the efficacy of ociperlimab in

[1] The ITT Analysis Set of BeiGene Study BGB-A317-A1217-302 includes all randomized patients, which are selected using the VENTANA PD-L1 (SP263) CDx Assay (PD-L1 expression level ≥ 50% TC) or in the US and Japan only, using a local PD-L1 result from an FDA approved or Ministry of Health, Labour and Welfare-approved assay, respectively (limited to 22C3, SP263, 28-8).

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combination with tislelizumab in the patient population identified by the investigational IVD device.

7.2.3. Additional Endpoints

Additionally, the following endpoints will be evaluated among specimens collected as part of enrollment screening and confirmation for BeiGene Study BGB-A317-A1217-302 and tested with VENTANA PD-L1 (SP263) CDx Assay:

- Initial and final staining acceptability rates
- Initial and final tissue morphology acceptability rates
- Initial and final background acceptability rates

There are no pre-determined acceptance criteria associated with these additional endpoints.

7.3. Bias Minimization

Specimens will be tested in approximately the order in which they are received/enrolled and therefore, adherence to a randomization is not required.

8. BeiGene Study BGB-A317-A1217-302 Population and Dx Protocol Specimens

8.1. BeiGene Study BGB-A317-A1217-302 Population

The target patient population is described in detail in the BeiGene Study BGB-A317-A1217-302 protocol, including a list of eligibility criteria.

8.2. Dx Protocol Specimens

8.2.1. Source and Number of Specimens

NSCLC tumor specimens from approximately 2400 patients undergoing screening for enrollment (or for central confirmatory testing applicable to the US and Japan only) in BeiGene Study BGB-A317-A1217-302 will be sent to the diagnostic testing sites. VENTANA PD-L1 (SP263) CDx Assay testing will occur at those sites in accordance with this Dx protocol. Sample collection methods and risks are the responsibility of the enrollment sites for BeiGene Study BGB-A317-A1217-302. Refer to the lab manual for BeiGene Study BGB-A317-A1217-302 for information on the biopsy procedures.

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Specimens must be provided as archival FFPE tissue blocks (preferred), fresh fixed biopsy samples, or as serial sections of a fresh or archival FFPE block. Slides must be freshly cut (ie, must have been prepared no more than 12 months prior to staining). Multiple specimens may be submitted for some patients.

8.2.2. Recommended Pre-Analytical Specimen Processing

In the VENTANA PD-L1 (SP263) CDx Assay package insert/method sheet, RTD makes the following recommendations for pre-analytical specimen processing:

- Specimens should be routinely-processed, FFPE sample.
- The recommended tissue and cell sample fixative is 10% neutral buffered formalin (NBF) for 6-72 hours.
- Fixatives with high concentration of alcohol (e.g. 95% ethanol) are unacceptable for use with this assay.

8.2.3. Specimen Eligibility Criteria

All tumor specimens submitted as part of screening (or for central confirmatory testing applicable to the US and Japan only) for BeiGene Study BGB-A317-A1217-302 that also satisfy the inclusion/exclusion criteria outlined below will be tested with VENTANA PD-L1 (SP263) CDx Assay. Reasons for excluding specimens from testing will be documented.

8.2.3.1. Inclusion Criteria

To be included in this Dx protocol, a specimen must meet all of the following criteria:

1. It must be a newly acquired tumor biopsy or an archival tumor specimen submitted for either patient enrollment screening or confirmatory testing for US and Japan patients enrolled with a local test result for BeiGene Study BGB-A317-A1217-302;
2. It must be an FFPE NSCLC specimen processed in accordance with standard practice;
3. It must contain sufficient tumor tissue for interpretation (at the discretion of the reviewing pathologist); and
4. If an FFPE tissue block is unavailable, unstained FFPE slides prepared from these specimens can be submitted.

8.2.3.2. Exclusion Criteria

A specimen will be excluded from the diagnostic testing if any of the following criteria are met:

1. It is a fine needle aspirate or cytology specimen;
2. It consists of tissue that has been decalcified; [2]
3. It is fixed in 95% alcohol or higher, AFA or PREFER™;
4. Cut slides from tissue blocks were prepared over 12 months prior to staining.

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8.2.4. Specimen Handling and Storage

Patient specimens and all materials being exposed to them will be handled as if potentially infectious and disposed of with proper precautions.

All unfixed human-sourced samples should be handled in accordance with the US Occupational Safety and Health Administration's standard on blood-borne pathogens (29 CFR 1910.1030).

Refer to Sections **10.3.1** and **10.3.2** for additional requirements for handling and storage of case slides and system-level control slides.

9. MATERIALS

9.1. Materials

Documentation of study materials provided to the Dx testing sites will be maintained in the TMF.

[2] *Evidence of decalcification should be obtained from the pathology report. If the pathology report does not specify whether the sample was decalcified or not, the processing lab should be contacted for confirmation.*

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Table 2. Investigational IVD Device Configuration

Reagent	Part Number
VENTANA PD-L1 (SP263) CDx Assay (50 tests)[a]	742-4907
Rabbit Monoclonal Negative Control Ig	790-4795
OptiView DAB IHC Detection Kit	760-700
EZ Prep Concentrate (10X)	950-102
Reaction Buffer (10X)	950-300
ULTRA LCS (Predilute)	650-210
ULTRA Cell Conditioning 1 (CC1)	950-224
Hematoxylin II Counterstain	790-2208
Bluing Reagent	760-2037
Platform/Software	**Part Number/Version**
BenchMark ULTRA instrument	N750-BMKU-FS
Operating software	VSS 12.3 or higher
BenchMark ULTRA Software Staining Procedure	U VENTANA PD-L1 (SP263) Assay IUO (v1.00.0000)

[a] *CAUTION: Investigational device limited by Federal (or United States) law to investigational use.*

The method sheet and safety data sheet (SDS) for the investigational reagents are provided separately.

9.2. Reagent Handling and Storage

All reagents must be handled according to the instructions of the supplier. Lot numbers and expiration dates for materials used in the execution of this protocol must be documented. Method sheets and Safety Data Sheets will be provided to Dx testing sites.

Bio-hazardous material and testing reagents must be disposed of in alignment with applicable regulations and with the policies of the testing facility.

9.3. Investigational IVD Device Accountability

The Principal Investigator(s) at each Dx testing site must ensure that the investigational IVD device is used only for activities within the protocol scope. Investigational product should be supplied only to persons authorized to receive it. Upon completion or termination of this study or the Principal Investigator's part in the conduct of this Dx protocol, or at RTD's request, the Principal Investigator shall return to RTD any remaining supply of the device or

otherwise dispose of the device as directed by RTD. The Dx testing site must document receipt, use, and disposition of all investigational products received and used during the course of the Dx protocol as directed by RTD.

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10. PROCEDURES

10.1. Site Familiarization

RTD will ensure that participating Dx testing sites are familiar with the investigational IVD device and its proper use. The activities planned for preparing Dx testing sites to use the investigational IVD device are documented separately in the Site Readiness Plan.

