Clinical Study Protocol

Protocol Title:	**A Phase 1/1b, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activity of the anti-PD-1 Monoclonal Antibody BGB-A317 in Combination with the PARP Inhibitor BGB-290 in Subjects with Advanced Solid Tumors**
Protocol Number:	**BGB-A317/BGB-290_Study_001**
EudraCT Number:	**2017-003580-35**
Date of Protocol:	**18 September 2018, Version 4**
Study Phase:	**1/1b**
Sponsor:	**BeiGene AUS Pty Ltd.** **c/o Becis Pty Ltd.** **1C/528 Compton Road** **Stretton, Queensland 4116** **Australia** **BeiGene, Ltd.** **c/o BeiGene USA, Inc.** **1900 Powell Street, 5th Floor** **Emeryville, CA 94608** **USA**
Sponsor Medical Monitor:	[redacted]
Coordinating Investigator:	[redacted]

Confidentiality Statement

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PROTOCOL TITLE: A Phase 1/1b, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activity of the anti-PD-1 Monoclonal Antibody BGB-A317 in combination with the PARP inhibitor BGB-290 in Subjects with Advanced Solid Tumors

PROTOCOL NO: BGB-A317/BGB-290_Study_001 Version 4, dated 18 September 2018

[redacted] _____ _____

Date

Sponsor Medical Monitor

PROTOCOL VERSION 4 - RATIONALE AND CHANGE INVENTORY

The purpose of this amendment is to incorporate the following changes:

- Updated the number of patients previously treated in the study.
- Updated Rationale for Dose Selection for Part B.
- Remove Disease-Specific Cohort for Non-Small Cell Lung Cancer.
- Added exploring potential predictive biomarkers for resistance to Exploratory Objectives.
- Clarified length of time for Safety Follow-up for AEs and irAEs.
- Clarified number of patients in Part B.
- Clarified number of lines of prior treatment a patient received prior to study treatment.
- Added allowance for urine pregnancy test after screening.
- Added new assessment for CK and CK-MB.
- Included alcohol consumption assessment.
- Updated Coagulation Parameters, Thyroid Function, Blood Sample, and Dose Modification.
- Added new section Treatment beyond Progression.
- Updated description of Investigational Product.
- Updated Recommended Diagnostic Tests in the Management of Possible Immune-related Adverse Events
- Included the International Nonproprietary Name, tislelizumab, in place of ‘BGB-A317’ and pamiparib, in place of ‘BGB-290’ throughout the protocol.
- Updated medical monitor.

SYNOPSIS

Name of Sponsor/Company:	BeiGene Ltd.
Name of Finished Product and Active Ingredients:	Tislelizumab (BGB-A317) and Pamiparib (BGB-290)
Title of Study:	A Phase 1/1b, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activity of the anti-PD-1 Monoclonal Antibody BGB-A317 in combination with the PARP inhibitor BGB-290 in Subjects with Advanced Solid Tumors
Protocol No:	BGB-A317/BGB-290_Study_001
Study Centers:	Approximately 30-50 study centers (global participation)
Study Duration: Screening up to 28 days, Treatment up to 2 years, Safety Follow-up up to 30 days, and Survival Follow-up (approximately every 3 months).	**Phase:**1/1b

Objectives:

Part A (Dose-escalation)

Primary:

- To assess the safety and tolerability of tislelizumab (BGB-A317) in combination with pamiparib (BGB-290)
- To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) for the combination

Secondary:

- To characterize the pharmacokinetics (PK) of pamiparib and tislelizumab in combination
- To assess the preliminary anti-tumor activity of tislelizumab in combination with pamiparib
- To assess host immunogenicity to tislelizumab

Exploratory:

- [redacted]

Part B (Expansion Cohorts)

Primary:

- To assess the preliminary anti-tumor activity of the combination of tislelizumab and pamiparib in patients with specific tumor types

Secondary:

- To further assess the safety and tolerability of the combination
- To further characterize the PK of tislelizumab and pamiparib in combination
- To further assess host immunogenicity to tislelizumab

Exploratory:

- [redacted]

Methodology:

Part A:

Part A is a multicenter, open-label, multiple-dose, dose-escalation study in patients with advanced solid tumors likely to harbor DNA damage repair deficiencies susceptible to treatment with poly (ADP-ribose) polymerase (PARP) inhibitor or known to be responsive to programmed cell death-1 (PD-1) blocker. Five combination dose levels (DLs) are planned. The study will follow a 3+3 dose-escalation scheme. The dose-limiting toxicity (DLT) assessments will be evaluated during the first cycle consisting of the first 21 days of treatment. The Safety Monitoring Committee (SMC), consisting of investigators, the sponsor's medical delegate, safety delegate, and the contract research organization's (CRO) medical monitor, will evaluate safety data after patients have completed at least one cycle of treatment in order to make a decision on dose-escalation, and to determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D). The SMC may decide to evaluate an intermediate, not pre-defined, previously evaluated or not previously-evaluated dose or a less frequent dosing schedule that will not exceed the MTD level, if evaluation of toxicity at such a dose or schedule is desired. If this approach is taken, up to 6 new patients should be enrolled at that dose or schedule.

Starting dose and dose-escalation rules

In all dose levels, tislelizumab will be administered as an intravenous (IV) infusion on Day 1 of each 21-day cycle, and pamiparib will be taken orally twice daily starting from Day 1. The starting dose for each agent and the starting DL of the combination was based on the doses evaluated in the on-going monotherapy dose-escalation study for each agent and is significantly lower than the highest safe dose that has been identified to date. The study will follow a 3+3 dose-escalation scheme at the pre-defined DLs until MTD and/or RP2D is determined for the combination. At least 3 patients will be enrolled into each cohort. Additional patient(s), up to a maximum of six (6) patients in total, will be enrolled. The DLT assessment and dose-escalation scheme will follow the same principle as stipulated for a 3+3 dose escalation design. When a minimum of 2 patients experience DLT at a given DL, this DL will be defined as intolerable. The MTD is the DL at which 0/6 or 1/6 patients experience DLT with at least two patients experiencing DLT at the next higher DL.

Part B

Part B will evaluate the safety and tolerability and anti-tumor activity of tislelizumab + pamiparib treatment in the arms of specific tumor types defined below. The RP2D is tislelizumab 200 mg IV Q3W + pamiparib 40 mg orally twice daily. Each arm will enroll approximately 20 patients. All patients must have received standard of care in the primary treatment of their disease. Patients with platinum-refractory disease are excluded. Platinum-refractory disease is defined as progressive disease at the time of the first tumor assessment while receiving a platinum-containing therapy. Enrollment into these disease-specific cohorts will occur simultaneously and independent of each other.

Arm 1a: Patients with relapsed, platinum-sensitive high grade epithelial, non-mucinous, ovarian cancer, fallopian tube, or primary peritoneal cancer (EOC) **with** either known germline or somatic *BRCA1/2* mutations or **with** homologous recombination deficiency (HRD). Patients must have received at least 2 prior lines of platinum-containing chemotherapy

Arm 1b: Patients with relapsed, platinum-sensitive high grade EOC **without** either known germline or somatic *BRCA1/2* mutations and **without** known HRD. Patients must have received at least 2 prior lines of platinum-containing chemotherapy.

Arm 2: Patients with triple negative breast cancer (TNBC) with either **known** germline or somatic *BRCA1/2* mutations or with **documented** HRD. Patients can have been treated with at least 1 but not more than 3 prior lines of treatment.

Arm 3: Patients with metastatic castration-resistant prostate cancer (mCRPC) with either **known** germline or somatic *BRCA1/2* mutations or with **documented** HRD. Chemotherapy-naïve patients must have received prior abiraterone acetate or enzalutamide treatment

Arm 4: Patients with extensive-stage disease small cell lung cancer (SCLC) treated at least 1 and not more than 2 prior lines of treatment; at least 1 regimen must include a platinum agent

Arm 5: Patients with *HER2*-negative gastric or gastroesophageal junction cancer. Patients with *HER2*-negative disease may be treated with at least 1 but no more than 2 prior lines of treatment.

Arm 6: Patients with locally advanced or metastatic urothelial (muscle invasive bladder, ureter, urethra or renal pelvis) cancer treated with at least 1 but no more than 2 prior lines of treatment, including a prior platinum-containing chemotherapy

Arm 7: Patients with advanced or metastatic pancreatic adenocarcinoma treated with at least 1 but no more than 2 prior lines of treatment. Any potential patient with a known deleterious germline or somatic *BRCA* is eligible even if platinum-naïve

Arm 8: Patients who may be expected to benefit from the combination of a PARP inhibitor and a PD-1 inhibitor. This arm will include patients with recurrent non-ovarian gynecological cancers (endometrial cancer, cancer of the cervix and patients with tumors known to be mismatch repair deficient [MMR] or HRD positive) that are not eligible for inclusion in any other arms of the trial. This is an exploratory signal seeking arm and is closed to enrollment.

For Arm 1 (ovarian cancer), Arm 2 (TNBC), and Arm 3 (mCRPC), patients with known eligible mutation status can be enrolled into the study if otherwise eligible. Tissue/blood specimens will be collected for a confirmatory test. Patients who do not have known germline or somatic *BRCA* mutation, or known HRD status must sign a separate pre-screening informed consent to evaluate HRD status prior to enrollment.

For Arm 1 (EOC), Arm 1a may be analyzed independently of Arm 1b. All Arms will enroll up to 40 patients.

Arm 8 is closed to enrollment.

Fresh blood samples will be collected at baseline and at defined times as indicated for all patients in Part B for the evaluation of germline mutations, which may include *BRCA* mutations and/or confirmation of prior *BRCA* results or other homologous recombination deficiency mutations. All patients enrolled in Part B must submit archival tumor tissue, unless previously discussed with sponsor's medical monitor or its designee. A fresh biopsy of an accessible tumor lesion is required at baseline (within 12 weeks of starting treatment) in the absence of archival tumor tissue, unless previously discussed with the sponsor's medical monitor or its designee. Optional tumor biopsies will also be obtained in consenting patients to evaluate the pharmacodynamic effects and resistance mechanisms.

Part A and Part B

Patients will be monitored for safety, tolerability, anti-tislelizumab antibodies, and anti-tumor activity throughout the study from the day of first administration of study drugs up to 30 days following last study treatment or initiation of new anticancer therapy, whichever occurs first. Radiological assessment of tumor response should be performed approximately every 9 ± 1 weeks in the first year and approximately every 12 ± 1 weeks thereafter.

Tumor response will be assessed by investigators based on Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. For patients with ovarian, fallopian tube, or primary peritoneal cancer, investigators may also incorporate GCIG CA-125 response criteria with RECIST Version 1.1 response criteria in assessing tumor response. For patients with prostate cancer, Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria will also be used to evaluate prostate-specific antigen (PSA) and modified RECIST responses.

Accumulating evidence indicates some patients treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD). Patients will be permitted to continue study treatment beyond initial RECIST v1.1 defined PD for the time periods below and if they meet the following criteria:

- Investigator-assessed clinical benefit
- Patient is tolerating study drug and agrees to continued study treatment

	• Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (Protocol Appendix 3) • Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that necessitates urgent alternative medical intervention • Patients must be reconsented to continue study treatment beyond disease progression. For suspected pseudo-progression, treatment may continue until confirmation of PD with repeat imaging at least 4 weeks later or at the next regularly scheduled imaging time point, but not more than 12 weeks from the initial documentation of pseudo-progression. All decisions to continue treatment beyond initial progression must be documented in the medical record, and agreed to by the sponsor medical monitor. This study will be considered complete once all patients have manifested disease progression; ceased study treatment due to death; exhibit intolerance; withdrawn consent from the study; or completed a total of 2 years of treatment. Any patient in this study who continues to demonstrate objective clinical benefit at the end of a 2-year treatment duration may continue in the study or on treatment.
Planned Number of Patients:	*Part A*: Approximately **50 patients** for the dose escalation until MTD and/or RP2D determination. *Part B*: Up to approximately **200 patients** for expansion in arms of specific tumor types. Each Arm will be evaluated independently for study endpoints and can either be closed due to suboptimal clinical anti-tumor activity or expanded by enrolling an additional 20 patients if sufficient anti-tumor activity (eg, higher objective response rate [ORR] or longer progression-free survival [PFS] than expected) is observed. Statistical justification of such sample size expansion will be included in the final statistical analysis plan as applicable.
Study Population	Key inclusion criteria: 1. Patients have voluntarily agreed to participate by giving written informed consent. 2. Patients must have received standard of care in the primary treatment of their disease. 3. Patients who have the below specified histologically confirmed malignancies that have progressed to the advanced or metastatic stage. a) In Part A, the patients must have an advanced malignancy including but not limited to high-grade serous cancer of the ovary, fallopian tube, or peritoneum, triple negative breast cancer, SCLC, primary peritoneal cancer, and any tumor likely to harbor DNA damage repair deficiencies susceptible to treatment with a PARP inhibitor or likely to be responsive to a PD-1 blocker. b) In Part B, the patients recruited to one of the eight expansion arms must have advanced solid tumors of the following types: *Arm 1*: Patients with relapsed, platinum-sensitive high grade epithelial, non-mucinous, ovarian cancer, fallopian tube, or primary peritoneal cancer (EOC) must meet the following criteria: i. Patients must have at least 2 prior platinum-containing treatments in any treatment setting. • Note: patients may have received additional therapy after the last platinum-containing regimen if the other eligibility criteria are met. ii. Patients must have platinum-sensitive recurrent disease and must not have progressed (by RECIST v1.1 criteria) within 6 months of the completion of the last platinum-containing line of treatment.

	• Note: patients may receive additional non-platinum based chemotherapy for recurrence after prior last platinum-containing regimen if the criteria for platinum-sensitivity are met. iii. **Arm 1a**: Patients with relapsed, platinum-sensitive high grade epithelial, non-mucinous, ovarian cancer, fallopian tube, or primary peritoneal cancer (EOC) with either known deleterious or suspected deleterious germline or somatic *BRCA1/2* mutations or with HRD. • If HRD or *BRCA1/2* mutation status from archival tissue is unknown or has not been previously evaluated, then the archival tissue must undergo tissue screening using a validated diagnostic test to determine eligibility. If the diagnostic test result is *BRCA1/2* or HRD positive the patient will be eligible for enrollment in Arm 1a. iv. **Arm 1b**: Patients with relapsed, platinum-sensitive high grade EOC who otherwise meet the above criteria and are without known germline or somatic *BRCA1/2* mutations and without HRD mutation. *Arm 2*: Patients with triple negative breast cancer must meet the following criteria: i. Patients with 0-1 prior platinum-containing treatment in any treatment setting. • Note: patients could have received additional therapy after the last platinum-containing line of treatment if the other eligibility criteria are met. ii. Patients who have received at least 1 prior treatment but not more than 3 prior lines of treatment in the advanced or metastatic setting. iii. Known deleterious or suspected deleterious germline or somatic *BRCA1/2* mutations or with documented HRD. • If HRD or *BRCA1/2* mutation status from archival tissue is unknown or has not been previously evaluated, then the archival tissue must undergo tissue screening using a validated diagnostic test to determine eligibility. If the diagnostic test result is HRD positive, then the patient will be eligible for enrollment in Arm 2. • If archival tissue is not available and the patient submits a fresh tumor biopsy, then the diagnostic test needs to demonstrate somatic *BRCA1/2* mutation or HRD positivity. *Arm 3:* Patients with metastatic castration-resistant prostate cancer, including but not limited to mutations in homologous recombination (HR) pathways and/or defined by HRD algorithms, and must meet the following criteria: i. The patient may be either chemotherapy-naïve, but must have received prior abiraterone acetate and/or enzalutamide treatment, or have previously had no more than 2 taxane-based chemotherapy lines of treatment including docetaxel and carbazitaxel. If docetaxel is used more than once, this will be considered as 1 line of treatment. ii. At least 2 weeks since the completion of prior flutamide, bicalutamide, and nilutimide, or enzalutamide and abiraterone treatment. iii. Documented prostate cancer with one of the following:

	• Surgically or medically castrated. The testosterone levels do not need to be checked if the patient has undergone surgical castration for > 4 months. Patients receiving chemical castration should have testosterone levels checked at baseline and confirmed to be in the castrate levels (< 0.5 ng/mL or 1.735 nM). In all cases the luteinizing hormone-releasing hormone (LHRH) antagonist/agonist is to be continued in these patients. • Patients with only non-measurable bone lesions must have disease progression based on PCWG3 with 2 or more new lesions or have prostate-specific antigen (PSA) progression before enrollment. iv. Known deleterious or suspected deleterious germline or somatic BRCA1/2 mutations or with documented HRD. • If HRD or *BRCA1/2* mutation status from archival tissue is unknown or has not been previously evaluated, then the archival tissue must undergo tissue screening using a validated diagnostic test to determine eligibility. If the diagnostic test result is HRD positive, then the patient will be eligible for enrollment in Arm 3. • If archival tissue is not available and the patient submits a fresh tumor biopsy, then the diagnostic test needs to demonstrate somatic *BRCA1/2* mutation or HRD positivity. *Arm 4*: Patients with extensive-stage disease small cell lung cancer (SCLC) must meet the following criterion: i. Patients received at least 1 and not more than 2 prior lines of treatment. ii. At least 1 prior line of treatment must have contained a platinum agent *Arm 5*: Patients with *HER2*-negative gastric or gastroesophageal junction cancer must meet the following criteria: i. Patients with *HER2*-negative may have received at least 1 and not more than 2 prior lines of treatment. *Arm 6*: Patients with locally advanced or metastatic urothelial (muscle-invasive bladder, ureter, urethra or renal pelvis) cancer must meet the following criteria: i. Patients received at least 1 and not more than 2 prior lines of treatment in the advanced or metastatic disease setting. ii. At least 1 prior line of treatment must have contained a platinum agent *Arm 7:* Patients with advanced or metastatic pancreatic adenocarcinoma must meet the following criteria: i. Received at least one but not more than 2 lines of treatment in either an advanced or metastatic setting; ii. At least 1 prior treatment for advanced or metastatic disease must have contained a platinum agent

	iii. Patients with known deleterious germline or somatic BRCA1/2 mutation can be considered for the study even if platinum-naive *Arm 8*: (NOTE: CLOSED TO ENROLLMENT) Patients with advanced or metastatic recurrent non-ovarian gynecological cancers (endometrial cancer, cancer of the cervix and patients with tumors known to be MMR deficient or HRD positive) must meet the following criteria: i. Patients with a complete response, partial response or stable disease from at least 1 prior platinum-containing treatment in any treatment setting. ii. The Sponsor medical monitor will approve tumor types for Arm 8 prior to screening. • Note: Excluded tumor types include patients with bone or soft tissue sarcoma; central nervous system (CNS) malignancies; colorectal cancer (except microsatellite instability-high [MSI-H] colorectal cancer is permitted); cutaneous or ocular melanoma; hematologic malignancies; HER2-negative breast cancer without *BRCA* mutation; mesothelioma, papillary, follicular, medullary or Hürthle cell thyroid cancer; unknown primary malignancy. 4. Patients who were treated with chemotherapy or any investigational therapies, if eligible, must have been completed at least 4 weeks or at least 5 half-lives (whichever is longer, but no less than 3 weeks) before the study drug administration, and all AEs have either returned to baseline or 5. At least 2 weeks from palliative radiotherapy. 6. Patients must have archival tumor tissue or agree to a tumor biopsy for mutation and biomarkers analysis unless previously discussed with sponsor's medical monitor or its designee (fresh tumor biopsies are recommended at baseline in patients with readily accessible tumor lesions and who consent to the biopsies). Patients with ovarian, fallopian tube, primary peritoneal, or breast cancer in Part A and all patients enrolled in Part B must also agree to provide fresh blood sample at the baseline for the evaluation of *BRCA* mutations and/or confirmation of prior *BRCA* results or other homologous recombination deficiency mutations even if it was previously tested. 7. Patients must have measurable disease as defined in RECIST v1.1. Patients with metastatic castration-resistant prostate cancer and epithelial, non-mucinous, ovarian cancer, fallopian tube, or primary peritoneal cancer may use separate disease-specific criteria (Protocol Appendix 4, Appendix 6, and Appendix 8). 8. Patients must be a male or female ≥ 18 years of age on the day of signing informed consent. 9. Patients must have an ECOG Performance Status (PS) ≤ 1 (Protocol Appendix 3). 10. Patients must have a life expectancy ≥ 12 weeks. 11. Patient must have adequate organ function as indicated by the following laboratory values independent of transfusion within 2 weeks: a) Absolute neutrophil count (ANC) ≥ 1,500/mL. b) Platelets ≥ 100,000/mL.