10.2. Training

RTD will provide training to participating Dx testing sites on this Dx protocol. Instrument operators conducting slide staining must have prior training and experience or must request training such that they are competent to perform the required tasks. Pathologist reading and interpreting the investigational IVD device will receive training as described in the assay interpretation section of this Dx protocol.

10.3. Slide Preparation Procedures

10.3.1. Case Slides

Dx testing sites will receive FFPE tissue blocks, FFPE slides, or fresh fixed NSCLC patient tissue submitted by clinical enrollment sites for BeiGene Study BGB-A317-A1217-302. Site personnel will embed fresh fixed tissue in paraffin as needed according to the site's standard procedures. Tissue blocks (as received or prepared in-house) will be cut into sections approximately 4-5 µm thick. The sections will be mounted on positively charged glass microscope slides (in the same direction on all slides if possible). The unstained slides may be stored in dry conditions at room temperature until stained. Cut slides must be stained with VENTANA PD-L1 (SP263) CDx Assay as soon as possible, but not later than 12 months from the date the tissue was cut.

VENTANA PD-L1 (SP263) CDx Assay requires at least three tissue sections per case, one for staining with H&E and two for IHC staining with Neg Ctrl Ig and the PD-L1 Ab. Additional slides for each case may be cut as backups for use if a retest is required.

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10.3.2. System-Level Control Slides

Site personnel will obtain and qualify FFPE normal human term placenta tissue for use as system ("run") control tissue for VENTANA PD-L1 (SP263) CDx Assay. Each assay staining run for this Dx protocol will include one system-level control slide consisting of an approximately 4-5 µm-thick normal human term placenta section mounted on a positively charged glass microscope slide. The tissue must be qualified for use as a system-level control according to the Dx testing site's standard procedures.

Control tissue should be fixed and processed in the same manner as the patient specimens under evaluation and according to the recommendations in the VENTANA PD-L1 (SP263) CDx Assay method sheet.

Unstained normal human term placenta tissue control slides may be stored in dry conditions at room temperature and must be stained with VENTANA PD-L1 (SP263) CDx Assay not later than 9 months from the date the tissue was cut.

10.4. Slide Staining Procedures

10.4.1. H&E Staining

Each case requires an H&E-stained slide for use by the pathologist at the Dx testing site to determine if the specimen contains sufficient viable tumor tissue consistent with NSCLC. H&E staining will be performed according to the Dx testing site's standard practice. To expedite Dx protocol procedures, H&E staining and VENTANA PD-L1 (SP263) CDx Assay staining may be conducted in parallel.

10.4.2. VENTANA PD-L1 (SP263) CDx Assay Staining

10.4.2.1. BenchMark ULTRA Instrument Operation

10.4.2.1.1. Instrument Operator Requirements

The BenchMark ULTRA instrument will be operated by laboratory personnel who have been properly trained in use of the instrument and have sufficient relevant scientific background and computer operation skills. Instrument operators should follow industry practices for safety and security when operating the instrument.

10.4.2.1.2. Set-up and Maintenance

Each BenchMark ULTRA instrument in use for the Dx protocol must undergo daily, weekly, monthly, and quarterly maintenance as described in the BenchMark ULTRA Operator Guide

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version 12.3 or higher. Maintenance records must be retained and made available for inspection by RTD and by authorized regulatory authorities. All BenchMark ULTRA reagents used for the Dx protocol must be registered ("buttoned") so that accurate information regarding reagent lot numbers and expiration dates appears on the "Consolidated Completed Staining Run report" printed from the host computer.

BenchMark ULTRA instruments will be installed (if needed) by qualified Roche technical personnel. All BenchMark ULTRA instruments used in the Dx protocol must pass installation qualification (if applicable) and pre-study qualification tests before study staining runs can begin.

10.4.2.1.3. Software Documentation

BenchMark ULTRA instruments will be controlled by VSS version 12.3 or higher. Before any BenchMark ULTRA instrument can be used to stain patient specimens for the Dx protocol, a "System Information Report" must be printed from the host computer and submitted to a RTD representative for approval. This report includes information about the system and staining procedure versions and will be maintained as a record to document that software requirements have been met.

10.4.2.1.4. Protocol Summary Report

This Dx protocol requires the use of the BenchMark ULTRA staining protocol-specific to the assay. Before a site can perform its initial staining run, the staining protocol programmed into the instrument must be approved by a RTD representative. For approval, the "Full Procedure Report" and the "Protocol Summary" should be printed from the instrument by the site, then reviewed and signed by a RTD representative to confirm that they are correct. These reports are filed in the TMF and monitored.

10.4.2.1.5. Keycode Enabling

The BenchMark ULTRA instrument will assign a unique identifier to each slide stained. This identifier will be captured on a "Consolidated Completed Staining Run Report" using the keycode-enabling feature. This feature is automatically enabled on the BenchMark ULTRA system and does not require any additional steps to activate. (However, it is recommended that the user confirm that the "Enable Keycode Slide Labeling" box in the VLM Options screen is checked.)

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10.4.2.1.6. Slide Label Template

A slide label template for the VENTANA Slide Labeling System is used to ensure that the information shown on case slides, staining protocols, and staining run reports allows the staining procedure information to be tracked during and after completion of the Dx protocol. Slide labels also direct the staining instrument as to which reagents to dispense on the slide. Slide labels must be set up properly before staining runs begin to ensure 1) correct slide staining and 2) that all necessary information will be printed on the run reports.

10.4.2.1.7. Staining Run Reports

A "Consolidated Completed Staining Run report" (not an "Extended Staining Run report") showing all slide positions should be printed immediately after each staining run is completed and before any subsequent staining runs are initiated. These reports must be maintained in the Dx protocol TMF. After confirming accuracy of the report or noting any discrepancies, the operator must sign and date the first page.

10.4.2.2. Staining Run Composition

The BenchMark ULTRA instrument can accommodate 30 slides at one time. For Dx protocol purposes the batch of slides included on the instrument at the same time will constitute a staining run. Because each case will require two slides for IHC staining, and each staining run will include one system-level control slide, up to 14 cases [$(14 \times 2) + 1 = 29$] can be included in each staining run. Depending on the patient screening rate, staining runs may or may not contain the full complement of slides.

10.4.2.2.1. Case Slides

VENTANA PD-L1 (SP263) CDx Assay IHC staining requires two slides per case: one for staining with the PD-L1 Ab (PD-L1 slide) and the other for staining with Neg Ctrl Ig to serve as a negative reagent control (NRC) for the assay (NRC slide). Both case slides must be stained in the same staining run. The staining protocol for VENTANA PD-L1 (SP263) CDx Assay on the BenchMark ULTRA instrument is shown in **Table 3**.

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Table 3. Staining Protocol for VENTANA PD-L1 (SP263) CDx Assay

Procedure	PD-L1 (SP263) Ab	Neg Ctrl Ig
Baking	Not selected	Not selected
Antibody	Primary Antibody Selected	Negative Control Selected
Counterstain	Hematoxylin II, 4 min	Hematoxylin II, 4 min

Note: The table lists only the procedures that are selectable by the instrument operator in the user interface; it does not include all steps in the staining protocol.

10.4.2.2.2. System-level Control Slides

Each VENTANA PD-L1 (SP263) CDx Assay staining run containing patient slides for the Dx protocol will also include one system-level control slide containing normal human term placenta tissue, which contains both PD-L1-positive staining elements and PD-L1-negative staining elements. This slide will be stained with the PD-L1 Ab using the staining protocol shown in **Table 3**.

10.4.2.3. Storage of Stained Slides

Case and system-level control slides stained with VENTANA PD-L1 (SP263) CDx Assay will be held at room temperature with no (or minimal) exposure to light in a secure location.

10.4.2.4. Staining Failures and Repeat Staining

10.4.2.4.1. Staining Failures

Case slide staining with VENTANA PD-L1 (SP263) CDx may fail for several reasons, including loss of the tissue section during processing and failure of the entire staining run due to instrument malfunction or human error. Reasons for slide staining failure (including those of the types mentioned above) will be captured on the case report form (CRF).

If a failure of a system-level control slide, instrument or human error, a power failure, or any other failure invalidates the slides from an entire staining run, those slides will be considered not evaluable. Any instrument malfunctions must be reported to the primary Dx protocol contact upon discovery and must be documented as an incident or protocol deviation on the Incident or Protocol Deviation Event form.

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Individual case slides that are deemed inadequate for assessment will also be considered not evaluable.

Data for PD-L1 slides that are not evaluable, including reasons for non-evaluability, will be provided to RTD for analysis of slide staining acceptability rates.

10.4.2.4.2. Repeat Staining

Repeat VENTANA PD-L1 (SP263) CDx staining using additional slides from the same patient specimen may be attempted if PD-L1 slides previously stained for that patient are inadequate for assessment. If the H&E slide used in the PD-L1 slide evaluation is acceptable, it may be used in subsequent evaluations of serial sections from the same specimen.

If the H&E slide used in the PD-L1 slide evaluation is not acceptable, repeat VENTANA PD-L1 (SP263) CDx staining using another specimen from the same patient may be attempted. In that event, a new H&E slide will be required.

All repeat staining attempts must be performed according to the procedures described in this Dx protocol. The number of staining attempts per specimen and the number of specimens stained per patient will depend on the rate of successful staining at the site and the size and number of the specimens.

10.5. Assay Interpretation Procedures

10.5.1. Assay Interpretation Training

RTD will hold investigator training sessions to instruct Dx testing site pathologists in the evaluation of slides for the VENTANA PD-L1 (SP263) CDx Assay in accordance with the instructions provided in the Method Sheet and Interpretation Guide. Slides used in the training session will be separate from those used in the conduct of the Dx protocol. All pathologists evaluating case slides must have documented, applicable qualifications and successfully complete the training provided by RTD. Documentation of successful completion of training will be maintained by RTD.

During the conduct of this Dx protocol, refresh training will be required for any pathologist who has not read PD-L1-stained slides for a period of more than six months. Refresh training will entail a review of key aspects of assay interpretation and representative cases (glass or slide images). It may be conducted either as in-person training, digital/virtual training, or by self-study. Refresh training success will be evaluated by a RTD pathologist who will

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determine if additional training is necessary. Documentation of reader refresh training activities will be maintained in the TMF.

10.5.2. Preparation of Reading Sets

Upon completion of a staining run, H&E slides will be matched with their corresponding case slide pairs, each containing a PD-L1 slide and an NRC slide. The case slides and the system-level control slide for that staining run will be presented to a Dx testing site pathologist for interpretation.

10.5.3. Slide Adequacy

A trained pathologist at the Dx testing site will evaluate the stained case slides and system-level control slide from each staining run according to the adequacy criteria listed below. Any PD-L1 slide failing to meet these criteria will be considered not evaluable, and the reason(s) will be recorded on the CRF.

- The system-level control slides from the same run must be acceptable (§**10.5.3.1**);
- The corresponding H&E slide must be acceptable (§**10.5.3.2**);
- The corresponding NRC slide must be acceptable (§**10.5.3.2**);
- The PD-L1 case slide must contain sufficient viable tumor tissue for interpretation (§**10.5.3.4**);
- The PD-L1 case slide must exhibit acceptable background (§**10.5.3.4.1**)
- The PD-L1 case slide must exhibit acceptable morphology (§**10.5.3.4.1**); and
- The PD-L1 case slide must exhibit otherwise acceptable staining (§**10.5.3.4.2**).

Data for tissue morphology and background staining acceptability rates will be included in the additional analyses of assay performance.

10.5.3.1. System-level Control Slide(s) Acceptability

One system-level control slide containing normal human term placenta tissue will be included in each BenchMark ULTRA staining run to confirm the validity of the staining run.

Normal human term placenta tissue contains both positive staining and negative-staining elements with VENTANA PD-L1 (SP263) CDx Assay. Acceptable staining of the positive

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elements provides reasonable assurance that the PD-L1 Ab was applied correctly, that the BenchMark ULTRA instrument functioned properly during the run, and the correct staining procedure was followed. Acceptable staining of the negative elements provides reasonable assurance against minor levels of reagent degradation or instrument out-of-specification issues.

The system-level control slide stained with the PD-L1 Ab is expected to exhibit moderate to strong uniform staining of the membrane and weak to strong uniform staining of the cytoplasm of trophoblast-lineage cells. Placental stromal tissue and vasculature can be used for assessment of any background staining. The pathologist will determine whether the system-level control slide is acceptable based on the criteria presented in **Table 4** and record this finding on the CRF.

If the system-level control slide is not acceptable, the run will be considered invalid, and the PD-L1 slides stained in that run will not be evaluated.

Table 4. Placenta Tissue Control Evaluation Criteria for the VENTANA PD-L1 (SP263) CDx Assay

Interpretation	Staining Description
Acceptable	Moderate to strong uniform membrane staining of trophoblast-lineage cells and placental stroma and vasculature with no staining.
Unacceptable	No to weak uniform membrane staining of trophoblast-lineage cells and/or specific staining within placental stromal and vascular tissue.

10.5.3.2. H&E Slide Acceptability

A case-matched H&E slide containing a serially adjacent tissue section will be available to the site pathologist reviewing the PD-L1 and NRC slides for that case, as would typically occur in clinical practice. The pathologist will determine whether the H&E slide contains sufficient tumor tissue consistent with NSCLC to allow interpretation of the case-matched IHC slides. If the H&E slide is not acceptable, this (and the specific reason) will be recorded on the CRF, and the case-matched NRC and PD-L1 case slides will not be evaluated.

10.5.3.3. NRC Slide Acceptability

In each case slide pair, the slide stained with Neg Ctrl Ig will serve as an NRC for the corresponding PD-L1 case slide. The NRC slide will be primarily evaluated based on the level of non-specific staining (background). If the NRC slide is not acceptable, this (and the

specific reason) will be recorded on the CRF and the case-matched PD-L1 case slide will not be evaluated.