	c) Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L. d) Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Protocol Appendix 18). e) Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) (On fractionation ≤ 90% of total bilirubin should be unconjugated. Total bilirubin must be < 4 X ULN for patients with Gilbert's syndrome). f) Aspartate aminotransferase (serum glutamic oxaloacetic transaminase [SGOT]) and alanine aminotransferase (serum glutamic pyruvic transaminase [SGPT]) ≤ 2.5 × ULN. g) International normalized ratio (INR) ≤ 1.5 × ULN (≤ 2.5 × ULN if on anticoagulants). 12. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study (Protocol Appendix 17), and for at least 6 months after the last dose of investigational drug, and have a negative serum pregnancy test within 7 days of the first dose of study drug(s). 13. Non-sterile males and their female partners must be willing to use a highly effective method of birth control for the duration of the study and for at least 6 months after the last dose of investigational drug (Protocol Appendix 17). Nonsterile males must avoid sperm donation for the duration of the study and for at least 6 months after last study drug. 14. Female patient must agree not to breastfeed starting at screening and throughout the study period, and for 6 months after the final study drug administration. <u>Key exclusion criteria:</u> 1. Platinum-resistant/refractory disease, defined as progressive disease at the first tumor assessment while receiving platinum-containing chemotherapy 2. Patient has history of severe hypersensitivity reactions to other monoclonal antibodies (mAbs). 3. Any major surgery within 28 days before first dose of study drugs. 4. Prior allogeneic stem cell transplantation or organ transplantation. 5. Patients with toxicities (as a result of prior anticancer therapy) which have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy and specific laboratory abnormalities). 6. Concurrent participation in another therapeutic clinical trial. 7. Prior malignancy within the previous 2 years except for locally curable non-melanoma dermatologic cancers that have been apparently cured, such as basal or squamous cell skin cancer, or carcinoma in situ of the skin, cervix, breast, bladder, or prostate. 8. Symptomatic CNS metastasis or leptomeningeal disease. <u>Note</u>: Baseline MRI of the brain and spinal cord is required for SCLC patients enrolled in Arm 4 if they have a history of CNS disease. <u>Note</u>: Patients with previously treated CNS metastatic disease are eligible for any arm if CNS metastatic disease is asymptomatic, clinically stable, and does

	not require corticosteroids or anticonvulsants within a minimum of 4 weeks of enrollment. 9. Prior therapies targeting PD-1, programmed death-ligand 1 (PD-L1), or PARP. The exception to this criterion are patients eligible for Arm 9; where patients may have received either a PD-1 inhibitor or PD-L1 inhibitor. 10. Active autoimmune diseases or history of autoimmune diseases that may relapse (Protocol Appendix 15). Note: Patients with the following diseases are not excluded and may proceed to further screening: a) Controlled Type I diabetes. b) Hypothyroidism managed with no treatment other than with hormone replacement therapy. 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. 11. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication within 2 weeks of the study drug administration. Note: Patients who are currently or have previously been on any of the following steroid regimens are not excluded: a) Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent). b) Topical, ocular, intra-articular, intranasal, or inhalational 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). 12. With severe chronic or active infections requiring systemic antibacterial, antifungal or antiviral therapy, including tuberculosis infection, etc. 13. History of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc. 14. History of non-viral hepatitis or cirrhosis. 15. Positive human immunodeficiency virus (HIV) status. 16. A known history of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. 17. History of alcohol abuse. 18. Underlying medical conditions or alcohol or drug abuse or dependence that, in the investigator's opinion, will be unfavorable for the administration of study drug or affect the explanation of drug toxicity or adverse events; or insufficient compliance during the study according to investigator's

	judgement. 19. Inability to swallow oral medications (capsules and tablets) without chewing, breaking, crushing, opening or otherwise altering the product formulation. Patients should not have gastrointestinal illnesses that would preclude the absorption of pamiparib, which is an oral agent. Please note Protocol Appendix 12 for a list of prohibited medications that are associated with possible interactions with pamiparib. 20. Has been administered a live vaccine within 4 weeks (28 days) of initiation of study therapy. Patients are eligible if 28 days have elapsed since receipt of vaccine and initiation of study treatment. (NOTE: seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines; and are not allowed). 21. Any of the following cardiovascular criteria: a) Current evidence of cardiac ischemia. b) Current symptomatic pulmonary embolism. c) Acute myocardial infarction ≤ 6 months prior to Day 1. d) Heart failure of New York Heart Association Classification III or IV (Protocol Appendix 16) ≤ 6 months prior to Day 1. e) Grade ≥ 2 ventricular arrhythmia ≤ 6 months prior to Day 1. f) History of cerebrovascular accident within 6 months before first dose of study drugs. 22. Use or have anticipated need for food or drugs known to be strong or moderate cytochrome P450 (CYP)3A inhibitors or strong CYP3A inducers ≤ 10 days (or ≤ 5 half-lives, whichever is shorter) prior to Day 1 (Appendix 12)
Test Product, Dose and Mode of Administration:	**Drugs:** Combination of tislelizumab and pamiparib Tislelizumab will be administered as an IV infusion over 30-60 minutes; once every 3 weeks (Q3W) (see Protocol Section 6.2 for instructions). Pamiparib will be administered orally, twice daily. In both Parts A and B of the study, tislelizumab will be administered as an IV infusion on Day 1 of a 21-day cycle, and pamiparib will be taken orally twice daily starting from Day 1. **Part A: Proposed Dose levels:** Level 1: tislelizumab, 2 mg/kg IV Q3W, pamiparib, 20 mg orally twice daily Level 2: tislelizumab, 2 mg/kg IV Q3W, pamiparib, 40 mg orally twice daily Level 3: tislelizumab, 2 mg/kg IV Q3W, pamiparib, 60 mg orally twice daily Level 4: tislelizumab, 200 mg IV Q3W, pamiparib, 40 mg orally twice daily Level 5: tislelizumab, 200 mg IV Q3W, pamiparib, 60 mg orally twice daily The proposed DLs may be further modified and additional doses may be considered based on the safety, tolerability, and efficacy observed during dose escalation, ie, flat dose of tislelizumab at 200 mg or 300 mg IV Q3W. An intermediate, not pre-defined, previously evaluated or not previously evaluated dose or a less frequent dosing

	schedule that will not exceed the MTD level, if evaluation of toxicity at such a dose or schedule is desired. **Part B:** Tislelizumab: 200 mg IV Q3W Pamiparib: 40 mg orally twice daily This combination will be given until disease progression or other discontinuation criteria are met.
Reference Therapy, Dose and Mode of Administration:	Not applicable

Criteria for Evaluation:

Part A:

Primary Endpoints:

- Safety and tolerability as assessed by the incidence and nature of AEs
- Incidence and nature of DLTs
- Determination of maximum tolerated dose of the combination of tislelizumab and pamiparib

Secondary Endpoints:

- Pharmacokinetic parameters, including but not limited to C_{trough} of tislelizumab and C_{max}, T_{max} and C_{trough} of pamiparib
- Efficacy parameters including:
  - Objective response rate (ORR) is defined as a best overall response of complete response (CR) and partial response (PR)
  - Disease control rate (DCR) is defined as a best overall response of CR, PR and stable disease (SD)
  - Clinical benefit rate (CBR) is defined as a best overall response of CR, PR and SD lasting ≥ 24 weeks
  - PFS is defined as the time from first dose of study medication to the first documented objective disease progression or death due to any cause, whichever occurs first
  - Overall survival (OS) is defined as the time from the date of first dose of study drug to death due to any cause
- Immunogenicity of tislelizumab

Exploratory Endpoints:

- [redacted]

Part B:

Primary Endpoint:

- Anti-tumor activity as determined by ORR, PFS, duration of response (DOR), DCR, CBR, and OS

Secondary Endpoints:

- Safety and tolerability as assessed by the incidence and nature of AEs
- Pharmacokinetic parameters, including but not limited to C_{trough} of tislelizumab and pamiparib
- Immunogenicity of tislelizumab

[redacted]

Statistical Methods:

Data will be listed and summarized according to the sponsor-agreed reporting standards, where applicable.

All patients (both parts) who are exposed to (or started receiving) the combination agents will be included in the safety analysis set. All patients for whom valid tislelizumab or pamiparib PK parameters can be estimated will be included in the PK analysis set on an as-treated basis.

As described in the objectives, the trial is designed to establish the safety and tolerability of tislelizumab and pamiparib combination and to assess the preliminary anti-tumor activity of the combination in selected tumor types. No formal hypothesis testing is planned. Descriptive statistical analyses will be performed for all patients in the safety analysis set. The safety and efficacy (eg, ORR, PFS, DOR, DCR, CBR and OS) data will be presented by part and arm.

Sample Size:

Number of patients in Part A will depend on the incidence of DLT reported. Approximately **50 patients** are expected in Part A of the trial.

Part B will include expansion arms of specific tumor types. Up to approximately 40 patients per cohort may be enrolled. The purpose of these expansion arms is to explore signals of clinical efficacy as well as to confirm the safety and tolerability of the combination in each selected tumor type. Anti-tumor activity will be evaluated in Part B. A decision can be made to stop an arm early due to suboptimal clinical anti-tumor activity. Up to a total of 40 patients may be enrolled in any disease cohort to evaluate the anti-tumor activity if evidence of activity is observed in the first 20 patients enrolled.

The probability of observing at least one responder is approximately 88% in an expansion arm (n = 20) when the underlying ORR is as low as 10%.

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1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ADP	adenosine diphosphate
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASAP	as soon as possible
AST	aspartate aminotransferase
ATM	Ataxia-Telangiectasia Mutated
AUC	area under the plasma concentration-time curve
BGB-290	code name for PARP inhibitor; pamiparib
BGB-A317	code name for monoclonal antibody BGB-A317; tislelizumab
BRCA1/2	breast cancer type 1/2 susceptibility gene
C1q	complement 1q, a subunit of complement 1
CA-125	carcinoma antigen 125
CBC	complete blood count
CBR	clinical benefit rate
CD	cluster of differentiation, such as CD274, CD279, and CD3
CDC	complement-dependent cytotoxicity
CEA	carcinoembryonic antigen
CNA	circulating nucleic acids
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CT	computed tomography
C_{trough}	minimum observed plasma concentration

CYP	cytochrome P450
DBP	diastolic blood pressure
DCR	disease control rate
DDI	drug-drug interaction
DL	dose level
DLT	dose-limiting toxicity
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eGRF	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
ENR	Enrolled set
EOC	high grade epithelial, non-mucinous ovarian, fallopian tube or primary peritoneal cancer
Fab	fragment antigen-binding
Fc	fragment crystallizable region (typically, of immunoglobulin G)
FcγR	gamma Fc receptor, such as Fc RI, and Fc RIII
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FDG-PET	PET scanning with the tracer fluorine-18 [F-18] FDG
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte macrophage colony-stimulating factor
GMP	Good Manufacturing Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HGSOC	high-grade serous ovarian cancer
HIV	human immunodeficiency virus

HNSCC	head and neck squamous cell carcinoma
HR	homologous recombination
HRD	homologous recombination deficiency
IB	Investigator's Brochure
IC_{50}	inhibitory concentration for 50% of maximal activity
ICF	informed consent form
ICU	Intensive Care Unit
ID	Identification
IEC	Independent Ethics Committee
IFN-α	interferon alpha
IFN-γ	interferon gamma
IgG	immunoglobulin G, such as IgG1, IgG2, IgG3 and IgG4; other types of immunoglobulins include IgM and IgD
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	international normalized ratio
IPI	Ipilumumab
irAEs	immune-related adverse events
IRB	Institutional Review Board
ITP	idiopathic thrombocytopenic purpura
IV	Intravenous
K_D	dissociation constant
LFT	liver function tests
mAbs	monoclonal antibodies
MAD	maximum administered dose
(m)CRPC	(metastatic) castration-resistant prostate cancer
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N	Number
NCI	National Cancer Institute

NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NE	not evaluable
NK	natural killer cells
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
pamiparib	BGB-290
PAR	poly (ADP-ribose)
PARP	poly (ADP-ribose) polymerase
PARPi	poly (ADP-ribose) polymerase inhibitors
PBMC	peripheral blood mononuclear cell
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1, programed death receptor ligand-1, Programed Death-1 Ligand-1
PD-L2	program death ligand-2
PDX	patient-derived xenograft
PET	positron emission tomography
PFS	progression-free survival
pH	negative of the logarithm to base 10 of the activity of the (solvated) hydronium ion
PK	Pharmacokinetics
PKS	pharmacokinetic analysis set
PR	partial response
PS	performance status
PSA	prostate-specific antigen
PT	prothrombin time
Q2W	once every 2 weeks

Q3W	once every 3 weeks
QT	QT interval of the electrocardiogram
QTc	QT interval corrected for heart rate
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAEs	serious adverse events
SAF	safety analysis set
SBP	systolic blood pressure
SCC	squamous cell carcinoma
SCLC	small cell lung cancer
SCr	serum creatinine concentration
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLE	systemic lupus erythematosus
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	standard operating procedure
SPR	surface plasmon resonance
$t_{1/2}$	half-life
T3	Triiodothyronine
T4	Thyroxine
TCGA	The Cancer Genome Atlas
TCR	T-cell receptor
TEAE	treatment emergent adverse event
TILs	tumor-infiltrating lymphocytes
Tislelizumab	BGB-A317
TLS	Tumor Lysis Syndrome
T_{max}	time to reach maximum plasma concentration
TNBC	triple negative breast cancer

TSH	thyroid-stimulating hormone
UK	United Kingdom
ULN	upper limit of normal
US	United States
V_d	volume of distribution
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary Enhanced
β-HCG	β-subunit of human chorionic gonadotropin

2.0 INTRODUCTION

2.1 Background and Pharmacology

The immune check point-inhibitory receptor, programmed cell death-1 (PD-1) is mainly expressed in activated T-cells including cluster of differentiation (CD)8+ cytotoxic T-lymphocytes and CD4+ T-helper lymphocytes. [1] It is believed that PD-1 plays an important role in immune modulation of tumor progression by regulating the key inhibitory signaling in the T-cells when engaged by its ligands. The PD-1 signaling cascade negatively regulates T-cell receptor (TCR) and attenuates T-cell proliferation and functional activities, leading to T-cell exhaustion. PD-1 expression is markedly up-regulated in tumor-infiltrating lymphocytes (TILs), while the expression of PD-1 ligand (PD-L1) is significantly increased in tumor cells and tumor-associated immune cells in the presence of stimulating cytokines such as interferon gamma (IFN-γ) and interferon alpha (IFN-α) in the tumor microenvironment. [2] Furthermore, the increased PD-1 expression in TILs and/or PD-L1 expression in tumor and tumor-associated stromal cells is observed in many types of solid human tumors including, but not limited to, melanoma, squamous cell carcinoma (SCC), uveal melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), triple negative breast cancer (TNBC), renal cell carcinoma (RCC), bladder cancer, ovarian cancer, and prostate cancer. [3-11] These findings provide the basis for cancer immunotherapeutic intervention via the approach of antagonizing PD-1.

Recent clinical trials utilizing anti-PD-1 monoclonal antibodies demonstrated significant therapeutic efficacy in advanced melanoma, refractory NSCLC, and RCC. Nivolumab (OPDIVO) has 7 Food and Drug Administration (FDA) approved indications: unresectable or metastatic melanoma, metastatic NSCLC, RCC, classical Hodgkin lymphoma, and SCC of the head and neck, and advanced urothelial cancer. Pembrolizumab (KEYTRUDA) has 4 FDA-approved indications: unresectable or metastatic melanoma, metastatic NSCLC, recurrent or metastatic HNSCC, and refractory classical Hodgkin lymphoma in both pediatric and adults. Atezolizumab (TECENTRIQ) has 2 FDA-approved indications: advanced urothelial cancer and metastatic NSCLC.

2.1.1 Tislelizumab

Tislelizumab is a humanized IgG4-variant monoclonal antibody against PD-1. Tislelizumab has been manufactured under Good Manufacturing Practice (GMP) quality control systems. The clinical trial drug product is formulated in an aqueous buffer with pH 6.5 and isotonic osmolality. The suggested administration route is intravenous (IV) infusion after the appropriate dilution in 0.9% sodium chloride solution.

Tislelizumab binds to the extracellular domain of human PD-1 with high specificity and affinity (K_D = 0.15 nM) as demonstrated by the receptor-binding assays based on surface

plasmon resonance (SPR). It competitively blocks the binding of both PD-L1 and PD-L2, inhibiting PD-1-mediated negative signaling in T-cells. In *in vitro* cell-based assays, the humanized antibody consistently and dose-dependently enhances the functional activity of human T-cells and pre-activated, primary PBMCs (peripheral blood mononuclear cells). In addition, tislelizumab demonstrated anti-tumor activity in several human cancer allogeneic xenograft models, including A431 human epidermoid carcinoma, BCCO-028 colon cancer, and BCLU-054 NSCLC models, where the PBMCs were co-injected with the human cancer cells (A431) or the tumor fragments (BCCO-028 and BCLU-054) into the immunocompromised mice.

The IgG4-variant antibody has very low binding affinity to Fcγ RIIIA and C1q by *in vitro* assays, suggesting a low or no antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity (CDC) effect in humans. Unlike the natural IgG4 antibody, tislelizumab has no observable Fab-Arm Exchange activity by the *in vitro* assay, predicting the antibody would be stable *in vivo*, unlikely forming a bispecific antibody.

Refer to the Investigator's Brochure (IB) for more detailed information on the background of tislelizumab. [12]

2.1.2 Pamiparib

Poly (ADP-ribose) polymerase (PARP) proteins are involved in deoxyribonucleic acid (DNA) replication, transcriptional regulation, and DNA damage repair. DNA-bound PARP1/2 catalyzes the synthesis of poly (ADP-ribose) (PAR) onto a range of DNA-associated proteins that mediate DNA repair. PARP1 also undergoes auto-PARylation, a molecular change that ultimately leads to its release from DNA. Inhibition of PARP converts common single-strand DNA breaks (SSBs) into double-strand breaks during DNA replication. Small-molecule inhibitors of PARP1/2 represent a class of anticancer agents that exert their cytotoxic effects by interfering with DNA repair mechanisms. Since the discovery of synthetic lethality of PARP inhibitors in *BRCA*-deficient cells and, more broadly, cells with homologous recombination deficiency (HRD), accumulation of unrepaired SSBs resulting from catalytic PARP inhibition has been considered central to the mechanism of action of PARP inhibitors. More recently, it has been demonstrated that PARP inhibitors also trap PARP1- and PARP2-DNA complexes at DNA damage sites and that PARP trapping can be more cytotoxic than unrepaired SSBs.

Recent data supports the evaluation of PARP inhibitors in solid tumors carrying mutations in *BRCA1* and *BRCA2*. Mutations of *BRCA1* and *BRCA2*, two tumor suppressor genes, predispose cells to increased risk of malignancies, particularly breast and ovarian cancer. Mutations in *BRCA1* and *BRCA2* were identified in up to 10% of pancreas adenocarcinoma patients with a higher incidence in those who had a family history. [13, 14] Recent sequencing data indicates

that approximately 20% of mCRPC have homologous recombination (HR) defects due to germline and /or somatic loss of function in key HR genes including *BRCA2*, *ATM*, *CHEK2*, *NSBP1*, and *FANCJ*, that could potentially confer a '*BRCA*-like' phenotype and susceptibility to PARP inhibition via synthetic lethality. [15-18]

In the clinic, PARP inhibitors (olaparib, rucaparib, niraparib, and talazoparib) have demonstrated sustained anti-tumor responses as a single agent in patients with *BRCA1*- or *BRCA2*-mutant tumors, with an acceptable safety profile.

Pamiparib is a potent and selective inhibitor of PARP1 and PARP2. Single agent pamiparib demonstrated excellent *in vivo* anti-tumor activity, 16-fold more potent than olaparib, in MDA-MB-436 breast cancer (*BRCA1* mutation) xenograft model. In pharmacokinetic/pharmacodynamic study, oral administration of pamiparib resulted in time-dependent and dose-dependent inhibition of PARylation in MDA-MB-436 breast cancer xenografts in mice. Inhibition of PARylation in the tumor tissues correlated well with tumor drug concentrations of pamiparib.