10.5.3.4. PD-L1 Case Slide Acceptability

PD-L1 case slides will be primarily evaluated for the presence of sufficient viable tumor cells, as well as acceptable staining, background, and morphology. If the PD-L1 slide is deemed as not acceptable, the specific reason will be recorded on the CRF and the PD-L1 expression level will not be assessed.

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10.5.3.4.1. Morphology and Background staining acceptability

For each PD-L1 case slide, the pathologist will assess tissue morphology and the level of background staining according to the criteria shown in **Table 5** and **Table 6**, respectively. If either of these characteristics is not acceptable, then the slide will be recorded as not acceptable on the CRF.

Table 5. Morphology Acceptability Criteria

Interpretation	Microscope Observation
Acceptable	Cellular elements of interest are visualized allowing interpretation of the stain.
Unacceptable	Cellular elements of interest are not visualized compromising interpretation of the stain.

Table 6. Background Acceptability Criteria

Interpretation	Microscope Observation
Acceptable	Non-specific staining that is not obtrusive to interpretation of specific staining.
Unacceptable	Non-specific staining that is obtrusive to interpretation of specific staining.

10.5.3.4.2. Overall staining acceptability

The pathologist will also evaluate each PD-L1 case slide for the presence of staining artifacts or other observations that might compromise interpretation of the slide. If the staining of the PD-L1 case slide is inappropriate, then the slide will be recorded as not acceptable on the CRF.

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10.5.4. Evaluation of PD-L1 Expression Level

The pathologists will interpret each evaluable PD-L1 (SP263) slide for its PD-L1 expression level at the 50% (TC < 50% vs TC ≥ 50%) threshold in TC. Evaluations will be performed per standard practice and in accordance with the method sheet and interpretation guide for VENTANA PD-L1 (SP263) CDx Assay.

PD-L1 expression level can only be assigned if the tissue control slides, the H&E slide, the NRC slide and the background, morphology and overall staining of the PD-L1 (SP263) slide are acceptable. If any of these elements are deemed as not acceptable by the pathologist, the PD-L1 (SP263) slide will be scored as not evaluable and an explanatory comment will be provided.

10.5.4.1. PD-L1 Expression in Tumor Cells

NSCLC neoplastic cells labeled with VENTANA PD-L1 (SP263) CDx Assay are evaluated for percent of tumor cells with membrane staining at any intensity of the diaminobenzidine (DAB) signal. The immunohistochemical staining in NSCLC is membranous and/or cytoplasmic, and may be expressed homogeneously or heterogeneously throughout the neoplasm. Membrane staining can have a discontinuous, circumferential or basolateral pattern. Cytoplasmic staining is generally diffuse with some cases displaying a finely granular quality. The total percentage of membrane positivity for PD-L1 at any intensity estimated and used to generate the PD-L1 expression level. Tumor cell cytoplasmic staining is disregarded for determining PD-L1 expression.

First, the pathologist will determine the percentage of TC that exhibit PD-L1 (SP263) membrane staining of any intensity and record it in the CRF as a raw percentage for exploratory purposes.

Then, the pathologist will assign a PD-L1 expression level at the 50% TC threshold. The relation between the staining pattern of a PD-L1 (SP263) slide and PD-L1 expression level in TC is provided in **Table 7** for the 50% threshold.

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Table 7. Scoring algorithm for the 50% PD-L1 Expression Threshold in Tumor Cells

Interpretation	Staining Description
PD-L1 Expression Level <50%	<50% of tumor cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control.
PD-L1 Expression Level ≥50%	≥50% of tumor cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control.

10.6. Close-Out

Upon completion of investigational IVD device testing-related study procedures at each particular Dx testing site, RTD will conduct a close-out visit at that site to ensure that required regulatory documents are complete and in order, CRFs have been completed, and all requests for data clarification and monitoring notes have been resolved. Additionally, Dx protocol supply accountability will be reviewed and reconciled, and storage of the case slides under appropriate conditions with the proper owner will be confirmed.

11. DATA COLLECTION, MONITORING, AND MANAGEMENT

Collection, monitoring, and management of the clinical data obtained as part of BeiGene Study BGB-A317-A1217-302 are the responsibility of the sponsor of BeiGene Study BGB-A317-A1217-302. The sections below describe data collection, monitoring, and management for activities occurring under this Dx protocol.

11.1. Data Collection and Handling

Data will be collected on electronic and/or paper Case Report Forms (CRFs) that will be entered into a 21 CFR Part 11-compliant database. Additionally, RTD will receive electronic data files transferred from the Dx testing sites performing Dx testing for Study BGB-A317-A1217-302, from BeiGene, and/or from the Interactive Voice/Web Response System (IXRS) at the pharma study enrollment sites as detailed in a separate Data Transfer Specifications document. Demographic data and specimen characteristic data associated with the specimens among the intent to diagnose population, including screen failures, is desired and when available will be provided to RTD via data transfer.

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The Principal Investigator at each Dx testing site is responsible for the overall completeness and accuracy of the data generated.

11.2. Data Monitoring

RTD's staff will monitor the Dx testing activities in accordance with federal regulations, GCP guidelines, and RTD's standard operating procedures. The monitor(s) will review Dx protocol records to confirm that data and documents are complete and accurate. RTD, its authorized agents, and appropriate regulatory authorities shall be granted direct access to all Dx protocol-related documents to perform this verification.

RTD's staff or a designee will perform routine monitoring checks of the data. Further details are given in a separate Dx protocol-specific monitoring plan.

11.3. Data Management

Data quality will be assured according to established procedures and industry regulations and guidance. Electronic consistency checks will identify potential data errors at the time of data entry. Manual data review may also be performed as outlined in the Data Management Plan. Unclear, incomplete, or illogical data will be queried for site clarification. The combination of electronic and manual data review will ensure data quality and integrity before the data are declared final and released to biostatistics for analysis.

Data Management activities are described in further detail in a separate protocol-specific Data Management Plan (DMP).

12. STATISTICAL METHODS

12.1. Sample Size and Justification

It is anticipated that approximately 2400 patients will be screened before approximately 660 subjects are identified who meet all of the eligibility criteria required for enrollment into BeiGene Study BGB-A317-A1217-302.

Refer to Section 9.6 of the BeiGene Study BGB-A317-A1217-302 protocol for justification of sample size in relation to the pharmaceutical study.

RTD's analyses of staining performance will include all tumor specimens tested with the VENTANA PD-L1 (SP263) CDx Assay at the Dx testing sites under this protocol, as part of

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screening for BeiGene Study BGB-A317-A1217-302. Tested cases include all specimens for which staining and evaluation was attempted.

The number of patients and the number of specimens included in the Dx protocol will be determined by the total number of patients screened or for which confirmatory central PD-L1 testing is done for BeiGene Study BGB-A317-A1217-302 and the number of specimens tested for each of these patients, respectively.

12.2. Planned Analyses

12.2.1. Primary analysis

A CDx device is an IVD device that is essential for the safe and effective use of a corresponding medicinal product. Since the intended use of an IVD device is to identify patients who are likely to benefit from treatment and not to diagnose the condition of the subject being tested, the approach to evaluate diagnostic performance is fundamentally different from the approach used for prognostic/diagnostic tests. For a prognostic/diagnostic test, diagnostic performance characteristics including diagnostic sensitivity and specificity, positive and negative predictive values, likelihood ratios and expected values in normal and affected populations can be consistently calculated and interpreted. In the standard drug-diagnostic co-development model, however, these performance characteristics are not applicable to assess clinical utility. Instead, the clinical performance of the IVD device is considered acceptable if the pharmaceutical study efficacy endpoint(s) are met.

BeiGene will perform the efficacy analyses to assess the primary endpoint: of OS in the ITT population. The details of the efficacy analyses are provided in Section 9.2.1 of the BeiGene Study BGB-A317-A1217-302 protocol. Results of BeiGene Study BGB-A317-A1217-302 will also serve as the performance evaluation for VENTANA PD-L1 (SP263) CDx Assay.

Note: *No hypothesis testing will be performed under this Dx protocol, as the results of BeiGene Study BGB-A317-A1217-302 will serve as the performance evaluation for VENTANA PD-L1 (SP263) CDx Assay.*

12.2.2. Additional analyses

The following aspects of VENTANA PD-L1 (SP263) CDx Assay performance will be evaluated by RTD for NSCLC specimens tested as part of patient screening and confirmation for BeiGene Study BGB-A317-A1217-302:

- Initial and final staining acceptability rates

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- Initial and final tissue morphology acceptability rates
- Initial and final background acceptability rates

Staining acceptability rates will be calculated at the subject level, for the initial and final staining attempts (initial and final staining acceptability rates, respectively) as:

$$Staining\ acceptability\ = \frac{\#\ of\ subjects\ with\ a\ valid\ PD-L1\ Status}{\#\ of subjects\ stained\ and\ assessed\ with\ VENTANA\ \mathrm{PD-L1\ (SP263)}\ assay}\ X\ 100\%$$

For each subject, the *initial staining attempt* will be defined as the single earliest attempt made to stain and evaluate any of that subject's specimens, while the *final staining attempt* will be the staining attempt used to determine the subject's PD-L1 expression level.

Initial and final background and tissue morphology acceptability rates will be calculated among cases that are evaluated for background and for morphology (separately), using the same principles.

Descriptive statistics will be reported for select demographic and clinical characteristic data. Listings and tables summarizing all results and descriptive statistics for slide staining acceptability rates for the assay will be generated and provided in the final report from RTD.

Commercial, validated statistical analysis software packages will be used for all data analyses conducted under the Dx protocol. Detailed methodology for statistical analyses of the data collected under the Dx protocol will be documented in a Dx protocol-specific SAP produced and maintained by RTD biostatisticians. The SAP may modify the analysis plans outlined in this protocol; however, any significant changes to the primary analysis will also be reflected in a protocol amendment. Deviations from the statistical plan will be presented in the final report.

13. ADVERSE EVENT REPORTING AND HANDLING

Adverse event (AE), Adverse Device Effect (ADE), and Device Deficiency (DD) reporting and handling for this Dx protocol are summarized below. Definitions are given in **§13.1**, and reporting requirements are further described in **§13.2**.

AE reporting associated with this Dx protocol is limited in scope to events that occur at the Dx testing sites among uses of RTD's investigational IVD device. All AEs associated with

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patients enrolled in the associated pharmaceutical study, AEs related to specimen collection, improper management decisions, or side-effects from therapies tested in the study, shall be reported by Investigators at the patient enrollment and treatment sites participating in BeiGene Study BGB-A317-A1217-302 and will be handled as directed by that study protocol. Device deficiencies associated with the investigational IVD device shall be handled as described in **§13.2.3**.

13.1. Definitions

13.1.1. Adverse Event (AE)

Per ISO 20916:2019, an AE is any untoward medical occurrence, inappropriate patient management decisions, unintended disease or injury, or any untoward clinical signs in a subject, user, or other person with any connection to study-related activities, whether or not related to the IVD device(s) under investigation.

AEs can be caused by, e.g., insufficient or inadequate instructions for use, deployment, installation, or operation of the IVD medical device under investigation or by any malfunction of the device (see also DD definition), including any malfunction or deterioration of the device that has not yet caused death or serious injury but could lead to death or serious injury.

For the purpose of this clinical performance study, this definition is restricted to events related to use of the investigational IVD medical device in BeiGene Study BGB-A317-A1217-302, whether affecting users of the device (i.e., personnel at the investigational Dx testing sites) or other persons associated with the study (i.e., patients whose samples are tested with the investigational IVD assay). False negative or false positive results will not be considered an AE unless inappropriate patient management decisions are made based on those false results.

This definition is not intended to be used in determining whether an event is reportable to a regulatory authority.

BeiGene Study BGB-A317-A1217-302 is the interventional study in which subjects are enrolled. As such, the BeiGene Study BGB-A317-A1217-302 sponsor must determine whether an event has led to inappropriate patient management. AEs for subjects will be handled and reported by the BeiGene Study BGB-A317-A1217-302 sponsor according to the BeiGene Study BGB-A317-A1217-302 protocol.

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***For sites operating under IVDR**, the following definition also applies:*

An AE is any untoward medical occurrence, inappropriate patient management decision, unintended disease, or injury or any untoward clinical sign, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a performance study, whether or not related to the device for performance study.

13.1.2. Device Deficiency (DD)

Per ISO 20916:2019, a DD is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. DDs may include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer, including labeling. This definition includes DDs related to the investigational medical device(s) or the comparator(s) used in the clinical performance study.

***For sites operating under IVDR**, the following definition also applies:*

A DD is any inadequacy in the identity, quality, durability, reliability, safety, or performance of a device for a performance study, including malfunction, use errors, or inadequacy in the information supplied by the manufacturer.

13.1.3. Adverse Device Effect (ADE)

Per ISO 20916:2019, an ADE is an AE related to the use of an IVD medical device under investigation.

This definition includes any AE resulting from insufficient or inadequate instructions for use, installation, or operation of an IVD medical device under investigation, or from any malfunction of the device. It also includes any AE resulting from use error or from intentional misuse of the device.

13.1.4. Serious Adverse Event (SAE)

Per ISO 20916:2019, an SAE is an AE that leads to any of the following:

- Death
- Serious deterioration in the health of the subject, user, or other person as defined by one or more of the following:
  - (i) a life-threatening illness or injury, or
  - (ii) a permanent impairment of a body structure or a body function, including chronic disease, or
  - (iii) in-patient or prolonged hospitalization, or

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(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

- fetal distress, fetal death, or a congenital abnormality or birth defect, including physical or mental impairment.

Planned hospitalization for pre-existing condition, or procedure required by the clinical investigation without serious deterioration in health, is not considered a serious adverse event.