In combination studies, pamiparib and paclitaxel in combination showed better anti-tumor activity than either single agent in primary gastric cancer model. In primary SCLC model, pamiparib significantly enhanced the anti-tumor activity of chemotherapy (etoposide plus carboplatin) during the concomitant treatment stage, and kept animals tumor-free throughout the maintenance treatment.

Refer to the IB for more detailed information on the background of pamiparib. [19]

2.1.3 Tislelizumab and Pamiparib combination

This study will investigate the safety, PK, and anti-tumor activity of the combination tislelizumab and pamiparib in patients with tumors likely to harbor DNA damage repair deficiencies and which have already shown responsiveness to checkpoint inhibition. This trial will evaluate the hypothesis that pamiparib treatment in these susceptible tumors may lead to the release of neo-antigens and increase the antigenicity of tumors, which may boost the efficacy of tislelizumab.

There are several reports describing a direct link between DNA damage and immune response. [20, 21] The DNA damage response alerts the innate immune system by inducing the expression of ligands for activating the immune receptor NKG2D. NKG2D plays an important role in the natural killer (NK) and T-cell-mediated immune response to tumors. [22] In addition, the specific killing of *BRCA* mutant or HRD tumor cells by PARP inhibitors can lead to release of neo-antigen and immune activation against the tumor, as demonstrated in preclinical experiments in both ovarian and breast cancers, supporting investigating the combination of a PARP inhibitor and a PD-1 inhibitor.

An *in vitro* study on murine epithelial ovarian cancer cell line reported that administration of modest amounts of talazoparib, a potent PARP-1 inhibitor belonging to the same class as pamiparib, significantly improved the survival of mice bearing subcutaneous or intraperitoneal tumors. [23] Talazoparib was found to have significantly increased the number of peritoneal CD8+ T cells and natural killer (NK) cells, as well as their production of IFN-γ and tumor necrosis factor alpha (TNF-α). The cell stress caused by talazoparib induced not only cancer cell-intrinsic apoptosis but also cancer cell-extrinsic anti-tumor immune effects in a syngeneic murine model of ovarian cancer. [23] These changes may enhance the anti-tumor immune response and lead to synergy of antitumor activity between a PARP inhibitor and anti-PD-1 antibodies.

Homologous recombination deficient high grade serous ovarian cancers, including *BRCA1/2*-mutated tumors, exhibit higher neo-antigen load compared to HR proficient tumors. In the Cancer Genome Atlas (TCGA) dataset, *BRCA1/2*-mutated tumors were associated with a higher ratio of CD8+/CD4+ in tumor-infiltrating lymphocytes (TILs), higher peri-tumoral T-cells, and increased PD-L1 expression. [24] These characteristics have been associated with better responses to anti-PD-1/PD-L1 immune checkpoint inhibitors. Furthermore, a recent study using breast cancer cell lines, xenograft and syngeneic tumors provided evidence for cross talk between PARP inhibition and tumor-associated immunosuppression. PARP inhibition upregulates tumor cell PD-L1 expression, which attenuates PARPi efficacy via PD-1/PD-L1 signaling associated immunosuppression. [25] The blockade of PD-L1 can restore the attenuated anti-tumor immunity and potentiate PARPi in tumor suppression. The efficacy of PD-1 pathway blockade correlates with DNA repair pathway mutations and neo-antigen burden. [26] In conclusion, platinum-sensitive tumors that are known to respond to PARP inhibitors are likely to show enhanced sensitivity to the combination of PARP inhibitor and anti-PD-1 therapy.

Clinical trials investigating the safety and efficacy of a PARP inhibitor in combination with a PD-1 or a PD-L1 inhibitor are ongoing (ClinicalTrials.gov Identifiers: NCT02657889; NCT02849496; NCT02734004; NCT02484404). Results from a Phase 1 study of durvalumab combined with olaparib are available (ClinicalTrials.gov Identifier: NCT02484404). [27] Grade 3 or higher adverse events were reported as lymphopenia in 2 of 12 treated patients and anemia in one patient. The recommended Phase 2 dose (RP2D) in this study was determined to be olaparib 300 mg twice daily with 1500 mg durvalumab IV every 28 days. The preliminary data from the BGB-A317/BGB-290_Study_001 and the data published by Lee, et al suggest that the checkpoint inhibitor + PARP inhibitor combination has an acceptable toxicity profile. [27]

The selection of disease-specific cohorts in Phase 1B is based on pathologic subtypes that may be associated with endogenous loss of DNA damage repair or exogenous DNA damage.

Endogenous mutational damage and exogenous DNA damage may limit cancer cells' capacity to carry out DNA repair making cancer cells susceptible to PARP inhibition. Moreover, high somatic nonsynonymous mutation burden has been associated with clinical efficacy of PD-1 inhibition. [28] The combination of pamiparib and tislelizumab may exploit the potential accumulation of DNA damage from PARP inhibition, which in turn may increase infiltration of immune cells into the tumor microenvironment, thereby increasing cancer cell killing. Section 2.5.2 describes each pathology in detail.

2.2 Overview of Clinical Pharmacology

2.2.1 Tislelizumab

The first-in-human study BGB-A317_001 is a 2-part study: Part A is a dose escalation evaluation and Part 2 is a schedule expansion evaluation. One hundred and three patients received at least one dose of tislelizumab in the Phase 1A part of the study, ranging from 0.5 mg/kg to 10 mg/kg Q2W (n = 62) and from 2 mg/kg to 5 mg/kg Q3W (n = 41). The maximum tolerated dose (MTD) was not reached and 10 mg/kg Q2W was the maximum administered dose (MAD). The RP2D was determined to 200 mg IV Q3W for the Phase 1B (indication expansion) study.

An interim PK analysis (with a cutoff date of 08 October 2016) was conducted by non-compartmental analysis methods, using serum concentrations from patients who received doses of 0.5, 2, 5 and 10 mg/kg Q2W and patients who received doses of 2 and 5 mg/kg Q3W (Phase 1a Part 1 and Part 2). The maximum observed plasma concentration (C_{max}) and the drug exposure (the area under the concentration-time curve [AUC]) increased in a nearly dose-proportional manner from 0.5 mg/kg to 10 mg /kg, both after single-dose administration and at steady state. Population PK analysis was conducted with a 2-compartment model with first order elimination. Systemic clearance of tislelizumab was 0.00794 L/h, volume of distribution in the central and peripheral compartment were 2.75 and 1.65 L, respectively, and terminal elimination half-life was approximately 17 days. Clear drug accumulation was observed after multiple doses

Refer to the IB for more detailed information on the background of tislelizumab. [12]

2.2.2 Pamiparib

By 08 April 2016, the dose escalation phase of the BGB-290-AU-002 study had completed. Doses at 2.5, 5, 10, 20, 40, 60, 80 and 120 mg twice daily have been evaluated in 45 patients. The MTD and RP2D were determined to be 80 mg twice daily and 60 mg twice daily, respectively. In the Phase 1 study, interim PK data of pamiparib showed that pamiparib is rapidly absorbed and eliminated after oral administration. The C_{max} and the drug exposure (AUC) increased in a nearly dose-proportional manner from 2.5 mg twice daily to 120 mg

twice daily both after the single dose administration and at the steady state. The terminal half-life was determined to be approximately 13 hours, with a range of 5.5 to 34 hours. At the steady state, from 2.5 mg twice daily to 120 mg twice daily, drug exposure was increased in dose-dependent manner. At 80 mg twice daily (MTD), mean steady state $AUC_{0\text{-}24h}$ was 78,348 ng/ml*h and mean C_{max} was 4,881 ng/ml. Refer to the IB for more detailed information on the background of pamiparib. [19]

2.3 Overview of Safety and Efficacy

2.3.1 BGB-A317 Study-001

2.3.1.1 Study BGB-A317_Study_001 Phase 1a

As of 13 January 2017, 111 patients with solid tumors have been treated with tislelizumab in Study BGB-A317_Study_001 for Parts 1, 2, and 3 combined. Patients had received tislelizumab treatment in Phase 1a at dose regimens including: 0.5 mg/kg, 2 mg/kg, 5 mg/kg, or 10 mg/kg Q2W; 2 mg/kg or 5 mg/kg Q3W; and 200 mg Q3W. The median duration of treatment for the combined patient population was 85 days (range: 1 to 471).

As of 13 January 2017, an MTD has not been determined. The RP2D was established as fixed dose of 200 mg IV Q3W.

The fixed dose of 200 mg was selected on the basis of both nonclinical studies and available clinical data. Simulations do not suggest any clinically meaningful differences in exposure following fixed dose or dose adjusted for weight. On the basis of this analysis, a fixed dose of 200 mg was selected (equivalent to a body weight−based dose of 3.3 mg/kg, calculated with 60 kg). Selection of an every-21-day dosing interval is both supported by this preliminary pharmacokinetics evaluation and allows for a convenient integration with common chemotherapeutic regimens. All available PK, safety, and efficacy data for tislelizumab will continue to be evaluated to support the 200 mg fixed dose.

Of the 111 patients in the Safety Analysis set for Phase 1a of Study BGB-A317_Study_001, 110 (99%) experienced at least 1 treatment emergent adverse event (TEAE). The most commonly occurring TEAEs for patients treated with the tislelizumab monotherapy in Study BGB-A317_Study _001 were fatigue (42%), nausea (31%), diarrhoea (24%), abdominal pain (21%), constipation (21%), back pain (18%), and decreased appetite (18%). TEAEs assessed as ≥ Grade 3 were experienced in 45 patients (41%). Grade 3 or higher TEAEs occurring in more than 3 patients included abdominal pain (6 patients, 5%), anaemia (5 patients, 5%), back pain (4 patients, 4%) and fatigue (4 patients, 4%).

Treatment-emergent AEs assessed as related to tislelizumab by the Investigator occurred in 72% of patients across all parts of Phase 1a. Adverse events that occurred in at least 10% of patients assessed as related to tislelizumab included fatigue (23%), pruritus (13%), diarrhoea

(13%), rash (12%), and nausea (10%). Twelve patients (11%) had at least 1 TEAE assessed as related to tislelizumab that were ≥ Grade 3 in severity. These included colitis (n = 1), autoimmune pancreatitis (n = 1), fatigue (n = 2), back pain (n = 1), alanine aminotransferase increased (n = 1), diabetes mellitus (n = 1), diabetic ketoacidosis (n = 2), hyperglycemia (n = 1), pneumonitis (n = 1), hypotension (n = 2). Some patients experienced more than one ≥ Grade 3 TEAE that was considered related to tislelizumab.

Forty-six patients (41%) had a treatment-emergent serious AE (TESAE). The most frequently occurring TESAEs included abdominal pain (5 patients, 5%), colitis (4 patients, 4%), and ascites, dyspnea, pneumothorax, and pulmonary embolism (3 patients each, 3%).

In the overall safety population available for analysis, 14 patients (13%) experienced a TEAE that led to treatment discontinuation. The most frequently occurring TEAEs leading to treatment discontinuation included dyspnoea (2%), pneumonitis (2%), and anaemia (2%). All other TEAEs that led to treatment discontinuation occurred in single patients. Of these TEAEs that led to treatment discontinuation, 8 (7%) were Grade 3 or greater in severity. The only TEAE leading to treatment discontinuation ≥ Grade 3 in severity that occurred in more than 1 patient was dyspnoea (2 patients, 2%).

In the overall safety population, 22 patients (20%) experienced a treatment-emergent immune-related adverse event (irAE). The most frequently occurring irAEs included colitis (4 patients, 4%), diarrhoea (3 patients, 3%), hypothyroidism (3 patients, 3%), and diabetes mellitus, diabetic ketoacidosis, and pneumonitis (2 patients each, 2%). All other irAEs occurred in single patients.

Five patients (5%) experienced a Grade 3 or Grade 4 irAE. These events included colitis (n = 1), diarrhea (n = 1), diabetes mellitus (n = 1), diabetic ketoacidosis (n = 2), pneumonitis (n = 1), autoimmune pancreatitis (n = 1), type 1 diabetes mellitus (n = 1). These toxicities are similar to those reported for other checkpoint inhibitors targeting PD-1 or PD-L1.

As of 13 January 2017, there were 3 patients had a TEAE with a fatal outcome. The associated PTs for these events were fatigue, multi-organ failure, and dyspnoea. None of the TEAEs with a fatal outcome were considered related to tislelizumab treatment.

Of the 111 patients enrolled to the Phase 1a study, 14 patients (13%) achieved a partial response and 21 patients had a best response of stable disease.

2.3.1.2 Study BGB-A317_Study_001 Phase 1b

As of 13 January 2017, 189 patients with solid tumors had received tislelizumab treatment in Phase 1b across 9 expansion cohorts in Study BGB-A317_Study_001. The median duration of treatment for the combined patient population was 64 days (range: 1 to 235). The most commonly occurring TEAEs were fatigue (22%), nausea (18%), decreased appetite (14%),

vomiting (14%), diarrhoea (13%), and constipation (12%). Grade 3 or higher TEAEs occurring in more than 3 patients included vomiting (n = 5), pneumonia (n = 5) anaemia (n = 4), and ascites (n = 4).

Treatment-emergent AEs assessed as related to tislelizumab reported ≥ 5% of patients included fatigue (9%), rash (5%), nausea (5%), and diarrhoea (5%). Eleven patients experienced ≥ Grade 3 TEAEs related to tislelizumab. These events included nausea (n = 1), diarrhea (n = 2), colitis (n = 2), stomatitis (n = 1), fatigue (n = 1), mucosal inflammation (n = 1), pneumonitis (n = 3), and hyperthyroidism (n = 1). Some patients experienced more than one ≥ Grade 3 TEAE considered related to tislelizumab.

Twenty patients (11%) experienced a TEAE that led to treatment discontinuation; Grade 3 or higher TEAE were reported in 18 of these 20 patients. TEAEs leading to treatment discontinuation reported in at least 2 patients included pneumonitis (n = 3) and vomiting (n = 2). All other TEAEs that led to treatment discontinuation occurred in single patients.

Nineteen patients (10%) experienced an irAE. The most frequently occurring irAEs included pneumonitis (n = 4); aspartate aminotransferase increased, hyperthyroidism, and rash (3 patients each); and colitis, dermatitis, diarrhoea, and hypothyroidism (2 patients each). All other irAEs occurred in single patients. Eight of these 19 patients experienced a ≥ Grade 3 irAE.

Preliminary efficacy results indicate 6 patients achieved confirmed partial response to tislelizumab monotherapy and 55 patients had stable disease.

2.3.2 Pamiparib

Pamiparib as a monotherapy is being evaluated in two Phase 1a studies (BGB-290-AU-002 in Australia, n = 53 [as of 30 September 2016] and BGB-290-102 in China, n = 8 [as of 13 March 2017]. The study data from BGB-290-AU-002 is the most mature and key interim results are summarized below.

2.3.2.1 Clinical Safety and Preliminary Efficacy for BGB-290-AU-002

BGB-290-AU-002 is a first-in-human trial evaluating pamiparib to characterize the safety, the MTD, preliminary anti-tumor activity and the PK of pamiparib given as a monotherapy in a 3+3 dose escalation scheme. Pamiparib was administered in doses ranging from 2.5 mg orally twice daily up to 120 mg orally twice daily.

The study is being conducted in 5 Australian study centers, and preliminary data for 45 patients of Part 1A are available (cut-off date of 30 September 2016).

The median age of enrolled patients was 58 years (range 37 to 74 years), 82% were female (n = 37) and 84% white (n = 38). The baseline Eastern Cooperative Oncology Group (ECOG)

performance status score, available for 45 patients, was 0 for 16 patients, 1 for 28 patients, and 2 for one patient. The median of prior systemic anticancer therapies was 3 (range 1 to 9). Most common cancer types were gynecologic cancer (n = 28; ovarian, fallopian tube, or primary peritoneal), followed by breast cancer (n = 4), lung cancer (n = 4 [n = 3 small cell, n = 1 non-small cell]), prostate cancer (n = 2) and one each of adenocarcinoma (not otherwise specified), leiomyosarcoma, gastroesophageal junction cancer, and uterine cancer. The disease under study was not available for 4 patients.

The pharmacokinetic profile of pamiparib indicates linear PK parameters with a half-life of 13 hours. A dose-dependent trend in PAR inhibition in PBMCs was seen from 2.5 mg to 10 mg twice daily, and was sustained at steady state at doses ≥ 10 mg twice daily.

The preliminary safety data indicates the most frequent AEs (≥ 10% of patients) assessed as related to pamiparib were nausea (51%, n = 23), fatigue (29%, n = 13), vomiting (18%, n = 8), diarrhea (16%, n = 7), and decreased appetite (11%, n = 5). Twenty-six patients experienced Grade 3 AEs (regardless of relatedness), and no Grade 4 AEs were reported. Eleven Grade 3 AEs in 9 patients (20%) were considered related to pamiparib: anemia (11%, n = 5), neutropenia (7%, n = 3), hypophosphatemia (2%, n = 1), paresthesia (2%, n = 1), nausea (2%, n = 1) and fatigue (2%, n = 1).

Hematologic AEs are of interest in this study. The most frequent hematologic AEs (≥ 10% of patients) assessed as related to pamiparib were anemia (22%, n = 10) and neutropenia (11%, n = 5). Hematologic AEs, regardless of relatedness, were reported in 40% of patients (n = 18). Anemia was most frequent (33%, n = 15), followed by neutropenia (11%, n = 5) and thrombocytopenia (2%, n = 1).

Serious AEs were reported in 25 patients, and for 3 patients they were considered related to pamiparib: anemia (n = 2) and nausea (n = 1). Three patients discontinued study drug because of an AE: vomiting (n = 1), oral paresthesia (n = 1), and right neck cutaneous metastases (n = 1).

Four patients experienced fatal AEs ≤ 28 days after the last pamiparib dose. All deaths were due to complications of the underlying malignancy, and none were considered related to pamiparib.

Four patients experienced AEs that were considered DLTs: experienced Grade 2 nausea that persisted despite optimal standard medical therapy in 2 patients; Grade 2 anorexia and Grade 2 nausea in one patient, and Grade 2 nausea and Grade 2 paresthesia in one patient. Based on the encountered DLTs and the overall safety profile of pamiparib, the maximum tolerated dose of pamiparib was determined to be 80 mg orally twice daily (160 mg/day). The pamiparib dose for further investigation in this study was determined to be 60 mg orally twice daily.

Myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) are recognized adverse events in patients receiving PARP inhibitors. [29] To date, no cases of either MDS or AML have been observed in any study that includes pamiparib.

Ten patients achieved either a complete (n = 2) or partial (n = 8) response; all responses were observed in patients with gynecological cancers in this ongoing study.

2.3.2.2 Clinical Update of BGB-A317/BGB-290_Study_001

As of 05 February 2018, a total of 49 patients were treated in five dose level (DL), as detailed below:

- DL 1: tislelizumab 2 mg/kg IV Q3W + pamiparib 20 mg orally twice daily (n = 12)
- DL 2: tislelizumab 2 mg/kg IV Q3W + pamiparib 40 mg orally twice daily (n = 12)
- DL 3: tislelizumab 2 mg/kg IV Q3W + pamiparib 60 mg orally twice daily (n = 6)
- DL 4: tislelizumab 200 mg IV Q3W + pamiparib 40 mg orally twice daily (n = 7)
- DL 5: tislelizumab 200 mg IV Q3W + pamiparib 60 mg orally twice daily (n = 4)

Patients enrolled in the study have a variety of solid tumors, including ovarian (n = 20), fallopian tube (n = 4), pancreatic (n = 3), prostate (n = 3), fallopian tube and ovarian (n = 1), breast (n = 2), bile duct (n = 1), bladder (n = 1), cervical (n = 1), lung (n = 1), peripheral nerve sheath tumor (n = 1), peritoneal (n = 1) and uterine cancer (n = 1).

Twenty-four patients discontinued one or both study drugs. Among these 24 patients, 20 patients discontinued the treatment due to either radiographic or clinical disease progression. Four patients discontinued tislelizumab due to treatment related adverse events: autoimmune hepatitis or elevated liver function tests (n = 3) and immune-related hypophysitis (n = 1). Of note, DLTs were defined only for the first cycle and, as these events occurred after the first cycle, they were not considered DLTs.