***For sites operating under IVDR**, the following definition also applies:*

An SAE is any AE that led to any of the following:

(a) A patient management decision resulting in death or an imminent life-threatening situation for the individual being tested, or in the death of the individual's offspring

(b) Death

(c) Serious deterioration in the health of the individual being tested or the recipient of tested donations or materials, that resulted in any of the following:

(i) life-threatening illness or injury, or

(ii) permanent impairment of a body structure or a body function, or

(iii) hospitalization or prolongation of patient hospitalization, or

(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, or

(v) chronic disease

(d) Fetal distress, fetal death, or a congenital physical or mental impairment or birth defect

13.1.5. Serious Adverse Device Effect (SADE)

Per ISO 20916:2019, an SADE is an ADE that has resulted in any of the consequences characteristic of an SAE (**§13.1.4**).

13.1.6. Anticipated Serious Adverse Device Effect (ASADE)

An ASADE is an SADE which by its nature, incidence, severity or outcome has been identified in the current version of the risk analysis report. Note 1: Anticipated serious adverse device effects can also be described in the study protocol, investigator brochure, and subject informed consent, when applicable.

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13.1.7. Unanticipated (Serious) Adverse Device Effect (USADE)

A USADE is an SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. Additional Definition from Code of Federal Regulations (CFR § 812.3(s)): An Unanticipated Adverse Device Effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

13.2. AE Recording and Reporting

13.2.1. AE Recording and Reporting Requirements

The Dx testing sites using the investigational IVD device test systems employed per this protocol are experienced in the day-to-day use of similar systems following the manufacturer's instructions for use.

The investigator(s) must record performance study-related safety events occurring at their site(s) using the appropriate form. Dx testing site investigators will report all study-related AEs including all anticipated or unanticipated AEs, serious or non-serious AEs, and any reoccurring events that may warrant consideration as an SAE based on the frequency of the event. Dx testing site personnel must contact RTD within 24 hours of becoming aware of the occurrence of any AE. An estimation of the severity and relationship to the investigational IVD device should be identified. They must also follow-up by documenting the AE on the RTD-provided AE/SAE CRF and return the signed form to RTD. AEs must also be reported in accordance with requirements of local regulations, the reviewing IRB/ECs and competent authorities (CAs).

13.2.2. Serious Adverse Events Reporting Requirements

The pharmaceutical study sponsor (BeiGene) has obligations for reporting relevant SAEs as follows:

- SAEs reported by RTD that occur during the conduct of this Dx protocol, from the time tissue specimens are received at the Dx testing site(s) until the Dx assessment of those specimens (i.e., the results of the investigational IVD device) are reported. RTD will train the staff at the Dx testing site(s) on the relevant adverse event handling and reporting.
- The BeiGene GmbH will report any SADE event that had led to inappropriate patient management.

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- Sponsor will ensure respective reporting to IRB(s)/EC(s) and other competent authorities as required.

Note: RTD will report to the pharmaceutical study sponsor (BeiGene) any events in which RTD has become aware that the accuracy of one or more reported results were compromised. The pharmaceutical study sponsor will determine if these Dx results have improperly impacted patient management decisions or otherwise meets the definition of an AE for study subjects. The pharmaceutical study sponsor will categorize the event and report it according to their AE reporting and handling procedures.

Other events that should be reported immediately to RTD and to the reviewing IRB/EC include:

- Other serious events that affect the rights, safety, or welfare of device users or other persons with any connection to activities associated with this Dx protocol;
- Other serious events encountered during use of the product systems employed in the study.

RTD's Contact for SAE/SADE Reporting
[redacted] Global Study Lead, Clinical Operations Tel: [redacted] Email : [redacted]

13.2.3. DD Reporting Requirements

Investigators at the Dx testing sites will immediately report all DDs to RTD within 24 hours of becoming aware of the occurrence and document them per RTD guidance. RTD will immediately report the event to the pharmaceutical study sponsor (BeiGene), who will categorize the event and report it according to their AE/SADE reporting and handling procedures.

13.2.4. AE Causality Assessment Procedure

Causality assessment determines the relationship between the use of the IVD device and the occurrence of a (S)AE. In the event that an anticipated or unanticipated user harm occurs, the Dx testing site investigator will report the event on the RTD-provided AE/SAE CRF as described above in **§13.2.1**. If applicable, the Dx testing site investigator will also report the event as a DD as described above in **§13.2.3**. The report will include the investigator's assessment of the relationship between the IVD device and the event based on their clinical judgement and relevant study documents, such as the Dx testing protocol and the

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Investigator's Brochure. Each event will be classified according to four different levels of causality: not related, unlikely related, possibly related and related.

1. Not related: Relationship to the device, comparator (if applicable), or procedures can be excluded

2. Possible: The relationship with the use of the investigational device or comparator (if applicable), or the relationship with procedures, is weak but cannot be ruled out completely.

3. Probable: The relationship with the use of the investigational device or comparator (if applicable), or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Causal Relationship: The (S)AE is associated with the investigational device, comparator (if applicable) or with procedures beyond reasonable doubt.

13.2.5. Complaints Associated With a Marketed IVD

Any deficiencies encountered during the conduct of the Dx protocol-related to the identity, quality, durability, reliability, safety, effectiveness, or performance of an on-market IVD or medical device that is being used according to its approved intended use should be reported to and handled by the Roche Technical Support Center 1-800-227-2155. The RTD staff should also be notified.

Complaints associated with on-market devices must adhere to IRB/EC reporting requirements and Medical Device Reporting regulation 21 CFR 803.

The BenchMark ULTRA automated slide stainer is a legally marketed medical device. Therefore, any serious injuries caused by a moving component of the instrument, electric shocks, slips/falls associated with fluid leaking from the instrument, or other instrument-related occurrences shall be considered customer complaints that must be immediately reported to both RTD staff team and the Roche Technical Support Center.

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14. ETHICS AND COMPLIANCE

14.1. Diagnostic Testing Protocol Risk Assessment

14.1.1. Risks Associated with Patient Biopsies

This Dx testing protocol involves testing specimens provided to the Dx testing sites. Specimen collection is the responsibility of pharmaceutical clinical sites in BeiGene study BGB-A317-A1217-302. All risks to patients associated with specimen collection (i.e., invasive sampling) are considered risks associated with efficacy study BGB-A317-A1217-302.

Collection of tissue samples is considered part of standard clinical practice to determine the most appropriate therapeutic option. If a new tumor biopsy is needed to enable central PD-L1 testing, tissue will be obtained using a medically routine sampling procedure. There is a remote probability that a new biopsy would be required because of the failure of the diagnostic device. Patients will only undergo a new biopsy when the risks are considered medically acceptable by their treating physicians. The potential risk associated with a new biopsy will be highlighted within the study's Patient Informed Consent Form.