2.3.2.3 Overview of Safety

The most commonly reported (> 10 % of the patients) treatment emergent adverse events regardless of the relationship were nausea (61%), fatigue (43.9%), vomiting (29.3%), diarrhea (26.8%), anemia (19.5%), headache (19.5%), constipation (17.1%), pyrexia (14.6%), urinary tract infection (14.6%), alanine aminotransferase increased (12.2%), aspartate aminotransferase increased (12.2%), back pain (12.2%), cough (12.2%), gastro-oesophageal reflux disease (12.2%). Treatment emergent adverse events regardless of the relationship that were Grade ≥ 3 and reported in > 5% patients were anemia (7.3%), and gamma-glutamyl transferase increased (7.3%).

The most commonly reported (> 10% of the patients) treatment emergent adverse event that was considered related to both pamiparib and tislelizumab was fatigue (31.7%: 26.8% as Grade 1, and 2.4% each for Grade 2 and Grade 3), and nausea (12.2%: 9.8% as Grade 1 and 2.4% as Grade 2).

One dose limiting toxicity of Grade 2 persistent nausea was reported in a patient treated in DL 4. Pamiparib was dose reduced to 20 mg twice daily and the patient continued combination treatment until radiographic disease progression approximately 4 weeks later.

After the data extraction, 2 additional dose-limiting toxicities were reported in DL 5. Dose-limiting toxicities in DL 5 were Grade 2 persistent nausea and Grade 4 auto-immune hepatitis. Study treatment was discontinued in both patients.

Pamiparib 60 mg twice daily/tislelizumab 200 mg Q3W was considered to be over MTD in this combination regimen. Dose Level 4, pamiparib 40 mg twice daily/tislelizumab 200 mg Q3W, is being further expanded.

Immune-related adverse events were reported in 10 patients (24.4%). Events that were reported in 2 or more patients were elevated ALT (one each for Grade 1 and Grade 3), elevated AST (one each for Grade 1 and Grade 2), autoimmune hepatitis (one each for Grade 3 and Grade 4), elevated GGT (one each for Grade 2 and Grade 3), and hypothyroidism (two for Grade 1 and one for Grade 2). Immune-related adverse events that lead to tislelizumab discontinuation occurred in 5 patients: Grade 4 autoimmune hepatitis (n = 1), Grade 3 autoimmune hepatitis (n = 1), Grade 2 elevated AST and ALT (n = 1), Grade 3 hypophysitis (n = 1) and Grade 3 hepatitis (n = 1).

As of 10 April 2017, 12 of 43 patients treated with the combination of tislelizumab and pamiparib experienced increases in liver function tests that were reported as adverse events of either elevated AST, ALT, hepatitis or auto-immune hepatitis. These events were clinically asymptomatic, and were characterized by a proportionally higher increase in alanine aminotransferase (ALT) compared to aspartate aminotransferase (AST). No significant changes in bilirubin were observed. These hepatic adverse events were observed in all dosing cohorts. The median time to onset was 49 days (range 18 to 202 days). The severity of these events was Grade 1 (n = 1), Grade 2 (n = 5), Grade 3 (n = 4), and Grade 4 (n = 2). Two patients (one Grade 1 event, one Grade 2 event) did not receive corticosteroid treatment and continued study treatment with both agents without consequence. For the remaining 10 patients, tislelizumab was discontinued or held. Three of these 10 patients had objective evidence of disease progression at the same time of the hepatic adverse events. Progressive disease did not seem to correlate with elevated liver function tests, and was not consistently associated with new liver metastases nor increases in existing liver metastases. tislelizumab was discontinued in 6 out of the 12 patients for hepatic adverse events and is being held in one patient. Pamiparib

treatment was continued in 3 patients, and permanently discontinued in 5 patients for progressive disease (n = 3) or the hepatic adverse event (n = 2). Four patients were re-challenged with pamiparib (one patient was re-challenged twice) following corticosteroid treatment and all 4 patients experienced liver function tests (LFT) increases with reinstatement of pamiparib. Of these 4 patients, 2 discontinued treatment, and 2 were able to continue pamiparib after additional corticosteroid treatment at the same or a reduced dose of pamiparib.

Fourteen patients had at least one SAE reported, only auto-immune hepatitis and hypophysitis (one event each and as above) were considered related to treatment.

There were 5 patients who died within 30 days of the last dose of study drug administration, all of which were associated with disease progression.

2.3.2.4 Preliminary Anti-tumor activity

Preliminary anti-tumor data suggests that the combination of pamiparib +tislelizumab results in tumor shrinkage. One complete response was reported in a patient with ovarian cancer; 7 patients achieved a partial response (ovarian cancer n = 5; pancreatic cancer n = 1; uterine cancer n = 1).

2.4 Benefit-Risk Assessment

Tislelizumab and pamiparib are the investigational products with safety data gathered from non-clinical and Phase 1 clinical studies, as described above. The emerging data supports an acceptable safety profile of each agent given as monotherapy. The preliminary safety data generated in the dose-escalation portion of this ongoing study indicates that the pamiparib + tislelizumab can be co-administered in the doses tested.

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been reported in a small number (< 1%) of patients treated with PARP inhibitors, especially in patients harboring a germline *BRCA* mutation. [29] Patients who develop MDS and AML while on PARPi therapy typically had a history of extensive previous chemotherapy which is a recognized risk for MDS and AML. Patients in this study will be monitored monthly for hematological toxicities and reports of MDS and AML will be reported as serious adverse events (SAEs).

Preliminary Phase 1 study data with durvalumab (MEDI4736) given concurrently with olaparib supports the tolerability of a PARP + PD-L1 combination similar the treatment being investigated in this study. [27] Patients enrolled in clinical studies using the tislelizumab and pamiparib combination will continue to be closely monitored by means of reporting AEs, recording vital signs and electrocardiograms (ECGs), and conducting clinical laboratory safety tests of blood and urine with particular attention paid to the safety profile of what is currently

known about both of these compounds as well as what is known about the therapeutic classes of both checkpoint and PARP inhibitors.

2.5 Study Rationale

This is a 2-staged, Phase 1/1b study consisting of two parts, to evaluate the combined use of tislelizumab and pamiparib. Part A of this study will evaluate safety and tolerability to determine the MTD and RP2D for the combination as well as whether the administration of pamiparib given for 7 days prior to the initiation of tislelizumab as a means to upregulate neo-antigen and PD-L1 production will be both tolerable and associated with anti-tumor activity. The PK profile, possibility of any potential drug-drug interaction (DDI), preliminary anti-tumor activity of the combination, as well as host immunogenicity to tislelizumab will also be studied. Part B of this study will further evaluate the anti-tumor activity of the combination, its safety and PK profile, as well as host immunogenicity to tislelizumab. Preliminary biomarkers for efficacy will also be explored through both parts of the study.

The study population used for both Parts A and B of this study are patients with tumors likely to harbor DNA damage repair deficiencies susceptible to treatment with PARP inhibitor or in tumor types, which have already shown responsiveness to PD-1 blockade. It is postulated that pamiparib treatment in these susceptible tumors may lead to the release of neoantigens that could boost the efficacy of tislelizumab, as discussed in Section 2.1.3.

2.5.1 Rationale for Dose Selection

Tislelizumab and pamiparib have demonstrated an acceptable toxicology and safety pharmacology profile individually, in clinical and non-clinical experiments. In preclinical mouse MTD studies, the combination of pamiparib and an anti-mouse PD-1 antibody was very well-tolerated without any apparent toxicity compared to either single agent.

The starting dose of pamiparib was selected as 20 mg twice daily, 1/4 of the monotherapy MTD dose (80 mg twice daily) that has been deemed to be safe in the on-going Phase 1 dose-escalation study. For tislelizumab, 2 mg/kg Q3W was selected as starting dose based on the efficacy and PK profile, which is significantly lower than the MAD tested, 10 mg/kg Q2W, in the single agent dose-escalation study.

The dose of each agent tested in the Phase 1B portion of the study was based on the totality of the safety data generated in the dose-escalation portion of the trial. The dose of pamiparib chosen for the disease-specific expansion cohorts was based on the number of dose-limiting toxicities observed across the dosing cohorts. Two dose-limiting toxicities (Grade 2 nausea that could not be managed with standard anti-emetic treatments, and Grade 4 auto-immune hepatitis; occurring in one patient each) were reported in the Dose Level 5 cohort (pamiparib 60 mg orally twice daily + tislelizumab 200 mg IV Q3W). The fixed dose of tislelizumab

200 mg Q3W was selected on the basis of available clinical data as outlined in Section 2.3.1.1. Based on these findings, the Safety Monitoring Committee for this study recommended the pamiparib 40 mg orally twice daily + tislelizumab 200 mg IV Q3W dosing be implemented for the disease-specific expansion cohorts in Part B of the study.

2.5.2 Rationale for Disease-Specific Cohorts (Phase 1B)

2.5.2.1 Ovarian Cancer

There are data to indicate that HRD status predicts response to PARP inhibition in patients with high grade epithelial, non-mucinous ovarian, fallopian tube or primary peritoneal cancer (EOC), which includes but may not be restricted to patients with germline or somatic *BRCA1/2* mutations. Published data with FDA-approved PARP inhibitors, olaparib, rucaparib, and niraparib, support the efficacy of this approach to treat selected patients with HRD tumors.

The rationale to treat patients with EOC whose cancer tests negative for *BRCA1/2* mutation or those without HRD is based on data generated in the NOVA study, which evaluated niraparib vs placebo when given in the maintenance setting to patients with platinum-sensitive, recurrent ovarian cancer. [30] In this study of 553 enrolled patients, niraparib significantly improved the duration of progression-free survival over placebo in patients whose ovarian cancers tested positive for a germline *BRCA* mutation (median PFS 21 vs 5.5 months; HR 0.27; 95% CI 0.07-0.41), in those with HRD positive (median PFS 12.9 vs 3.8 months; HR 0.38; 95% CI 0.24-0.59) and in those with no germline *BRCA* mutation or HRD (median PFS 9.3 vs 3.9 months; HR 0.45; 95% CI 0.34-0.61).

There is a strong rationale to evaluate checkpoint inhibition in patients with ovarian cancer. First, high expression of PD-L1 in ovarian cancer is associated with lower 5-year survival rate (52.6%) relative to low PD-L1 expressing ovarian tumors (80.2%), suggesting that suppression of PD-1 pathway may be associated with clinical benefit. [4] Second, preclinical experiments in syngeneic ovarian cancer murine models show tumor regression with PD-1/PD-L1 blockade. [31] Third, there are several immune checkpoint inhibitors being evaluated in clinical trials in ovarian cancer, many of which have reported disease stability and tumor shrinkage in patients with recurrent epithelial ovarian cancer. [32] There are ongoing clinical trials, including three Phase 3 trials, that are evaluating immune checkpoint inhibitors across both platinum-sensitive and platinum-resistant epithelial ovarian cancer patients.

The current data with the ongoing Phase 1 clinical trial BGB-A317/BGB-290_Study_001 has generated preliminary data supporting both the safety and anti-tumor activity of this combination. There are other ongoing clinical trials in patients with recurrent ovarian cancer in which a PARP inhibitor will be combined with an immune checkpoint inhibitor. (ClinicalTrials.gov Identifiers: NCT02484404, NCT02485990, NCT02571725, and NCT02657889).

2.5.2.2 Breast Cancer

BRCA mutations in TNBC are predictive for response to platinum compounds, which has been demonstrated in both *in vitro* experiments and in clinical trials. [33, 34] The TNT trial [35] reported that in unselected patients with metastatic triple negative breast cancer, the response rates were similar with either carboplatin or docetaxel. However, patients with *BRCA1/2* mutations had a significantly higher response and a longer progression-free survival with carboplatin compared to docetaxel treatment. Additionally, a Phase 1 trial of olaparib combined with paclitaxel demonstrated clinical activity in patients with TNBC, but was complicated by higher than expected rates of neutropenia. [36]

BRCA mutation status is also predictive for response to PARP inhibitors in TNBC. [36-39] Evidence of clinical activity has been observed in all PARP inhibitors (olaparib, niraparib, veliparib, rucaparib, and talazoparib) in early phase clinical trials evidenced by overall response rates as high as 71% and clinical benefit rates as high as 86% in patients with TNBC testing positive for *BRCA1/2* mutation. Multiple clinical studies investigating PARP inhibitors in patients with *BRCA1/2* mutated breast cancer are on-going in both the adjuvant and metastatic treatment settings either as single agents or in combination with targeted agents or standard chemotherapy regimens. [40]

There are also preliminary data supporting the role of immune checkpoint inhibitors in TNBC. [41] TNBC has a high mutational frequency and an increased concentration of tumor-infiltrating lymphocytes, presence of CD8+ infiltrates, and high FOXP3 infiltrates, relative to other breast cancer subtypes, findings that support treatment with an immune-modulating agent. Two checkpoint inhibitors, pembrolizumab (ClinicalTrials.gov Identifier: NCT02447003) and atezolizumab (ClinicalTrials.gov Identifier: NCT01375842), have published data supporting the efficacy of such an approach in women with heavily pretreated metastatic TNBC, with overall response rates of 18.5% and 24%, respectively.

In summary, both PARP inhibitors and checkpoint inhibitors when given as monotherapies have demonstrated preliminary evidence of anti-tumor activity in patients with advanced TNBC, thereby supporting the evaluation of the combination of pamiparib with tislelizumab.

2.5.2.3 Metastatic Castration-Resistant Prostate Cancer

There is a strong rationale to target DNA repair deficiencies in patients with castration-resistant prostate cancer (CRPC). The prevalence of germline or somatic mutations in genes key to DNA damage repair pathways is approximately 19% in patients with CRPC, suggesting that there is a population of patients who could be identified for targeted therapy, such as PARP inhibitors. The recently reported TOPARP trial showed that the incidence of DNA repair defects in unselected patients with mCRPC was 32%. Intriguingly, the incidence of *BRCA2* and *ATM* mutations in this unselected cohort was 16% and the response rate in this subset that

was identified to have an underlying HR defect was more than 80% using a composite measure of response. [16] Others reported germline gene variants associated with increased risk of prostate cancer and underlying homologous recombination deficiency (HRD) include *BRCA1*, *MSH5*, *MUTYH*, *PMS2*, *RAD51B*, and *BRIP1*. [15, 17, 18, 42] Patients with germline *BRCA1/2* mutation carriers have a higher risk of nodal or distant metastases and poorer overall survival in prostate cancer than non-carriers. [43]

Furthermore, the results of clinical trials evaluating oral PARP inhibitors such as olaparib, niraparib and rucaparib in patients with CRPC demonstrate significant activity and support further development of agents targeting DNA repair pathways. [44]

Translational studies of T-cell infiltration in the prostate gland suggest a role for immunotherapy as a therapeutic strategy for prostate cancer. [45] Tumor tissue from men treated with anti-androgen therapy was evaluated for lymphocyte markers and cytokines. Anti-androgen therapy was associated with prominent T-cell infiltration in both epithelial tissue and at the tumor site, a finding that was hypothesized to be potentially synergistic with ipilimumab, a monoclonal antibody against CTLA-4. While early clinical trial results suggested promise with ipilimumab treatment for prostate cancer patients [46], a Phase 3 trial evaluating ipilimumab in men with CRPC who had failed docetaxel and were receiving bone-directed radiation therapy failed to demonstrate improvement in overall survival relative to a placebo control. [47]

PD-L1 expression both at the tumor cell membrane and in the cytoplasm has been associated with poor prognosis in men with prostate cancer and may be an independent prognostic indicator of biochemical recurrence. [48] It follows that treatment with an immune checkpoint inhibitor combined with PARP inhibition may have therapeutic value in men with mCRPC.

2.5.2.4 Small Cell Lung Cancer

Small cell lung cancer (SCLC) constitutes about 15% of newly diagnosed lung cancer cases and occurs predominantly in cigarette smokers. [49] SCLC is an aggressive disease treated most commonly with platinum-based chemotherapy. Approximately 50% of SCLC patients have brain metastases at the time of postmortem examination. Overall survival is typically < 12 months. [50]

SCLC is characterized by its high mutational load, including defects in DNA repair genes. [51, 52] Several lines of evidence support the evaluation of pamiparib in SCLC. First, PARP inhibition with pamiparib was shown to enhance DNA damaging effects of temozolomide in both sensitive and resistant SCLC cell lines. Second, pamiparib has demonstrated anti-tumor activity in several SCLC patient-derived xenograft (PDX) models when given with carboplatin/etoposide or as a maintenance treatment following the completion of

carboplatin/etoposide. Finally, preclinical data support pamiparib activity in intracranial models of central nervous system (CNS) metastases, a common metastatic site of SCLC.

Preliminary data from Phase 1 studies has demonstrated some efficacy of PARP inhibitors in SCLC patients. In a Phase 1 study, talazoparib was administered as a single agent in patients with previously treated advanced SCLC. [53] In this study, 10% of patients treated with talazoparib had a partial response and 25% had a clinical benefit (complete response, partial response and stable disease ≥ 16 weeks) with a median duration or response of 13.7 weeks (95% CI; 12.0, 15.3 weeks). The most common adverse events in this study were myelo-suppression, fatigue, nausea, and alopecia.

A Phase 1 study of velaparib administered in combination with standard doses of cisplatin and etiposide was conducted in treatment-naïve patients with extensive stage SCLC (n = 9). [54] The recommended phase 2 dose of velaparib was 100 mg. The preliminary efficacy in 7 evaluable patients were: 1 complete response (14.3%), 4 partial response (57.1%), and 2 had stable disease (28.6%). Grade 3-5 hematologic adverse events included neutropenia, leukopenia, lymphopenia, and thrombocytopenia.

The correlation of anti-tumor activity of immune checkpoint inhibitors with high mutational burden in solid tumors provides a rationale for investigating tislelizumab in extensive stage SCLC. The reported rates of PD-L1 expression on SCLC range between 27% to 72%. [55, 56] Early phase clinical trials with pembrolizumab and nivolumab have demonstrated anti-tumor activity with overall response rates ranging between 13% with nivolumab and 35% with pembrolizumab; confirmatory trials are ongoing (ClinicalTrials.gov Identifiers: NCT02359019, NCT02481830).

2.5.2.5 Gastric Cancer (existing cohort)

Genetic abnormalities in gastric cancer include alterations in the DNA damage response gene ATM. The loss of ATM has been demonstrated to be synthetically lethal with inhibition of PARP, supporting the use of platinum-based treatment as well as PARP inhibitors.

Studies showed that gastric cancer cell lines, particularly those with a low expression level of ATM protein, are sensitive to olaparib. [57, 58] A randomized double-blind placebo-controlled Phase 2 study was conducted in 124 patients with recurrent or metastatic gastric cancer treated with olaparib (100 mg twice daily) in combination with paclitaxel (80 mg/m^2 on days 1, 8, and 15 of every 28-day cycle) or placebo. [59] Results from this study showed the combination therapy significantly improved overall survival (OS) in both the overall population (median 13.1 vs 8.3 months) and in those whose tumors contained low levels of ATM protein. However, there was no difference in progression-free survival (PFS) in either the overall population or in those with ATM-low tumors.

A Phase 3 clinical study with paclitaxel with or without olaparib as a second line treatment recently reported results. [60] In this study, Asian patients with advanced, previously treated gastric cancer were treated with either paclitaxel or paclitaxel in combination with the PARP inhibitor olaparib. Eighteen percent of 535 patients randomized were ATM-deficient. Results of the study in the overall population demonstrated numerically higher overall survival for patients treated with olaparib plus paclitaxel (6.9 vs 8.8 months, HR 0.79, $p = 0.0262$). However due to a statistical correction made due to inclusion of a co-primary endpoint of the ATM deficient subgroup, this did not reach statistical significance (which would have required a p-value of < 0.025). In the ATM deficient subgroup, radiological response rates were significantly higher for patients treated with olaparib (37% vs 16%, $p = 0.03$), and a non-statistically significant trend towards improvement in overall survival was also noted (10 vs 12 months, HR 0.73, $p = 0.2458$). Combination therapy was well-tolerated, with no new safety signals demonstrated. A Phase 1 clinical study with veliparib is currently ongoing. [61]

Several preclinical and clinical studies support targeting the PD-1 pathway in gastric cancer. A comprehensive genomic characterization of gastric carcinoma identified a subset of gastric cancers that may have elevated PD-1/PD-L1 expression, which provides the rationale for treating patients with gastric cancer with immune checkpoint inhibitors. [62] The incidence of PD-L1 expression in gastric cancer samples is approximately 40%, but the clinical relevance of this finding is inconsistently reported. [63, 64] The rationale to evaluate immune checkpoint inhibitors in gastric cancer is, therefore, based on the recognized immune-modulatory mechanisms of action of these molecules. As such, multiple agents targeting the PD-1/L-1 system are currently in development for patients with gastro-esophageal cancer. Preliminary results of these trials support anti-tumor activity of these agents when given as monotherapy. [63, 65]

To date, the preliminary data combining pamiparib with tislelizumab supports the safety of the combination when given to patients with advanced solid tumors. Given the unmet medical need in advanced gastric cancer, exploring the efficacy of this combination has merit.

2.5.2.6 Urothelial (muscle-invasive bladder, ureter, urethra, renal pelvis) Cancer

The standard of care for patients who have muscle-invasive bladder cancer is platinum-based chemotherapy. [66] The median overall survival in patients with metastatic disease is approximately 9-15 months, an indication that more effective treatment is needed for this patient population.

Whole genome sequencing on bladder cell lines was performed as part of a TCGA collaboration to identify biologic and genomic profiles that may be predictive of platinum response in patients with bladder cancer. [67] In this experiment, alterations in the *BRCA* DNA repair pathway were identified in 44% of the cell lines tested, and in 32% of the tumors from

patients in the TCGA database. Another collaboration found a significant association between somatic mutations in DNA repair genes and improved clinical outcomes. [68] To date, there are no clinical trials of PARP inhibition in the bladder cancer population.

The recent data from the KEYNOTE-045 study (ClinicalTrials.gov Identifier: NCT02256436) demonstrates an improved survival in patients with metastatic urothelial cancer with pembrolizumab treatment. Other checkpoint inhibitors, atezolizumab and nivolumab, have demonstrated efficacy in advanced urothelial cancer and are FDA-approved for this indication. [69, 70] Administering pamiparib prior to tislelizumab in advanced urothelial cancer will evaluate if upregulating neoantigens with pamiparib will influence the response to checkpoint inhibition with tislelizumab. Eligible patients will be required to have disease considered to be responsive to platinum-based chemotherapy to increase the chance of responding to PARP inhibition.

2.5.2.7 Pancreatic Cancer

Whole genome analysis of pancreatic tumors estimate 10% to 12% of patients with pancreatic cancers have either germ-line or somatic mutations of *BRCA2*-, *BRCA1*- or *PALB2*. [71] There are an additional 12% to 13% of patients who are characterized with '*BRCA*ness' and who might be sensitive to PARP inhibition. Platinum-containing regimens or PARP inhibitors have been used in patients with pancreatic cancer with known *BRCA* mutations. [72, 73] Data from an open-label Phase 2 study of rucaparib supports the use of PARP inhibitors in patients with advanced *BRCA1/2* mutated pancreatic cancer. One complete and 2 partial responses were observed in the 19 patients enrolled. All responses were observed in patients who had received only one prior treatment for advanced pancreatic cancer. One retrospective report evaluating the clinical significance of *BRCA1/2* mutations in pancreatic cancer reported an improvement in overall survival in patients with Stage 3 or 4 pancreatic adenocarcinoma who received platinum–based treatment relative to historic reports. [74] This data supports the use of PARP inhibitors in patients with pancreatic cancer. Multiple trials with PARP inhibitors are ongoing with veliparib, talazoparib, neraparib, and olaparib.

Immune checkpoint inhibitors are currently being evaluated in early phase clinical trials in patients with pancreatic cancer in both the neo-adjuvant and palliative care settings. Historically, pancreatic cancer was considered a "non-immunogenic" tumor, with low PD-L1/PD-1 expression, low amounts of CD8+ T-cell infiltration and a low tumor mutation burden. These characteristics were thought to be indicators of a relative unresponsiveness to immune checkpoint inhibitors as well as the poor prognosis associated with this disease. Recently, an investigation using murine models and human tissue specimens detailed a mechanism to up-regulate PD-L1 in pancreatic cancer. MLL1, a human mixed lineage leukemia protein-1, was expressed in the majority (11 of 13) of the pancreatic tumor cell lines evaluated, and after binding to a promotor of the *CD274* gene, PD-L1 expression increased, as did the efficacy of anti-PD-1 monoclonal antibodies.

In summary, there is a scientific rationale to administer PARP inhibitors and immune checkpoint inhibitors in combination to patients with advanced pancreatic cancer.

3.0 STUDY OBJECTIVES

3.1 Part A (Dose Escalation)

3.1.1 Primary Objectives

- To assess the safety and tolerability of tislelizumab in combination with pamiparib
- To determine the MTD and RP2D for the combination

3.1.2 Secondary Objectives

- To characterize the PK of pamiparib and tislelizumab in combination
- To assess the preliminary anti-tumor activity of tislelizumab in combination with pamiparib
- To assess host immunogenicity to tislelizumab

3.1.3 Exploratory Objectives

- [redacted]
- [redacted]

3.2 Part B (Expansion Cohorts)

3.2.1 Primary Objectives

- To assess the preliminary anti-tumor activity of the combination of tislelizumab and pamiparib in patients with specific tumor types

3.2.2 Secondary Objectives

- To further assess the safety and tolerability of the combination
- To further characterize the PK of tislelizumab and pamiparib in combination
- To further assess host immunogenicity to tislelizumab

3.2.3 Exploratory Objectives

- [redacted]
- [redacted]

4.0 STUDY ENDPOINTS

4.1 Part A (Dose Escalation)

4.1.1 Primary Endpoints

- Safety and tolerability as assessed by the incidence and nature of AEs
- Incidence and nature of DLTs
- Determination of MTD of the combination of tislelizumab and pamiparib

4.1.2 Secondary Endpoints

- Pharmacokinetic parameters, including but not limited to C_{trough} of tislelizumab and C_{max}, T_{max} and C_{trough} of pamiparib
- Efficacy parameters including:
    - Objective response rate (ORR) is defined as a best overall response of complete response (CR) and partial response (PR)
    - Disease control rate (DCR) is defined as a best overall response of CR, PR and stable disease (SD)
    - Clinical benefit rate (CBR) is defined as a best overall response of CR, PR and SD lasting ≥ 24 weeks
    - Progression-free survival (PFS) is defined as the time from first dose of study medication to the first documented objective disease progression or death due to any cause, whichever occurs first
    - Overall survival (OS) is defined as the time from the date of first dose of study drug to death due to any cause
- Immunogenicity of tislelizumab

4.1.3 Exploratory Endpoints

- [redacted]

4.2 Part B (Expansion Cohorts)

4.2.1 Primary Endpoints

- Anti-tumor activity as determined by ORR, PFS, duration of response (DOR), DCR, CBR, and OS

4.2.2 Secondary Endpoints

- Safety and tolerability as assessed by the incidence and nature of AEs
- Pharmacokinetic parameters, including but not limited to C_{trough} of tislelizumab and pamiparib
- Immunogenicity of tislelizumab

4.2.3 Exploratory Endpoints

- [redacted]

5.0 INVESTIGATIONAL PLAN

5.1 Summary of Study Design

This is a 2-part Phase 1, open label, multiple dose, dose-escalation and expansion study to investigate the safety, pharmacokinetics and antitumor activity of the anti-PD-1 monoclonal antibody tislelizumab in combination with the PARP inhibitor pamiparib in patients with advanced solid tumors.

Part A consists of a dose-escalation and dose-finding component to establish the MTD and/or RP2D to evaluate the safety, PK, preliminary anti-tumor activity of tislelizumab and pamiparib combination and immunogenicity of tislelizumab. Part B will evaluate the safety and tolerability, PK and preliminary anti-tumor activity of tislelizumab 200 mg IV Q3W combined with pamiparib 40 mg orally twice daily (see Section 6.2 for instructions).

In Part A of the study in all DLs, tislelizumab will be given intravenously (IV) on Day 1 of each 21-day cycle, and pamiparib will be taken orally twice daily starting from Day 1.

Part A of the study will follow a 3+3 dose-escalation scheme at pre-defined DLs until MTD and/or RP2D is determined for the combination. Dose escalation continues until 2 patients experience DLT at a DL, ie, 2 in 3 to 6 treated patients. The DLT assessments will be evaluated during the first cycle consisting of the first 21 days of treatment. However, if during dose-escalation, a MTD cannot be established after the evaluation of all planned doses, eg, because further increase in dose does not result in significant increases in exposure, then a RP2D will be determined after the evaluation of available data on safety, PK, and efficacy data. The selection of the RP2D will be based on the safety and preliminary anti-tumor activity observed in Part A, and other complementary data and made at the SMC meeting at the time that the dose for Part B is decided.

After the first patient in the first DL receives Day 1 dose of the Cycle 1, subsequent patients will not be dosed until the first patient has been observed for at least 24 hours to exclude unexpected acute toxicity.

An SMC (see Section 8.4.1 for committee composition) will determine the DLs to be administered and dose regimen during dose escalation and at the SMC meetings. The decision will depend on the available data on safety, PK and preliminary anti-tumor activity. The SMC will also decide and select the RP2D.

Part B will be to further evaluate the PK, safety, and tolerability of the combination of tislelizumab and pamiparib and to assess the preliminary anti-tumor activity of the combination in patients in the arms of specific tumor types defined in Section 5.1.2. The number of patients planned in each arm is listed in Section 5.1.2.

Baseline tumor tissue is mandatory for biomarker analysis, either from archived tumor tissue or fresh tumor biopsies unless it has been previously discussed with the sponsor's medical monitor or its designee. Fresh blood samples at baseline for all patients with ovarian, fallopian tube, primary peritoneal, or breast cancer in Part A and all patients enrolled in Part B must be collected for evaluation of germline *BRCA* mutations and/or confirmation of prior *BRCA* results.

Patients will be monitored for safety, tolerability, anti-tislelizumab antibodies, and anti-tumor activity throughout the study from the day of first administration of study drugs up to 30 days after the last dose of pamiparib and 90 days following last dose of tislelizumab or initiation of new anticancer therapy, whichever occurs first. The exception are irAEs, which will be recorded up to 90 days after the last dose of tislelizumab, regardless of initiation of subsequent anticancer therapy.

Radiological assessment of tumor response should be performed approximately every 9 ± 1 weeks in the first year and approximately every 12 ± 1 weeks thereafter.

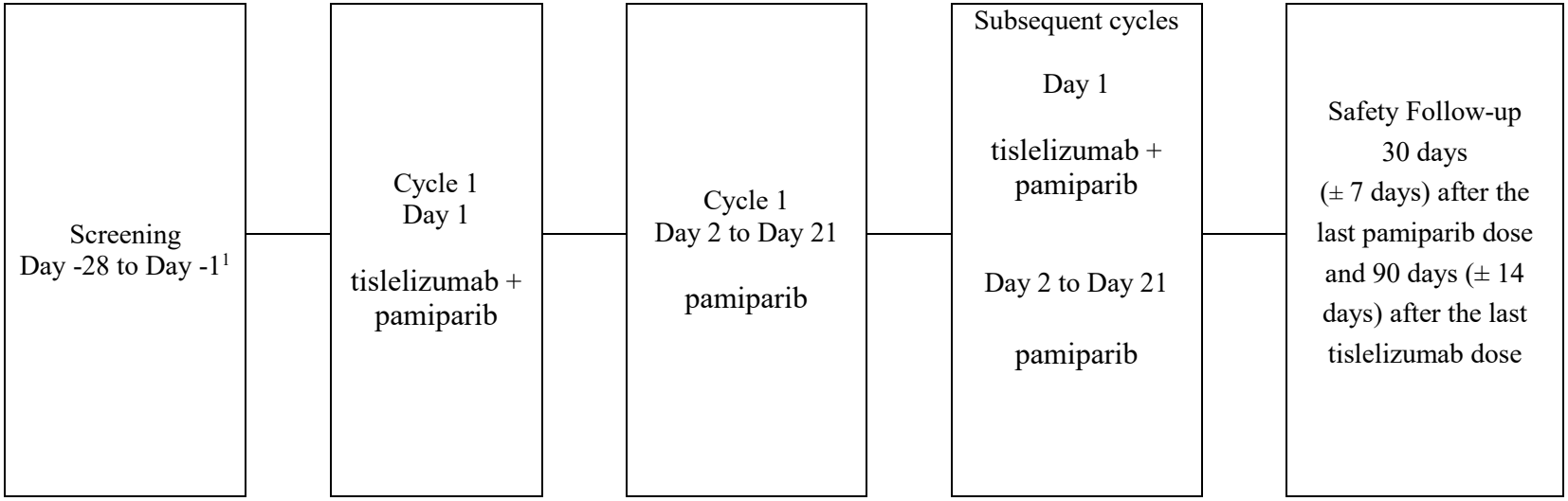
If any subject has a confirmed CR, PR, or SD after 2 years of study treatment, either tislelizumab or pamiparib or both agents can be stopped provided the study assessments and procedures are performed every 12 weeks with every radiographic tumor assessment. If a subject has evidence of PD within 1 year of treatment interruption, the Investigator can consider restarting the combined study treatment after discussion with the Sponsor, contingent on the continued availability of study medications.

The rationale for this change: a treatment hiatus for patients who have durable responses is allowed at the discretion of the treating investigator in consultation with the Sponsor. The optimal duration of combined study treatment is not known, and a treatment hiatus may reduce patient burden. During the treatment hiatus, patients will be monitored with routine radiographic tumor assessments according to the protocol schedule and If there are indications of tumor progression, study treatment can be resumed.

This study will be considered complete once all patients have manifested disease progression, ceased study treatment due to death, exhibited intolerance, withdrawn consent from the study, or completed a total of 2 years of treatment. Any patient in this study who continues to demonstrate objective clinical benefit at the end of a 2-year treatment duration may continue in the study or on treatment.

A flow chart of the study design is presented in Figure 1 and Figure 2 below.

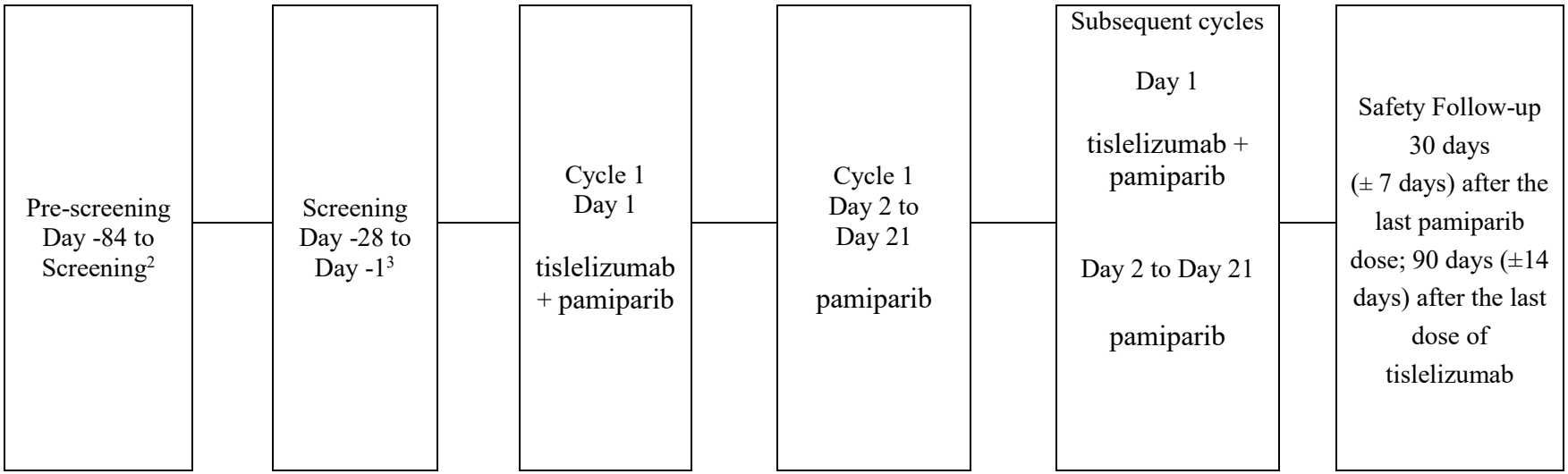
Figure 1: Overall Study Design (Part A; All Dose Levels)



1. Screening assessments will be completed within 28 days prior to the first dose of the study drug.

Note: tislelizumab 200 mg will be administered as an IV infusion on Day 1 of a 21-day cycle, and pamiparib 40 mg will be taken orally twice daily starting from Day 1.

Figure 2: Overall Study Design (Part B[1])



1. The decision to implement this schedule in Part B will be made after all the data from Part A is reviewed.
2. Patients who do not have known germline or somatic *BRCA* mutation or known HRD for Arm 1 (ovarian cancer), Arm 2 (TNBC), and Arm 3 (mCRPC) will have a HRD pre-screening period of up to 12 weeks prior to eligibility screening (see Section 8.1 for details). A separate pre-screening informed consent must be obtained. Any tissue taken during pre-screening period will not be re-collected during screening stage.
3. Screening assessments will be completed within 28 days prior to the first dose of the study drug.

Note: Tislelizumab 200 mg will be administered as an IV infusion on Day 1 of a 21-day cycle, and pamiparib 40 mg will be taken orally twice daily starting from Day 1.

5.1.1 Part A: Dose Escalation and Dose Finding

Five DLs are planned, as shown in Table 1. The starting dose for pamiparib and tislelizumab was based on the doses evaluated in the on-going monotherapy Phase 1 study of pamiparib and tislelizumab and is significantly lower than the highest safe dose that has been identified to date.

The suggested dose-escalation scheme is presented in Table 1 below. The proposed DLs may be further modified and additional doses may be considered based on the safety, tolerability, and efficacy observed during dose escalation, ie, flat dose of tislelizumab at 200 mg IV Q3W, an intermediate, not pre-defined or not previously evaluated dose or a less frequent dosing schedule that will not exceed the MTD level, if evaluation of toxicity at such a dose or schedule is desired.

Table 1: Suggested Dose-Escalation Scheme

Proposed Dose Level	Total daily dose[1]	
	Tislelizumab	**Pamiparib**
1	2 mg/kg IV Q3W	20 mg orally twice daily
2	2 mg/kg IV Q3W	40 mg orally twice daily
3	2 mg/kg IV Q3W	60 mg orally twice daily
4	200 mg IV Q3W	40 mg orally twice daily
5	200 mg IV Q3W	60 mg orally twice daily

Abbreviations: IV: intravenous; Q3W: every 3 weeks

[1] The actual dose levels and dose regimens administered in each step will depend on the data available from the previous step, as determined by the Safety Monitoring Committee.

The evaluable patients are those who have met the minimum treatment and safety evaluation requirements of the study and/or who experience a DLT during the first cycle (21 days). The minimum treatment and safety evaluation requirements include 1) treatment of > 90% of tislelizumab infusion on Cycle 1 Day 1 (C1D1); 2) a minimum of total 16 days of pamiparib treatment (> 75% of the expected dose) during Cycle 1; and 3) observation of ≥ 21 days following C1D1 treatment and completion of the scheduled safety assessments. If patients do not meet these minimum treatment and safety evaluation requirements, they will be regarded as ineligible for inclusion for MTD evaluation and may be replaced, if needed, based on 3+3 escalation scheme.

5.1.1.1 Dose-Limiting Toxicity

A DLT (Table 2) is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications, and occurs

during the first 21 days following the first dose of tislelizumab and pamiparib in Cycle 1 and meets any of the following criteria:

Table 2: Dose-limiting Toxicity Assessment Criteria

Toxicity	**Any of the following criteria:**
Hematologic	1. Grade 4 neutropenia lasting > 7 days 2. Febrile neutropenia (defined as absolute neutrophil count [ANC] < 1000/mm^3 with a single temperature of 38.3ºC or a sustained temperature of 38ºC for > 1 hour) 3. Grade 3 thrombocytopenia with bleeding 4. Grade 4 thrombocytopenia 5. Grade 4 (life threatening) anemia
Non-hematologic	1. Grade 5 adverse events 2. Grade 4 toxicity 3. Grade 3 toxicities irrespective of duration, with the exception of laboratory abnormalities, diarrhea, nausea and vomiting, and asymptomatic biochemical abnormalities that improve to Grade 2 or lesser severity within 3 days of institution of supportive care 4. Grade 3 tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor) of > 7-day duration 5. Immune-related adverse events (irAE) of Grade 3 or greater severity 6. Grade 4 laboratory abnormalities irrespective of duration 7. Grade 2 ophthalmologic toxicities 8. Persistent Grade 2 toxicity such as nausea, vomiting, fatigue despite optimal standard medical therapy that in the opinion of the investigator prevents continuous dosing.
CTCAE version 4.03 will be used for all grading. Optimal therapy for vomiting or diarrhea will be based in institutional guidelines, with consideration of the prohibited medications listed in this protocol.	