14.1.2. Risks Associated with False Results of the Investigational IVD Device

Regarding patient management decisions based on the VENTANA PD-L1 (SP263) CDx Assay, there is a potential risk for a patient who would otherwise be eligible for enrollment in efficacy study BGB-A317-A1217-302 to be excluded from that efficacy study if the VENTANA PD-L1 (SP263) CDx Assay yields a false negative or non-evaluable result. In that event, the patient would discuss alternative treatment with their doctor. The resulting harm would likely be anxiety due to the delay of treatment, with no additional physical harm.

A false positive result from the assay could lead to enrollment of a patient who would otherwise have been excluded. In that event, if the patient is randomized into one of the treatment arms, (i) the patient may be less likely to benefit from investigational therapy, (ii) could experience drug toxicity from the investigation treatment(s), and/or (iii) could experience the progression of their disease.

If during the conduct of this Dx protocol, there is definitive evidence to confirm a false result was reported, this event will be reported to the pharmaceutical study sponsor and handled reported according to AE handling procedures described in the BeiGene study BGB-A317-A1217-302 protocol.

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14.1.3. Risks Associated with Patient Data Privacy

A breach in-patient confidentiality could occur if patient data are not properly coded before data are transferred to RTD. If during the conduct of diagnostic testing protocol, it is discovered that a breach of patient confidentiality has occurred within the context of the diagnostic testing activities, this event will be handled as an adverse event and reported according to AE handling procedures described in **§13** of this diagnostic testing protocol. The event will also be reported to the pharmaceutical study sponsor and may be considered an AE in the efficacy study.

14.1.4. Potential Risks to Study Personnel at the Dx testing sites

Potential risks to personnel at the CDx testing sites include contact with hazardous materials and injury to the operator of a BenchMark ULTRA instrument.

14.1.5. Potential Benefits of the Investigational IVD Device and Clinical Investigation

A potential benefit of the clinical investigation is that validation of the investigational IVD device may improve the ability of physicians to direct patients to therapies appropriate for their specific disease.

14.1.6. Minimization of Risks

To minimize the risk of false results from the VENTANA PD-L1 (SP263) CDx Assay, the assay has been analytically validated, appropriate controls are included as part of the staining procedure, and all pathologists evaluating patient slide for the Dx study will be medical professionals trained in the interpretation of the assay-stained slides. The pathologists will be required to demonstrate competence in assay interpretation before evaluating any patient slides for the study.

In the course of the BeiGene Study BGB-A317-A1217-302 conduct, personal data will be collected, de-identified, and stored. The de-identified data might be transferred to RTD (or RTD's designee) and used to support safety reporting and regulatory submissions to health authorities globally to obtain marketing approval for the investigational diagnostic test and the drug. As described in the Study BGB-A317-A1217-302 informed consent form, the data must be protected from unauthorized access, and decoding can only take place under the conditions stipulated by law.

To minimize the risk of violating patient confidentiality, all cases will be unlinked from patient identifiers before received at the laboratory(ies) for diagnostic testing described in this diagnostic study protocol.

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Instrument operators will be trained in the operation of the staining instrument to minimize their risk of injury and in the proper handling of materials and reagents.

14.1.7. Risk Benefit Conclusion

Given the unmet medical need for effective treatment options for PD-L1-positive front-line metastatic NSCLC patients and the risks and benefits summarized above, RTD concludes that the potential for clinical benefit for the patients participating in BeiGene Study BGB-A317-A1217-302 outweigh the identified risks.

14.2. Ethical Considerations

The Principal Investigator(s) will ensure that the Study RD005805 is conducted in full conformance with:

- Guidelines for Good Clinical Practice (GCP)
- RTD's requirements for adherence to good documentation practices
- The ethical principles originating in the Declaration of Helsinki (as described in the current version)
- Data privacy laws applicable in the country in which or for which the Dx protocol is conducted (e.g. GDPR, HIPAA)
- All national regulations or laws of the country in which or for which the Dx protocol is conducted (e.g., studies intended for submission in the US must adhere to FDA regulations; studies in EU must adhere to specific regulations, including those from National Health Authorities from EU member states, etc.).

Furthermore, the Dx testing activities per this protocol shall not begin until documentation of approval or waiver of the protocol approval has been obtained from the reviewing IRB/EC and from all appropriate regulatory authorities according to their regional specific requirements. Planned non-clerical changes to the diagnostic protocol must also be approved by the reviewing IRB/EC before implementation, and when applicable, by health authorities.

In countries where national health authorities require approvals or notifications related to the use of an investigational diagnostic in a pharmaceutical clinical trial, Dx testing site(s) may not begin testing specimens received from clinical enrollment sites until requisite permissions have been obtained. The pharmaceutical study sponsor is responsible to ensure the requisite permissions have been obtained prior to submitting tumor samples to Dx testing sites.

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Any ethical concerns identified during the conduct of this Dx protocol should be reported to and handled by the IRB/ethics committee providing oversight for this Dx protocol. The RTD contact person should also be notified, as appropriate.

14.3. Data Privacy

RTD, BeiGene, and the Principal Investigator must use safeguards to protect the patients' privacy, in accordance with applicable data privacy laws (including, as applicable, EU Regulations 2016/679 General Data Protection Regulation, FDA regulations, and/or HIPAA) and laws related to the conduct of this Dx protocol. In case of a transfer of the records or copies thereof to another country, safeguards will be in place to adequately protect the patient's data.

If a subject withdraws from BeiGene Study BGB-A317-A1217-302, data collected on the subject's specimens up to the point of withdrawal remain part of the study database and may not be removed. An investigator may review study data related to the subject collected prior to the subject's withdrawal from the study and use it to complete the research.

14.4. Informed Consent for Study Participation

Eligible patients may only be screened for enrollment in BeiGene Study BGB-A317-A1217-302 after providing written (witnessed, where required by law or regulation), IRB/EC-approved informed consent for screening.

Informed consent for screening must be obtained by the clinical enrolling site(s) before any study-specific screening procedures (including VENTANA PD-L1 (SP263) CDx Assay testing under this Dx protocol) are conducted. Before prospective participants provide informed consent, they must be informed in writing and orally on the nature and scope of the planned investigation and its possible health risks and benefits, including the risks associated with a tumor biopsy.

Dx testing sites receiving specimens for this Dx protocol will not receive or monitor any informed consent documents. The informed consent process is the responsibility of the pharmaceutical study enrolling study sites and will be monitored by BeiGene. The process of obtaining informed consent and the date of informed consent will be documented in-patient source documents for BeiGene Study BGB-A317-A1217-302.

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14.5. Monitoring and Auditing Responsibilities

RTD staff will monitor the activities within the scope of the Dx protocol in accordance with federal regulations, GCP guidelines, and RTD standard operating procedures as outlined in the Clinical Study Monitoring Plan and the DMP. The monitor(s) will review records to confirm that the data and documents are complete and accurate. RTD, its authorized agents, and appropriate regulatory authorities shall be granted direct access to all Dx protocol-related documents to perform this verification.

RTD, its authorized agents, or appropriate regulatory authorities may perform audits during the course of the Dx protocol or following the completion of the Dx protocol. Dx testing site personnel should contact RTD staff immediately upon receipt of an audit request.