The investigator must notify the sponsor or its designee as soon as possible of any unexpected CTCAE Grade ≥ 3 adverse events or laboratory abnormalities.

5.1.2 Part B: Expansion

Part B is a multicenter, open-label, multiple-arm, expansion study that will evaluate the safety and tolerability and anti-tumor activity of tislelizumab + pamiparib treatment. Up to 40

enrolled patients/cohort are planned to be included for expansion in Part B of the study in the arms of specific tumor types defined below. Each Arm will be evaluated independently for study endpoints. The purpose of these expansion arms is to explore signals of clinical efficacy as well as to confirm the safety and tolerability of the combination in each selected tumor type. Anti-tumor activity will be evaluated in Part B. Initially, 20 patients per cohort will be enrolled and evaluated for anti-tumor activity. A decision can be made to stop an arm early due to suboptimal clinical anti-tumor activity or to enroll an additional 20 patients to evaluate further the anti-tumor activity. Statistical justification of such sample size expansion will be included in the final statistical analysis plan as applicable.

The RP2D is tislelizumab 200 mg IV Q3W + pamiparib 40 mg orally twice daily. This combination will be given until disease progression or other discontinuation criteria are met.

All patients must have received standard of care in the primary treatment of their disease. Patients with platinum-refractory disease are excluded. Platinum-refractory disease is defined as progressive disease at the time of the first tumor assessment while receiving a platinum-containing therapy. Enrollment into these disease-specific cohorts will occur simultaneously and independent of each other. For all disease-specific cohorts, a line of treatment begins with the administration of the first agent in a regimen and ends at the time of disease progression. Except as noted, at least 1 prior line of treatment should have contained a platinum compound.

Arm 1a: Patients with relapsed, platinum-sensitive high grade epithelial, non-mucinous, ovarian cancer, fallopian tube, or primary peritoneal cancer (EOC) **with** either known germline or somatic *BRCA1/2* mutations or **with** homologous recombination deficiency (HRD). Patients must have received at least 2 prior lines of platinum-containing chemotherapy

Arm 1b: Patients with relapsed, platinum-sensitive high grade EOC **without** either known germline or somatic *BRCA1/2* mutations and **without** known HRD. Patients must have received at least 2 prior lines of platinum-containing chemotherapy.

Arm 2: Patients with triple negative breast cancer (TNBC) with either **known** germline or somatic *BRCA1/2* mutations or with **documented** HRD. Patients can have been treated with at least 1 but no more than 3 prior lines of treatment.

Arm 3: Patients with metastatic castration-resistant prostate cancer (mCRPC) with either **known** germline or somatic *BRCA1/2* mutations or with **documented** HRD. Chemotherapy-naïve patients must have received prior abiraterone acetate or enzalutamide treatment

Arm 4: Patients with extensive-stage disease small cell lung cancer (SCLC) treated with at least 1 but no more than 2 prior lines of treatment, at least 1 must include a platinum agent

Arm 5: Patients with *HER2*-negative gastric or gastroesophageal junction cancer. Patients with *HER2*-negative disease may be treated with at least 1 but no more than 2 prior lines of treatment

Arm 6: Patients with locally advanced or metastatic urothelial (muscle invasive bladder, ureter, urethra or renal pelvis) cancer treated with at least 1 but no more than 2 prior lines of treatment, including a prior platinum-containing chemotherapy

Arm 7: Patients with advanced or metastatic pancreatic adenocarcinoma treated with at least one but no more than 2 prior lines of therapy. At least 1 prior treatment for advanced or metastatic disease must have contained a platinum agent. Any potential patient with a known deleterious germline or somatic *BRCA* is eligible even if platinum-naïve

Arm 8: (NOTE: CLOSED TO ENROLLMENT) Patients who may be expected to benefit from the combination of a PARP inhibitor and a PD-1 inhibitor. This arm will include patients with recurrent non-ovarian gynecological cancers (endometrial cancer, cancer of the cervix and patients with tumors known to be mismatch repair deficient [MMR] or HRD positive) that are not eligible for inclusion in any other arms of the trial. This is an exploratory signal seeking arm

For Arm 1 (ovarian cancer), Arm 2 (TNBC), and Arm 3 (mCRPC), patients with known eligible mutation status can be enrolled into the study if otherwise eligible. Tissue/blood specimens will be collected for a confirmatory test. Patients who do not have known germline or somatic *BRCA* mutation, or known HRD status must sign a separate pre-screening informed consent to evaluate HRD status prior to enrollment. Please see Section 8.1 for details.

For Arm 1 (EOC), Arm 1a will be analyzed independently of Arm 1b. All Arms may enroll up to 40 patients.

The Sponsor's medical monitor will approve tumor types for Arm 8 prior to screening.

The cycle length for tislelizumab and pamiparib combination treatment is 21 days.

5.1.3 Schedule of Assessments

The schedule of assessments for Part A; all Dose Levels and Part B of the study are presented in Table 3, Table 4, Table 5, and Table 6.

Table 3: Part A; All Dose Levels: Study Assessments and Procedures Schedule

Procedure	Screening[1]	Treatment Period				Safety Follow-up[2]	Survival Follow-up[3]
		Cycle 1 (21 Days)			Cycles ≥ 2		
Day	**-28 to -1**	**1**	**8 ± 1**	**15 ± 1**	**1 ± 2**	**Day 30 ± 7 Days after the last pamiparib dose and 90 days (± 14 days after last tislelizumab dose**	**Approximately Every 3 months**
Informed consent[4]	X						
Inclusion/exclusion criteria	X						
Demographic/Medical History/ Prior Medications[5]	X						
Vital signs/Weight[6]	X	X	X	X	X	X	
Physical examination[7]	X	X		X	X	X	
Ophthalmologic examination[8]	X	As clinically indicated				X	
ECOG performance status	X	X			X	X	
12-lead ECG[9]	X[9]	X			X[9]	X	
Adverse Events Assessment[10]	X	X	X	X	X	X	
Review Concomitant Medications	X	X	X	X	X	X	
CBC with Differential[11]	X	X		X	X	X	

Table 3: Part A; All Dose Levels: Study Assessments and Procedures Schedule

Procedure	Screening[1]	Treatment Period				Safety Follow-up[2]	Survival Follow-up[3]
		Cycle 1 (21 Days)			Cycles ≥ 2		
Day	**-28 to -1**	**1**	**8 ± 1**	**15 ± 1**	**1 ± 2**	**Day 30 ± 7 Days after the last pamiparib dose and 90 days (± 14 days after last tislelizumab dose**	**Approximately Every 3 months**
Comprehensive Serum Chemistry Panel[11]	X	X	X	X	X	X	
CK, CK-MB[11]	X	X			X	X	
Coagulation Parameters[12]	X					X	
Urinalysis[11]	X					X	
Pregnancy Test[13]	X				X		
Thyroid Function[14]		X			X[14]	X	
Immunoglobulins[15]		X			X[15]	X	
Anti-tislelizumab Antibodies[16]		X	X[16]		X[16]		
Pharmacokinetics blood sampling[17]		X	X[17]		X[17]		
HIV, hepatitis B and C[18]	X						
[redacted]	[redacted]	[redacted]				[redacted]	
Tumor Imaging[20]	X				X	X	

Table 3: Part A; All Dose Levels: Study Assessments and Procedures Schedule

Procedure	Screening[1]	Treatment Period				Safety Follow-up[2]	Survival Follow-up[3]
		Cycle 1 (21 Days)			Cycles ≥ 2		
Day	**-28 to -1**	**1**	**8 ± 1**	**15 ± 1**	**1 ± 2**	**Day 30 ± 7 Days after the last pamiparib dose and 90 days (± 14 days after last tislelizumab dose**	**Approximately Every 3 months**
Tislelizumab administration (30-60 minutes infusion every 21 days) [21]		X			X		
Pamiparib administration (twice daily) [21]		Continuous					
Archival Tumor Tissue[22]	X						
Fresh Tumor Tissue[23]	X			X		X	
BRCA test of Blood sample collection[24]	X						
[redacted]		X			X[25]	X	
Survival Status							X

Abbreviations: ECOG: Eastern Cooperative Oncology Group; X: to be performed; DLT: dose-limiting toxicity; ECG: electrocardiogram; CBC: complete blood count

[1] If screening laboratory tests are completed within 14 days prior to first dose, pre-dose samples on Day 1 of Cycle 1 will not be repeated.

[2] The mandatory Safety Follow-up Visits should be conducted 30 days (± 7 days) after the last dose of study therapy, or before initiation of a new anticancer treatment. Patients who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the AE to Grade 0-1, baseline or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.

[3] Following completion or discontinuation of the treatment and/or Safety Follow-up phases of the study, every effort should be made to follow up all patients for their survival status until patient death.

[4] Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (eg, within 28 days prior to Cycle 1, Day 1). A patient-specific patient number will be assigned when the study informed consent is signed.

[5] Includes history of all prior systemic, radiation, and surgical treatment for the primary cancer diagnosis. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report non-cancer treatment medication up to 30 days prior to the Screening visit. Date and response to last platinum-containing chemotherapy treatment and date of the progression must be documented unless no platinum-containing treatment has been received before.

[6] Vital signs to include temperature, heart rate, respiratory rate and blood pressure.

[7] Full physical examination includes the following items: 1. general appearance; 2. head, eyes, ears, nose and throat; 3. neck; 4. heart; 5. chest (including lungs); 6. abdomen; 7. extremities; 8. skin; 9. lymph nodes; 10. cardio-vascular; 11. neurological status.

[8] Ophthalmologic examination includes visual acuity, funduscopic, and slit lamp microscopy. The exam will be performed during the screening period, on Cycle 2 Day 1 ± 2 days, Cycle 4 Day 1 ± 2 days, Safety Follow-up, and whenever clinically indicated.

[9] Electrocardiogram assessments are to be performed with the patient in semi-recumbent supine position and rested for 5 minutes. Electrocardiogram (12-lead ECG) should be performed at Screening within 14 days of Cycle 1 Day 1 as baseline, and at the mandatory Safety Follow-up Visits. Triplicate ECG recordings (3 readings in rapid succession and not more than 2 minutes apart) will be obtained locally at the site in conjunction with blood sampling for pharmacokinetics as per Table 4. Additional ECGs may be obtained if clinically indicated (Section 8.3.4).

[10] Adverse Events and laboratory safety measurements will be graded per NCI-CTCAE version 4.03. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness and causality.

[11] Routine laboratory tests (eg, CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory. Serum chemistry and hematology will be performed at Screening, prior to the first dose of pamiparib if it was not done within 14 days of Cycle 1 Day 1, Days 1 and 15 of Cycles 1 through 3, and Day 1 of subsequent cycles and more frequently as clinically indicated. CK and CK-MB will be performed at Screening, prior to the first dose on Day 1 of all treatment cycles, and Safety Follow-up Visit. If your laboratory does not perform CK-MB testing, serum troponins (troponin I and/or T) measurements should be performed instead; if only either troponin is assessed per local standards the same should be evaluated throughout. See Appendix 10 for management of immune-related adverse events corresponding to abnormalities based on laboratory testing.

[12] PT/INR and activated partial thromboplastin time (aPTT) should be collected at Screening and at the mandatory Safety Follow-up Visits after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.

[13] Women of childbearing potential must have a negative serum pregnancy test at Screening (within 7 days of the first investigational product administration). A urine or serum pregnancy test must be performed if any woman suspects that she has become pregnant during the study. For subsequent pregnancy testing,

urine pregnancy tests, performed at a central or local laboratory, are allowed. If a urine pregnancy test is positive, a confirmatory serum pregnancy test is required.

14 T3, T4, thyroid-stimulating hormone (TSH); will be collected at pre-dose of Day 1 of every cycle and at the mandatory Safety Follow-up Visits. Analysis of T3, T4 and TSH will be performed by the local study site laboratory. If feasible, early morning ACTH and cortisol will be obtained as part of the screening assessments and only repeated during the study if it is clinically indicated.

15 Analysis of IgG and IgM will be performed at pre-dose of Day 1 every cycle in first 12 months, approximately every 2 months thereafter, and at Safety Follow-up Visits. Analysis will be performed by the local study site laboratory.

16 Blood for anti-tislelizumab antibodies should be collected within 24 hours before the start of infusion on Day 1 of Cycle 1, on Day 8 of Cycle 1, and before the start of infusion on Day 1 of Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 9 and approximately every 8 cycles thereafter (ie, Cycle 17, Cycle 25 and Cycle 33). In patients who discontinue study therapy before 6 months, every effort should be made to collect blood sample for analyzing anti-tislelizumab antibodies approximately 6 months after the first dose. Corresponding tislelizumab PK samples will be collected at the same time when the anti-drug antibody (ADA) samples are collected to assess the neutralizing capacity of ADA. Analysis will be performed by a central laboratory.

17 Cannulation for blood sampling for pharmacokinetics will be performed according to Table 4. In addition, corresponding tislelizumab PK samples will be collected at the same time when the ADA samples are collected to assess the neutralizing capacity of ADA.

18 Testing will be performed by the local laboratory at Screening. Include HCV antibody, HBsAg, HBcAb and HIV 1/2 antibodies, patients who are HBsAg and/or HBcAb positive or HCV antibody positive at Screening must not be enrolled until further definite testing with HBV DNA titers and HCV ribonucleic acid (RNA) tests can conclusively rule out presence of active infection requiring therapy with Hepatitis B and C respectively.

19 [redacted]

20 Tumor imaging (either computed tomography [CT] or magnetic resonance imaging [MRI], with preference for CT) will be performed within 28 days prior to enrollment, and while on study approximately every 9 ± 1 weeks in the first 12 months and approximately every 12 ± 1 weeks thereafter. The same imaging technique should be used in a patient throughout the study. After first documentation of response (CR or PR), imaging performed at the next regularly scheduled time point will be used for response confirmation. Progressive disease suspected as pseudo-progression needs to be confirmed in a subsequent imaging not less than 4 weeks later or at the next regularly scheduled time point but not more than 12 weeks, before discontinuation of study treatment. Patients who stop treatment prior to documentation of progressive disease will undergo repeated imaging for tumor response assessments as described in Section 5.2.5.1. In patients with prostate cancer, baseline bone scans will be performed during the Screening window, and repeat bone scans will be performed approximately every 9 ± 1 weeks for the first 12 months and approximately every 12 ± 1 weeks thereafter.

21 Both tislelizumab and pamiparib treatments start from Cycle 1 Day 1. On Day 1 of each cycle, tislelizumab will be given intravenously after the morning dosing of pamiparib. See Section 6.2 for additional information regarding the administration of study drugs. If any subject has a confirmed CR, PR, or SD after 2 years of study treatment, either tislelizumab or pamiparib or both agents can be stopped provided the study assessments and procedures are performed every 12 weeks with every radiographic tumor assessment. If a subject has evidence of PD within 1 year of treatment interruption, the Investigator can consider restarting the combined study treatment after discussion with the Sponsor, contingent on the continued availability of study medications. The rationale for this change: a treatment hiatus for patients who have durable responses is allowed at the discretion of the treating investigator in consultation with the Sponsor. The optimal duration of combined study treatment is not known, and a treatment hiatus may reduce patient burden. During the treatment

hiatus, patients will be monitored with routine radiographic tumor assessments according to the protocol schedule and If there are indications of tumor progression, study treatment can be resumed.

[22] Collection of archival tumor tissue for purpose of biomarker analysis. This is a mandatory requirement for patient enrollment and should be specified in the consent form. Specific instructions for tissue collection and shipment are provided in the Laboratory Manual.

[23] Archival tumor tissue will be collected for evaluation of potential biomarkers, although a fresh baseline tumor biopsy (within 12 weeks of starting treatment) is recommended. In the absence of archival tumor tissue, a fresh baseline biopsy of an accessible tumor lesion is mandatory, unless previously discussed with the sponsor's medical monitor or its designee. For those patients who consent to fresh biopsy, an optional biopsy for biomarker analysis during the third week of the first cycle is recommended. For the patients who have confirmed disease progression, an optional biopsy may be taken at the Safety Follow-up visit. The purpose of this biopsy sample is to evaluate mechanisms of resistance to the study treatment(s). If feasible, any follow up biopsy should be ideally taken from the same anatomical location as the baseline biopsy. Additional written patient consent is required for optional fresh tumor biopsies. Fresh biopsies should be limited to readily accessible tumor lesions (eg, skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed using CT guidance). If performed, a tissue cylinder should be obtained that has proper size for histological examination and biomarker analysis. If any subject has a confirmed CR, PR, or SD after 2 years of study treatment, either tislelizumab or pamiparib or both agents can be stopped provided the study assessments and procedures are performed every 12 weeks with every radiographic tumor assessment. If a subject has evidence of PD within 1 year of treatment interruption, the Investigator can consider restarting the combined study treatment after discussion with the Sponsor, contingent on the continued availability of study medications. The rationale for this change: a treatment hiatus for patients who have durable responses is allowed at the discretion of the treating investigator in consultation with the Sponsor. The optimal duration of combined study treatment is not known, and a treatment hiatus may reduce patient burden. During the treatment hiatus, patients will be monitored with routine radiographic tumor assessments according to the protocol schedule and If there are indications of tumor progression, study treatment can be resumed.

[24] A blood sample must be collected at screening stage for ovarian, fallopian tube, primary peritoneal, and breast cancer patients for germline *BRCA* and/or other mutations analysis.

[25] [redacted]

Table 4: Part A; All Dose Levels: Pharmacokinetic Sampling

Procedure		Days	Time Points	Part A escalation cohorts[1]				
				PK sampling of pamiparib [2]	PK sampling of tislelizumab[2]	ADA sampling of tislelizumab[2]	12-lead ECG time points for PK sampling[3]	Vital signs[3]
Treatment Period	Cycle 1 (21 Days)	1 ± 1	0 h[4]		X	X	X	
		8 ± 1	0 h[4]		X	X		
	Cycle 2 (21 Days)	1 ± 2	0 h[4]	X	X	X	X	X
			0.5 h[5]	X				
			1 h[6]	X				
			2 h[7]	X			X	X
			4 h[7]	X	X			
			7 h[8]	X				
	Cycle 3 (21 Days)	1 ± 2	0 h[4]	X	X	X	X	X
			4 h[8]		X			
	Cycle 4 (21 Days)	1 ± 2	0 h[4]		X	X	X	X
			4 h[8]		X			
	Cycle 5 (21 Days)	1 ± 2	0 h[4]		X	X		
	Cycle 9 (21 Days)	1 ± 2	0 h[4]		X	X		
	Cycle 17 (21 Days)	1 ± 2	0 h[4]		X	X		

Please note: Actual drug dosing and PK sampling times have to be documented by the sites and will be captured in the database.
Abbreviations: X: to be performed; PK: pharmacokinetic; ADA: anti-drug antibody; ECG: electrocardiogram.

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 should be from a different site.

1. In addition, corresponding tislelizumab PK samples will be collected at the same time points when the ADA samples are collected to assess the neutralizing capacity of ADA. **General note: <u>It is important that pharmacokinetic (PK) sampling occurs as close as possible to the scheduled time</u>. In order to achieve this, some of the other assessments scheduled at the same time need to be initiated prior to or after the time point <u>to allow for completion of these measurements in enough time for the PK sampling to be taken at the designated time point</u>. Thus, the sequence at a particular time point is: 1) scheduled ECG; 2) PK blood samples 3) vital sign measurements; and 4) any other scheduled or unscheduled measurements at that time point.**
2. Except for pre-dose PK, each PK/ADA sampling time point of tislelizumab and pamiparib will be in correspondence with the end of dosing of each agent, respectively.
3. The time points of performing ECG and vital signs will be associated with the time of pamiparib administration. Triplicate ECG recordings (3 readings in rapid succession and not more than 2 minutes apart) will be obtained locally at the site.
4. Within 2 hours prior to dosing.
5. A window period of ± 5 minutes exists for all procedures occurring after the study drug is taken.
6. A window period of ± 10 minutes exists for all procedures occurring after the study drug is taken.
7. A window period of ± 30 minutes exists for all procedures occurring after the study drug is taken.
8. A window period of ± 1 hour exists for all procedures occurring after the study drug is taken.