14.6. Revisions to the Dx Testing Protocol

If RTD identifies that a change to this Dx protocol is required, such as changes to the scope of the investigation, RTD will make the appropriate changes via a Dx protocol amendment. In this event, RTD will adhere according to applicable local regulations including MPG §22c. Under MPG §22c, this would include:

- Notifying the competent higher federal authority on the changes to the document.
- Essential changes to the protocol must receive authorization by the competent higher federal authority and the applicable EC involved. Essential changes would include:
    - Changes that could have an effect on the safety of the clinical investigation participants;
    - Influence the interpretation of the documents on which the conduct of the clinical investigation is based; or
    - Influence the other requirements assessed by the ethics committee.
- If the changes were approved by the EC and the competent higher federal authority within 30 days of submission with no objections by the competent higher federal authority, the sponsor would be authorized to conduct the clinical investigation according to the modified investigational plan. If conditions are imposed, the Sponsor will observe these and adapt the documentation accordingly, or withdraw the application for changes.

The Dx protocol amendment will be subject to the same standard procedures as the initial version of the Dx protocol. RTD-approved versions of a revised Dx protocol must be signed by all Principal Investigator(s) for the Dx protocol unless their involvement is complete at the time of the Dx protocol change. All non-clerical changes (Dx protocol amendments) to the design or conduct of the Dx protocol will be documented by RTD staff and approved by the reviewing IRB/EC prior to implementation at a Dx testing site.

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Changes restricted to clerical edits only may be implemented via an administrative memo provided to Dx testing sites and reviewing IRB/EC and filed in the study file with the Dx protocol. The memos are effective immediately.

Where applicable, major changes may be reportable to applicable national health authorities. Waivers permitting deviations from the study protocol are not permitted.

14.7. Dx Protocol Deviations and Incidents

14.7.1. Protocol Deviations

A protocol deviation is an unplanned excursion from or an instance of non-compliance with the protocol as written. All Dx protocol deviations shall be documented and reported to RTD-provided Incident or Protocol Deviation Event CRF, reported to RTD staff. As required by the Principal Investigator's reviewing IRB/EC, they may also be reportable to that body. Each protocol deviation and its assessed impact upon the data will be described in the final Dx report.

14.7.2. Incidents

For purposes of this Dx protocol, an incident is an unplanned Dx testing failure(s) that cannot be attributed to lack of adherence to the Dx protocol. Examples include instrument errors (e.g., hardware failures or software errors), external power failures, or reagent issues. Such incidents are to be reported to RTD staff using the Incident or Protocol Deviation Event CRF. The RTD staff will be responsible for assessing the impact of the issue on the validity of the data and for determining how it should be handled.

14.8. Early Termination

Temporary suspension or premature termination of this Dx protocol may occur at the RTD's discretion, pharmaceutical partner decision, or because of a regulatory authority decision or an opinion change by the reviewing IRB/EC. In addition, RTD retains the right to discontinue development of the IVD device under investigation in this Dx protocol at any time. If this trial is prematurely terminated or discontinued, RTD's staff will promptly notify the pharmaceutical partner, Principal Investigator(s), IRB/EC and applicable health authorities. In this event, the appropriate regulatory agencies (e.g., BfArM) will be informed on the early termination of the activities under this Dx protocol along with providing the rationale for the early termination within 15 days.

As directed by RTD, all Dx protocol materials must be collected, and all data must be completed to the maximum extent possible. Follow-up of subjects, if required, will be

documented. The study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy RTD, IRB, and/or regulatory authorities. Regardless of outcome, RTD will document Dx protocol activities and circumstances surrounding early termination in a written Dx report.

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14.9. Investigator/Study Site Withdrawal

The Principal Investigator(s) at any of the Dx testing sites shall notify RTD study staff in advance if withdrawal from the diagnostic study is planned for any reason. If an investigator withdraws suddenly due to unforeseen circumstances, RTD must be notified as soon as possible. In the event of withdrawal, study records must be transferred to RTD or to an acceptable designee, such as another study investigator or another study institution.

14.10. Dx Protocol Documentation

14.10.1. Documents Required Prior to the Start of Dx Protocol Testing

Before the start of study testing at a study site, RTD must receive the following documents from the Dx testing site:

- Documentation of IRB/EC approval(s) or waiver(s) for the diagnostic testing protocol, investigator(s), and Dx testing site(s)
- Completed Financial Disclosure Forms from all investigators participating at the diagnostic testing study
- Curriculum vitae of the Principal Investigator(s) and other key study staff
- Protocol Signature Page, signed and dated by the Principal Investigator(s)
- Investigator Agreement / Statement of Principal Investigator(s)
- IRB/EC approval letter for the testing informed consent form
- Notice of approval by member state(s) Competent Authority, if applicable

14.10.2. List of Documents Available to the Dx Testing Site(s)

In addition to this diagnostic protocol, the following documents will be made available to the study site(s).

- CRFs
- Investigational product method sheet/Package Insert (P/N 1019701ENa)
- SDS
- VENTANA PD-L1 (SP263) CDx Assay Interpretation Guide (P/N 1016119EN)

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- Training materials, as required

In addition to the above listed items, the following documents will be kept in the TMF maintained by RTD.

- BeiGene Study BGB-A317-A1217-302 protocol
- BeiGene Study BGB-A317-A1217-302 informed consent form
- Clinical study monitoring plan
- DMP
- Statistical analysis plan
- List of diagnostic investigative study sites (laboratories) and investigators

14.10.3. Access to Dx Protocol Records

The Principal Investigator(s) at Dx testing sites must maintain adequate records to fully document the diagnostic testing activities associated with study conduct. On request, Principal Investigator(s) shall provide RTD, its authorized agents, or appropriate regulatory authorities direct access to all study-related documentation. This access will allow reviewers to verify adherence to the diagnostic testing protocol, applicable GCP guidelines, and applicable regulations and to confirm the completeness and accuracy of study records. Records access is particularly important for resolving problems arising from illegible data or from suspected errors in data transcription.

The Principal Investigator(s) and his/her/their relevant personnel shall make every effort to be available during monitoring visits, audits, and inspections related to the diagnostic study, and to allot sufficient time for the process.

14.10.4. Retention of Dx Protocol Records

Principal Investigator(s) must maintain all study records until the latest of the following dates:

- Ten years after product approval
- Ten years after study termination
- The date specified in the clinical study agreement

Before destroying any study records, the Principal Investigator(s) must contact RTD for permission, even if the records retention period has passed.

If the Principal Investigator(s) is unable to maintain the study records as required above, s/he/they must contact RTD to arrange for the appropriate records transfer.

14.11. Publication of Data and Protection of Proprietary Information

Data obtained from participation in this diagnostic testing study are considered confidential. The Principal Investigator(s) at the Dx testing sites must adhere to the non-disclosure requirements and publication policy set forth in the clinical trial agreement.

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16. **APPENDICES** *(None)*

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