Table 5: Part B: Study Assessments and Procedures Schedule

	Pre-screening[1]	Screening[2]	Treatment Period (21 Day Cycles)						Safety Follow-up[3]	Follow-up[4]
			Cycles 1 to 3			Cycle 4 through 6		Cycle ≥ 7		
Day	**-84 to screening**	**-28 to -1**	**Day 1 -1**	**Day 8 ± 1**	**Day 15 ± 1**	**Day 1 ± 2**	**Day 15 ± 1**	**Day 1 ± 2**	**Day 30 ± 7 Days after the last pamiparib dose and 90 days (± 14 days after last tislelizumab dose**	**Approximately Every 3 months**
Pre-screening informed consent	X									
Informed consent[5]		X								
Inclusion/exclusion criteria		X								
Demographic/Medical History/ Prior Medications[6]		X								
Vital signs/Weight[7]		X	X	X	X	X		X	X	
Physical examination[8, 9]		X	X			X		X	X	
Optical Coherence Tomography (or equivalent diagnostic test), eye examination and visual acuity tests [10]		X	Every 15 weeks (± 7 days) during treatment						X[11]	
ECOG performance status		X	X			X		X	X	
12-lead ECG[12]		X							X	

Table 5: Part B: Study Assessments and Procedures Schedule

	Pre-screening[1]	Screening[2]	Treatment Period (21 Day Cycles)						Safety Follow-up[3]	Follow-up[4]
			Cycles 1 to 3			Cycle 4 through 6		Cycle ≥ 7		
Day	**-84 to screening**	**-28 to -1**	**Day 1 -1**	**Day 8 ± 1**	**Day 15 ± 1**	**Day 1 ± 2**	**Day 15 ± 1**	**Day 1 ± 2**	**Day 30 ± 7 Days after the last pamiparib dose and 90 days (± 14 days after last tislelizumab dose**	**Approximately Every 3 months**
Review Adverse Events[13]	X	X	X	X	X	X		X	X	X AEs for tislelizumab only to 90 days
Review alcohol consumption, concomitant Medications, herbals, mushroom containing products and supplements		X	X	X	X	X		X	X	
CBC with Differential[14]		X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel[14]		X	X	X	X	X	X	X	X	
CK, CK-MB		X	X	X	X	X		X	X	
Coagulation Parameters[15]		X	Collect if Grade 2 or higher hepatic AE occurs at any time during the study and as clinically indicated						X	
Urinalysis[14]		X	As clinically indicated						X	
Pregnancy Test[16]		X				X		X	X	
Thyroid Function[17]		X	X			X[17]		X[17]	X	

Table 5: Part B: Study Assessments and Procedures Schedule

	Pre-screening[1]	Screening[2]	Treatment Period (21 Day Cycles)						Safety Follow-up[3]	Follow-up[4]
			Cycles 1 to 3			Cycle 4 through 6		Cycle ≥ 7		
Day	**-84 to screening**	**-28 to -1**	**Day 1 -1**	**Day 8 ± 1**	**Day 15 ± 1**	**Day 1 ± 2**	**Day 15 ± 1**	**Day 1 ± 2**	**Day 30 ± 7 Days after the last pamiparib dose and 90 days (± 14 days after last tislelizumab dose**	**Approximately Every 3 months**
Anti-tislelizumab Antibodies[18]			X	X[18]		X[18]		X[18]		
Pharmacokinetics blood sampling[19]			X	X[19]		X[19]		X[19]		
HIV, hepatitis B, C and E[20]		X	Collect if Grade 2 or higher aminotransferase enzyme increases occur at at any time during the study and as clinically indicated							
[redacted]		[redacted]	[redacted]						[redacted]	
Tumor Imaging[22]		X	Every 9 weeks ± 1 week (calendar days)						X	
Tislelizumab administration (30-60 minutes infusion) [23]			X			X		X		
Pamiparib administration (twice daily) [23]			Continuous							
Archival Tumor Tissue[24]	X	X								
Fresh Tumor Tissue[25]	X	X	X						X	

Table 5: Part B: Study Assessments and Procedures Schedule

	Pre-screening[1]	Screening[2]	Treatment Period (21 Day Cycles)						Safety Follow-up[3]	Follow-up[4]
			Cycles 1 to 3			Cycle 4 through 6		Cycle ≥ 7		
Day	**-84 to screening**	**-28 to -1**	**Day 1 -1**	**Day 8 ± 1**	**Day 15 ± 1**	**Day 1 ± 2**	**Day 15 ± 1**	**Day 1 ± 2**	**Day 30 ± 7 Days after the last pamiparib dose and 90 days (± 14 days after last tislelizumab dose**	**Approximately Every 3 months**
Blood sample collection for *BRCA* and/or other mutation test[26]		X								
[redacted]		X	X			X[27]			X	
Survival Status and subsequent anticancer therapy										X
Pulmonary function tests[28]		X								

Abbreviations: AE: adverse event; ECOG: Eastern Cooperative Oncology Group; X: to be performed; DLT: dose-limiting toxicity; ECG: electrocardiogram; CBC: complete blood count

[1] Patients who do not have known germline or somatic *BRCA* mutation or known HRD for Arm 1 (ovarian cancer), Arm 2 (TNBC), and Arm 3 (mCRPC) will have a HRD pre-screening period of up to 12 weeks prior to eligibility screening (see Section 8.1 for details). A separate pre-screening informed consent must be obtained. Any tissue taken during pre-screening period will not be re-collected during screening stage.

[2] If screening laboratory tests, physical examination are completed within 14 days prior to first dose, pre-dose samples on Day 1 of Cycle 1 treatment will not be repeated.

[3] The mandatory Safety Follow-up Visits should be conducted 30 days (± 7 days) after the last dose of pamiparib, 90 days (± 14 days) after the last dose of tislelizumab or before initiation of a new anticancer treatment. Patients who are discontinued from the study due to an unacceptable drug-related adverse

event will be followed until the resolution of the AE to Grade 0-1, baseline or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.

[4] Patients will be followed for survival, cause of death, and additional cancer treatment, if available, every 3 months, or when requested by the sponsor.

[5] Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (eg, within 28 days prior to Cycle 1, Day 1). Assign patient number when the study informed consent is signed.

[6] Includes history of treatment for the primary cancer diagnosis, including prior systemic, radiation treatment and surgical treatment for the cancer. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report non-cancer treatment medication up to 30 days prior to the Screening visit. Date and response to last platinum-containing chemotherapy treatment and date of the disease progression must be documented unless no platinum-containing treatment has been received before.

[7] Vital signs to include temperature, heart rate, respiratory rate and blood pressure.

[8] Full physical exam at the Screening and Safety Follow-up. At all other times, targeted or symptoms-directed physical examination, at the investigator's discretion.

[9] Investigators should evaluate patients for changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.

[10] Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of randomization may be used rather than repeating tests. Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed at the Screening Visit. Patients will undergo repeat assessments approximately every 15 weeks (± 7 days) and at the safety follow up visit. Investigators should evaluate patients for changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.

[11] The ophthalmologic assessments including eye exam, visual acuity test, and OCT (or equivalent diagnostic test) should be performed during safety follow up, within 30 days of study treatment end.

[12] Electrocardiogram assessments are to be performed with the patient in semi-recumbent supine position and rested for 5 minutes. Electrocardiogram (12-lead ECG) should be performed at Screening within 14 days of Cycle 1 Day 1 as baseline, as clinically indicated during the treatment period at the investigator's judgement, and at the mandatory Safety Follow-up Visits. Additionally, triplicate ECG recordings (3 readings in rapid succession and not more than 2 minutes apart) will be obtained locally at the site in conjunction with blood sampling for pharmacokinetics as per Table 6.

[13] Adverse Events and laboratory safety measurements will be graded per NCI CTCAE version 4.03. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness criteria and causality. No adverse events will be reported during the pre-screening stage. Only serious adverse events will be reported during the pre-screening stage if the serious adverse event is related to the pre-screening procedure. All AEs and SAEs, regardless of the relationship to the investigational product, will be collected throughout the study until 30 days after the last study treatment or initiation of new anticancer therapy. The exception are irAEs, which will be recorded up to 90 days after the last dose of tislelizumab, regardless of initiation of subsequent anticancer therapy.

[14] Routine laboratory tests (eg, CBC with differential, comprehensive serum chemistry panel, and urinalysis) will be performed by the local study site laboratory or their contract laboratory. Serum chemistry and hematology will be performed at Screening, prior to the first dose of pamiparib if it was not done within 14 days of Cycle 1 Day 1, Days 1, 8, and 15 of Cycles 1 through 3, Days 1 and 15 of Cycles 4 through 6, and Day 1 of subsequent cycles and more frequently as clinically indicated, and at the mandatory Safety Follow-up Visits. CK and CK-MB will be performed at Screening, prior to the first dose

on Day 1, Day 8, and Day 15 of Cycles 1 through 3, prior to dosing on Day 1 for all remaining cycles, and Safety Follow-up Visit. If your laboratory does not perform CK-MB testing, serum troponins (troponin I and/or T) measurements should be performed instead; if only either troponin is assessed per local standards the same should be evaluated throughout. See Appendix 10 for management of immune-related adverse events corresponding to abnormalities based on laboratory testing.

[15] PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visits after discontinuation of study therapy. Coagulation parameters should be evaluated in the event of a Grade 2 or higher aminotransferase increases occur and as clinically necessary. Coagulation parameters will be analyzed by the local study site laboratory.

[16] Women of childbearing potential must have a negative serum pregnancy test at Screening (within 7 days of the first investigational product administration). A urine or serum pregnancy test must be performed on Day 1 of each cycle and at the Safety Follow-up and evaluated at the local site laboratory.

[17] T3, T4, thyroid-stimulating hormone (TSH); will be collected at Screening, every 2 cycles, or more frequently as clinically indicated during treatment, and at the mandatory Safety Follow-up Visits. Analysis of T3, T4 and TSH will be performed by the local study site laboratory. If feasible, early morning ACTH and cortisol will be obtained prior to the first dose of tislelizumab and only repeated during the study if it is clinically indicated.

[18] Blood for anti-tislelizumab antibodies should be collected within 24 hours before the start of infusion on Day 1 and one sample between Day 7 through 10 of Cycle 1, and before the start of infusion on Day 1 of Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 9 and Cycle 17. Refer to Table 6 for details on timing of ADA sample collection. In patients who discontinue study therapy before 6 months, every effort should be made to collect blood samples to analyze anti-tislelizumab antibodies approximately 6 months after the first dose. Corresponding tislelizumab PK samples will be collected at the same time when the ADA samples are collected to assess the neutralizing capacity of ADA. Analysis will be performed by a central laboratory.

[19] Blood for pharmacokinetics will be collected in Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 9 and Cycle 17. Refer to Table 6 for details on timing of pharmacokinetics sample collection. In addition, corresponding tislelizumab PK samples will be collected at the same time when the ADA samples are collected to assess the neutralizing capacity of ADA.

[20] Testing will be performed by the local laboratory at Screening. Include HCV antibody, HBsAg, HBcAb and HIV 1/2 antibodies, patients who are HBsAg and HBcAb positive or HCV antibody positive at Screening must not be enrolled until further definite testing with HBV DNA titers and HCV RNA tests can conclusively rule out presence of active infection requiring therapy with Hepatitis B and C respectively.

[21] [redacted] If any subject has a confirmed CR, PR, or SD after 2 years of study treatment, either tislelizumab or pamiparib or both agents can be stopped provided the study assessments and procedures are performed every 12 weeks with every radiographic tumor assessment. If a subject has evidence of PD within 1 year of treatment interruption, the Investigator can consider restarting the combined study treatment after discussion with the Sponsor, contingent on the continued availability of study medications. The rationale for this change: a treatment hiatus for patients who have durable responses is allowed at the discretion of the treating investigator in consultation with the Sponsor. The optimal duration of combined study treatment is not known, and a treatment hiatus may reduce patient burden. During the treatment hiatus, patients will be monitored with routine radiographic tumor assessments according to the protocol schedule and If there are indications of tumor progression, study treatment can be resumed.

[22] Tumor imaging (either computed tomography [CT] or magnetic resonance imaging [MRI], with preference for CT with contrast of chest, abdomen and pelvis, including bone scan for patients with bone metastasis) will be performed within 28 days prior to enrollment (bone scans can be within 56 days), and while on study approximately every 9 ± 1 week (calendar days) in the first 12 months and approximately every 12 ± 1 weeks thereafter. The same imaging technique should be used in a patient throughout the study. After the first documentation of response (CR or PR), imaging performed at the next regularly

scheduled time point will be used for response confirmation. Progressive disease suspected as pseudo-progression needs to be confirmed in a subsequent imaging at least 4 weeks later or at the next regularly scheduled time point but not to exceed 12 weeks, before discontinuation of study treatment. Patients who stop treatment prior to documentation of progressive disease will undergo repeated imaging for tumor response assessments as described in Section 5.2.5.1. For patients with extensive-stage disease SCLC or patients with NSCLC, baseline brain MRI must be obtained, and will be repeated if brain metastases are noted at baseline as part of the assessment of anti-tumor activity during study treatment.

[23] Both tislelizumab and pamiparib treatments start from Cycle 1 Day 1. On Day 1 of each cycle, tislelizumab will be given intravenously after the morning dosing of pamiparib. See Section 6.2 for additional information regarding the administration of study drugs. If any subject has a confirmed CR, PR, or SD after 2 years of study treatment, either tislelizumab or pamiparib or both agents can be stopped provided the study assessments and procedures are performed every 12 weeks with every radiographic tumor assessment. If a subject has evidence of PD within 1 year of treatment interruption, the Investigator can consider restarting the combined study treatment after discussion with the Sponsor, contingent on the continued availability of study medications. The rationale for this change: a treatment hiatus for patients who have durable responses is allowed at the discretion of the treating investigator in consultation with the Sponsor. The optimal duration of combined study treatment is not known, and a treatment hiatus may reduce patient burden. During the treatment hiatus, patients will be monitored with routine radiographic tumor assessments according to the protocol schedule and If there are indications of tumor progression, study treatment can be resumed.

[24] Collection of archival tumor tissue for purpose of biomarker analysis. This is a mandatory requirement for patient enrollment and should be specified in the consent form. Specific instructions for tissue collection and shipment are provided in the Laboratory Manual. If tumor samples have been collected at pre-screening stage, there is no need to collect it again during Screening.

[25] Archival tumor tissue will be collected for evaluation of potential biomarkers, although a fresh baseline tumor biopsy (within 12 weeks of starting treatment) is recommended. In the absence of archival tumor tissue, a fresh baseline biopsy of an accessible tumor lesion is mandatory, unless previously discussed with the sponsor's medical monitor or its designee. For those patients who consent to fresh biopsy, an optional biopsy for biomarker analysis during the third week of the first cycle is recommended. For the patients who have confirmed disease progression, an optional biopsy may be taken at the Safety Follow-up visit. The purpose of this biopsy sample is to evaluate mechanisms of resistance to the study treatment(s). If feasible, any follow up biopsy should be ideally taken from the same anatomical location as the baseline biopsy. Additional written patient consent is required for optional fresh tumor biopsies. Fresh biopsies should be limited to readily accessible tumor lesions (eg, skin; peripheral lymph nodes; and lung, liver or internal lymph node metastases which can be readily accessed using CT guidance). If performed, a tissue cylinder should be obtained that has proper size for histological examination and biomarker analysis.

[26] A blood sample at Screening stage will be collected for all patients in Part B, regardless of tumor type, for *BRCA* and/or other mutational analysis, even if it has been previously tested.

[27] [redacted]

[28] Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer will have pulmonary function testing which may include but is not limited to spirometry and assessment of diffusion capacity done during the Screening period to assist the determination of suitability on the study. These tests may include, but are not limited to, forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), diffusing capacity (DLCO), and FEV_1/FVC.

Table 6: Part B: Pharmacokinetic/ADA Sampling[1]

Procedure	Days	Time Points	PK sampling of pamiparib [2]	PK sampling of tislelizumab[2]	12-lead ECG time points for PK sampling[3]	ADA Sampling of tislelizumab[4]
Cycle 1 (21 days)	1	0 h[5]	X	X	X	X
		2 h[6]	X		X	
		4 h[7]		X		
	7 to 10 ± 1 (one sample)	0 h		X		X
Cycle 2 (21 days)	1 ± 2	0 h[5]		X		X
Cycle 3 (21 days)	1 ± 2	0 h[5]		X		X
Cycle 4 (21 days)	1 ± 2	0 h[5]		X		X
Cycle 5 (21 days)	1 ± 2	0 h[5]	X	X	X	X
		2 h[6]	X		X	
		4 h[7]		X		
Cycle 9 (21 days)	1 ± 2	0 h[5]		X		X
Cycle 17 (21 days)	1 ± 2	0 h[5]		X		X

Please note: Actual drug dosing and PK/ADA sampling times have to be documented by the sites and will be captured in the database.

Abbreviations: X: to be performed; PK: pharmacokinetic; ADA: anti-body antibody

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 should be from a different site.

1. General note: It is important that pharmacokinetic (PK) sampling occurs as close as possible to the scheduled time. **In order to achieve this, some of the other assessments scheduled at the same time need to be initiated prior to or after the time point to allow for completion of these measurements in enough time for the PK sampling to be taken at the designated time point. Thus, the sequence at a particular time point is: 1) scheduled ECG; 2) PK blood samples 3) vital sign measurements; and 4) any other scheduled or unscheduled measurements at that time point.**

2. Except for pre-dose PK, each PK sampling time point of tislelizumab and pamiparib will be in correspondence with the end of dosing of each agent, respectively.
3. Triplicate ECG recordings (3 readings in rapid succession and not more than 2 minutes apart) will be obtained locally at the site in conjunction with blood sampling for pharmacokinetics of pamiparib.
4. Tislelizumab PK samples will be collected at the same time points when the ADA samples are collected to assess the neutralizing capacity of ADA. Blood for anti-tislelizumab antibodies should be collected within 24 hours before the start of the first dose of tislelizumab in Cycle 1 and one sample prior to dosing between Day 7 through 10 in Cycle 1, and Day 1 of Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 9 and Cycle 17.
5. Within 2 hours prior to dosing.
6. A window period of ± 10 minutes exists for all procedures.
7. A window period of ± 30 minutes exists for all procedures occurring after the study drug is taken. Assessment to be performed 4 hours after the end of the infusion.

5.1.4 Dose Modifications, Dose Delay, and Missing Dose

There will be no dose reduction of tislelizumab in this study. Dose delays of < 12 weeks will be permitted. The Investigator should make every effort to maintain dose intensity in patients.

Patients may temporarily suspend study treatment if they experience a toxicity that is considered related to tislelizumab and requires that a dose be withheld. Patients should resume tislelizumab treatment as soon as possible after the AE recovers to baseline or Grade 1 severity (whichever is more severe) within 12 weeks after the last dose of tislelizumab. If the patient is unable to resume tislelizumab in that timeframe, study treatment should be discontinued.

If any subject has a confirmed CR, PR, or SD after 2 years of study treatment, either tislelizumab or pamiparib or both agents can be stopped provided the study assessments and procedures are performed every 12 weeks with every radiographic tumor assessment. If a subject has evidence of PD within 1 year of treatment interruption, the Investigator can consider restarting the combined study treatment after discussion with the Sponsor, contingent on the continued availability of study medications.

The rationale for this change: a treatment hiatus for patients who have durable responses is allowed at the discretion of the treating investigator in consultation with the Sponsor. The optimal duration of combined study treatment is not known, and a treatment hiatus may reduce patient burden. During the treatment hiatus, patients will be monitored with routine radiographic tumor assessments according to the protocol schedule and If there are indications of tumor progression, study treatment can be resumed.

The Investigator should try his/her best to assess whether an adverse event is possibly related to tislelizumab only or pamiparib only or both, and treat the patient accordingly.

In general dose delays for reasons other than management of AEs are discouraged. A dose delay of ≤ 21 consecutive days for pamiparib or a dose delay of ≤ 42 consecutive days for tislelizumab is allowed under the following guidance and at the discretion of the investigator after consultation with the sponsor or its designee.

For tislelizumab, please refer to Appendix 10 for guidance for the management of irAEs including dose interruption and discontinuation.

In case a patient is benefiting from the study treatment while meeting the discontinuation criteria, continuation of study treatment may occur upon discussion and agreement with Sponsor Medical Monitor.

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 (refer to the visit window in

Table 3 and Table 5), with subsequent dosing continued on the 21-day intervals afterward, with a minimum of 14 days between tislelizumab dosing.

For pamiparib, please refer to Appendix 11 for dose interruption and/or modification of pamiparib. Pamiparib may be dose-reduced or delayed to manage unacceptable toxicity. In Part B of this study, dose reductions to pamiparib 20 mg orally twice daily are allowed. If the patient cannot tolerate pamiparib 20 mg orally twice daily, it should be discontinued. Pamiparib treatment can be held during management of AEs, according to **Appendix 11**. Any dose increase after dose reduction should be agreed upon between and investigator and the sponsor or its designee.

If a dose is missed on any day for any reason, then it should not be made up and the patient should remain on their normal schedule.

If a dose is delayed for pamiparib, the patient can continue tislelizumab dosing every 21 days and can resume pamiparib at any time. If a dose is delayed for tislelizumab for ≤ 10 days for a planned dosing cycle (eg, Cycle 3 Day 1), tislelizumab should be administered and all assessments should be conducted according to the original cycle (ie, Cycle 3); if the delay is more than 10 days, the patient should skip tislelizumab dose, and tislelizumab will be administered on Day 1 of the next planned cycle (ie, Cycle 4 Day 1). Patients who experience AE related to one investigational agent may continue treatment with the other investigational agent according to the protocol schedule after consultation with the sponsor or its designee.

If tislelizumab cannot be resumed within 42 consecutive days of last dose due to tislelizumab treatment-related events, or if corticosteroid dose for an irAE is not able to be reduced to ≤ 10 mg prednisone or equivalent per day by the end of 42 days' dose interruption, the patient should be discontinued from tislelizumab, and continue pamiparib monotherapy once the irAE is resolved. If pamiparib cannot be resumed within 21 consecutive days of the last dose due to pamiparib treatment-related events, pamiparib will be permanently discontinued and the patient may continue tislelizumab monotherapy alone. Exemptions may be considered for those patients who are determined by the investigator to have received clinical benefit and it is considered safe and to be in the best interest of the patient to resume the treatment after consultation with the sponsor or its designee.

Palliative radiation to existing sites of metastatic disease to alleviate the tumor obstruction and/or pain will be allowed provided tislelizumab dosing does not occur within 1-week pre- or post-radiation. Pamiparib should be held 3 days before and resume 3 days after completion of radiation. Patients who require palliative radiotherapy to manage the symptoms of progressive disease should be discontinued. Any exception will need to be discussed with and agreed by the sponsor's medical monitors.

5.1.5 Treatment beyond Progression

In the absence of unacceptable toxicity, patients may continue with administrations of the combination of tislelizumab and pamiparib at the same dose unless a dose interruption or modification is required based on the guidance described below, or at the discretion of the investigator after consultation with the sponsor or its designee. The patients with disease progression that the investigator considers to be consistent with "pseudo-progression" will be allowed to continue the study drug treatment of pamiparib alone or tislelizumab alone or the combination of tislelizumab and pamiparib if the patient is benefiting from the treatment in the judgment of the investigator after consultation and agreement with the sponsor's medical monitor or its designee. The criteria for pseudo progression will not be met if the only change is reflected in tumor markers, such as CA-125 or PSA.

If pseudo-progression is suspected, the patient will be allowed to continue study treatment if they meet all of the following criteria:

- Investigator-assessed benefit
- Patient is tolerating study drug(s) and agrees to continue study treatment
- Stable (ie, not deteriorating) Eastern Cooperative Oncology Group (ECOG) performance status
- Absence of rapid progression of disease or of progressive tumor at critical anatomic sites (eg, spinal cord compression) that necessitates urgent alternative medical intervention
- The patient must be reconsented to continue study treatment

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

Patients may be enrolled in the study only if they meet all the following criteria:

1. Patients have voluntarily agreed to participate by giving written informed consent.
2. Patients must have received standard of care in the primary treatment of their disease.
3. Patients who have the below specified histologically confirmed malignancies that have progressed to the advanced or metastatic stage.
   a) In *Part A*, the patients must have an advanced malignancy including but not limited to high-grade serous cancer of the ovary, fallopian tube, or peritoneum, triple negative breast cancer, SCLC, primary peritoneal cancer, and any tumor likely to harbor DNA

damage repair deficiencies susceptible to treatment with a PARP inhibitor or likely to be responsive to a PD-1 blocker.

b) In *Part B*, the patients recruited to one of the eight expansion arms must have advanced solid tumors of the following types:

Arm 1: Patients with relapsed, platinum-sensitive high grade epithelial, non-mucinous, ovarian cancer, fallopian tube, or primary peritoneal cancer (EOC) must meet the following criteria:

i. Patients must have at received least 2 prior platinum-containing treatments in any treatment setting.
   - Note: patients may have received additional therapy after the last platinum-containing line of treatment if the other eligibility criteria are met.

ii. Patients must have platinum-sensitive recurrent disease and must not have progressed (by Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 criteria) within 6 months of the completion of the last platinum-containing line of treatment.
   - Note: patients may receive additional non-platinum based chemotherapy for recurrence after the prior platinum-containing line of treatment if the criteria for platinum-sensitivity are met.

iii. **Arm 1a:** Known deleterious or suspected deleterious germline or somatic *BRCA1/2* mutations or with HRD.
   - If HRD or *BRCA1/2* mutation status from archival tissue is unknown or has not been previously evaluated, then the archival tissue must undergo tissue screening using a validated diagnostic test to determine eligibility. If the diagnostic test result is *BRCA1/2* or HRD positive the patient will be eligible for enrollment in Arm 1a.

iv. **Arm 1b**: Without known germline or somatic *BRCA1/2* mutations and without HRD mutation.

Arm 2: Patients with triple negative breast cancer must meet the following criteria:

i. Patients with 0-1 prior platinum-containing treatment in any treatment setting.
   - Note: patients could have received additional therapy after the last platinum-containing line of treatment if the other eligibility criteria are met.

ii. Patients who have received at least 1 but no more than 3 prior lines of treatment in the advanced or metastatic setting..

iii. Known deleterious or suspected deleterious germline or somatic *BRCA1/2* mutations or with documented HRD.

- If HRD or *BRCA1/2* mutation status from archival tissue is unknown or has not been previously evaluated, then the archival tissue must undergo tissue screening using a validated diagnostic test to determine eligibility. If the diagnostic test result is HRD positive, then the patient will be eligible for enrollment in Arm 2.
- If archival tissue is not available and the patient submits a fresh tumor biopsy, then the diagnostic test needs to demonstrate somatic *BRCA1/2* mutation or HRD positivity.

Arm 3: Patients with metastatic castration-resistant prostate cancer, including but not limited to mutations in HR pathways and/or defined by HRD algorithms, and must meet the following criteria:

i. The patient may be either chemotherapy-naïve, but must have received prior abiraterone acetate and/or enzalutamide treatment, or have previously had no more than 2 taxane-based chemotherapy lines of treatment including docetaxel and carbazitaxel. If docetaxel is used more than once, this will be considered as 1 line of treatment.

ii. At least 2 weeks since the completion of prior flutamide, bicalutamide, and nilutimide, or enzalutamide and abiraterone treatment.

iii. Documented prostate cancer with one of the following:

- Surgically or medically castrated. The testosterone levels do not need to be checked if the patient has undergone surgical castration for > 4 months. Patients receiving chemical castration should have testosterone levels checked at baseline and confirmed to be in the castrate levels (< 0.5 ng/mL or 1.735 nM). In all cases the luteinizing hormone-releasing hormone (LHRH) antagonist/agonist is to be continued in these patients.
- Patients with only non-measurable bone lesions must have disease progression based on PCWG3 with 2 or more new lesions or have prostate-specific antigen (PSA) progression before enrollment.

iv. Known deleterious or suspected deleterious germline or somatic *BRCA1/2* mutations or with documented HRD.

- If HRD or *BRCA1/2* mutation status from archival tissue is unknown or has not been previously evaluated, then the archival tissue must undergo tissue screening using a validated diagnostic test to determine eligibility. If the diagnostic test result is HRD positive, then the patient will be eligible for enrollment in Arm 3.
- If archival tissue is not available and the patient submits a fresh tumor biopsy, then the diagnostic test needs to demonstrate somatic *BRCA1/2* mutation or HRD positivity.

Arm 4: Patients with extensive-stage disease small cell lung cancer (SCLC) must meet the following criterion:

i. Patients received at least 1 but no more than 2 prior lines of treatment.

ii. At least 1 prior treatment for must have contained a platinum agent

Arm 5: Patients with *HER2*-negative gastric or gastroesophageal junction cancer must meet the following criteria:

i. Received at least 1 but no more than 2 prior lines of treatment.

ii.

Arm 6: Patients with locally advanced or metastatic urothelial (muscle-invasive bladder, ureter, urethra or renal pelvis) cancer must meet the following criteria:

i. At least 1 but no more than 2 prior lines of treatment in the advanced or metastatic disease setting.

ii. At least 1 prior treatment must have contained a platinum agent.

Arm 7: Patients with advanced or metastatic pancreatic adenocarcinoma must meet the following criteria:

i. At least 1 prior treatment for advanced or metastatic disease

ii. At least 1 prior treatment must have contained a platinum agent

iii. Patients with known deleterious germline or somatic BRCA1/2 mutations can be considered for the study even if platinum-naïve.

Arm 8: (NOTE: CLOSED TO ENROLLMENT) Patients with advanced or metastatic recurrent non-ovarian gynecological cancers (endometrial cancer, cancer of the cervix and patients with tumors known to be MMR deficient or HRD positive) must meet the following criteria:

i. Patients with a complete response, partial response or stable disease from at least 1 prior platinum-containing treatment in any treatment setting.

ii. The Sponsor medical monitor will approve tumor types for Arm 8 prior to screening.

- Note: Excluded tumor types include patients with bone or soft tissue sarcoma; central nervous system (CNS) malignancies; colorectal cancer (except microsatellite instability-high [MSI-H] colorectal cancer is permitted); cutaneous or ocular melanoma; hematologic malignancies; HER2-negative breast cancer without *BRCA* mutation; mesothelioma, papillary, follicular, medullary or Hürthle cell thyroid cancer; unknown primary malignancy.

4. Patients who were treated with chemotherapy or any investigational therapies, if eligible, must have been completed at least 4 weeks or at least 5 half-lives (whichever is longer, but no less than 3 weeks) before the study drug administration, and all AEs have either returned to baseline or stabilized.

5. At least 2 weeks from palliative radiotherapy.

6. Patients must have archival tumor tissue or agree to a tumor biopsy for biomarkers analysis unless previously discussed with sponsor's medical monitor or its designee (fresh tumor biopsies are recommended at baseline in patients with readily accessible tumor lesions who can safely undergo the procedure and who consent to the biopsies). Patients with ovarian, fallopian tube, primary peritoneal, or breast cancer in Part A and all patients enrolled in Part B must also agree to provide fresh blood sample at the baseline for the evaluation of *BRCA* mutations and/or confirmation of prior *BRCA* results or other homologous recombination deficiency mutations even if it was previously tested.

7. Patients must have measurable disease as defined in RECIST v1.1. Patients with metastatic castration-resistant prostate cancer and epithelial, non-mucinous, ovarian cancer, fallopian tube, or primary peritoneal cancer may use separate disease-specific criteria (see Appendix 4, Appendix 6, and Appendix 8).

8. Patients must be a male or female ≥ 18 years of age on the day of signing informed consent.

9. Patients must have an ECOG Performance Status (PS) ≤ 1 (Appendix 3).

10. Patients must have a life expectancy ≥ 12 weeks.

11. Patient must have adequate organ function as indicated by the following laboratory values independent of transfusion within 2 weeks:

    a) Absolute neutrophil count (ANC) ≥ 1,500/mL.

    b) Platelets ≥ 100,000/mL.

    c) Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L.

    d) Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 18).

    e) Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) (On fractionation ≤ 90% of total bilirubin should be unconjugated. Total bilirubin must be < 4 X ULN for patients with Gilbert's syndrome).

    f) Aspartate aminotransferase (serum glutamic oxaloacetic transaminase [SGOT]) and alanine aminotransferase (serum glutamic pyruvic transaminase [SGPT]) ≤ 3 × ULN.

    g) International normalized ratio (INR) ≤ 1.5 × ULN (≤ 2.5 × ULN if on anticoagulants).

12. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study (Appendix 17), and for at least 6 months after the last dose of investigational drug, and have a negative serum pregnancy test within 7 days of the first dose of study drug(s).

13. Non-sterile males and their female partners must be willing to use a highly effective method of birth control for the duration of the study and for at least 6 months after the last dose of investigational drug (see Appendix 17). Nonsterile males must avoid sperm donation for the duration of the study and for at least 6 months after last study drug.

14. Female patient must agree not to breastfeed starting at screening and throughout the study period, and for 6 months after the final study drug administration.

5.2.2 Exclusion Criteria

Patients will not be enrolled in the study for any of the following reasons:

1. Patients with ovarian cancer who have platinum-resistant/refractory disease, defined as progressive disease at the first RECIST v1.1 tumor assessment while receiving platinum-containing chemotherapy.

2. Patient has history of severe hypersensitivity reactions to other monoclonal antibodies (mAbs).

3. Any major surgery within 28 days before first dose of study drugs.

4. Prior allogeneic stem cell transplantation or organ transplantation.

5. Patients with toxicities (as a result of prior anticancer therapy) which have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy and specific laboratory abnormalities).

6. Concurrent participation in another clinical trial.

7. Prior malignancy within the previous 2 years except for locally curable non-melanoma dermatologic cancers that have been treated with curative intent and are at very low risk for recurrence, such as basal or squamous cell skin cancer, or carcinoma *in situ* of the skin, cervix, breast, bladder, or prostate.

8. Symptomatic CNS metastasis or leptomeningeal disease.

   Note: Baseline MRI of the brain and spinal cord is required for SCLC patients enrolled in Arm 4

   Note: Patients with previously treated CNS metastatic disease are eligible for any arm if CNS metastatic disease is asymptomatic, clinically stable, and does not require corticosteroids or anticonvulsants within a minimum of 4 weeks of enrollment.

9. Prior therapies targeting PD-1, programmed death-ligand 1 (PD-L1), or PARP.

10. Active autoimmune diseases or history of autoimmune diseases that may relapse (Appendix 15).

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

    a) Controlled Type I diabetes.

    b) Hypothyroidism managed with no treatment other than with hormone replacement therapy.

    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.

11. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication within 2 weeks of the study drug administration.

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

    a) Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent).

    b) Topical, ocular, intra-articular, intranasal, or inhalational 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).

12. With severe chronic or active infections requiring systemic antibacterial, antifungal or antiviral therapy, including tuberculosis infection, etc.

13. History of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc.

14. History of non-viral hepatitis or cirrhosis.

15. Positive human immunodeficiency virus (HIV) status.

16. A known history of hepatitis B virus (HBV), or hepatitis C virus (HCV) infection.

17. History of alcohol abuse.

18. Underlying medical conditions or alcohol or drug abuse or dependence that, in the investigator's opinion, will be unfavorable for the administration of study drug or affect the explanation of drug toxicity or adverse events; or insufficient compliance during the study according to investigator's judgement.

19. Inability to swallow oral medications (capsules and tablets) without chewing, breaking, crushing, opening or otherwise altering the product formulation. Patients should not have gastrointestinal illnesses that would preclude the absorption of pamiparib, which is an oral agent. Please note Appendix 12 for a list of prohibited medications that are associated with possible interactions with pamiparib.

20. Has been administered a live vaccine within 4 weeks (28 days) of initiation of study therapy. Patients are eligible if 28 days have elapsed since receipt of vaccine and initiation of study treatment. (NOTE: seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines; and are not allowed).

21. Any of the following cardiovascular criteria:

    a) Current evidence of cardiac ischemia.

    b) Current symptomatic pulmonary embolism.

    c) Acute myocardial infarction ≤ 6 months prior to Day 1.

    d) Heart failure of New York Heart Association Classification III or IV (see Appendix 16) ≤ 6 months prior to Day 1.

    e) Grade ≥ 2 ventricular arrhythmia ≤ 6 months prior to Day 1.

    f) History of cerebrovascular accident within 6 months before first dose of study drugs.

22. Use or have anticipated need for food or drugs known to be strong or moderate cytochrome P450 (CYP)3A inhibitors or strong CYP3A inducers ≤ 10 days (or ≤ 5 half-lives, whichever is shorter) prior to Day 1 (Appendix 12).

5.2.3 Other Eligibility Criteria Considerations

To assess any potential impact on the patient eligibility with regard to safety, the investigator must refer to the IB for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the investigational product being used in this study. [12, 19] Any patient in this study who continues to demonstrate objective clinical benefit at the end of a 2-year treatment duration may continue in the study or on treatment.

5.2.4 Patient Restrictions

The following restrictions may affect patient participation in this study:

- The investigator must be informed as soon as possible (ASAP) about any medications or other study agents taken from the time of screening until the patient is discharged from the study.
- Consumption of grapefruit and Seville oranges or their juices are not allowed throughout the study. No other dietary restrictions will apply.

5.2.5 Patient Discontinuation and Withdrawal

Patients may withdraw at any time or be discontinued from the study at the discretion of the investigator should any untoward adverse effects occur. In addition, a patient may be withdrawn by the investigator or the sponsor if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the sponsor immediately when a patient has been discontinued/withdrawn due to an adverse event. When a patient discontinues/withdraws, all applicable evaluations scheduled for the final study visit should be performed at the time of discontinuation. Any adverse event which is present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

In the event that a patient is prematurely discontinued from the study at any time due to an AE (as defined in Section 10.3), the procedures stated in Section 8.5 must be followed.

In addition to the post-study assessments, if a DLT occurs, the investigator will obtain, when possible, a blood sample for analysis of serum tislelizumab and plasma pamiparib concentration.

Patients who discontinue or are withdrawn for any reason other than DLT during Cycle 1 of any DL will be considered for replacement after due consideration by the sponsor and/or SMC if the minimum number of patients needed for the evaluation of MTD is not met.

Premature discontinuation of tislelizumab and pamiparib would be any time when a patient is discontinued for reasons other than unacceptable toxicity. The reason for discontinuation of the study drugs will be recorded in the electronic case report form (eCRF). These reasons may include:

- Withdrawal of consent by the patient;
- Discontinuation of tislelizumab/pamiparib by the sponsor;
- Pregnancy;
- Any significant AE that compromises the patient's ability to participate in the study;

- The investigator or sponsor determines it is in the best interest of the patient;
- Death;
- Lost to follow up;
- Confirmed progression of disease at any time during the study (refer to Section 8.8.1);
- Significant deviation from the protocol by the investigator without the consent of the sponsor.

5.2.5.1 Patients Withdraw Prior to Documentation of Progressive Disease

Patients who stop treatment prior to documentation of progressive disease (PD) will undergo repeated imaging for tumor response assessments during the study approximately every 9 ± 1 weeks in the first 12 months and approximately every 12 ± 1 weeks thereafter until unequivocal PD is documented or the patient starts new anticancer therapies or patient withdraws consent from the trial. This imaging schedule will be maintained and will never be adjusted regardless of any intermediate unscheduled scans. Patients who withdraw from the study for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort will be made to confirm a clinical diagnosis of PD by imaging.

6.0 STUDY TREATMENTS

6.1 Description of Investigational Product

Tislelizumab is a monoclonal antibody drug which is formulated for IV injection in a single-use vial (20R glass, USP type I) containing a total of 100 mg antibody in 10 mL of isotonic solution. See Section 6.5 below for handling and product storage conditions.

Refer to the IB for more detailed information on the product description for tislelizumab. [12]

The patients will receive pamiparib as 10 mg or 40 mg [redacted] capsules, depending on dose level and availability ([redacted] capsules for [redacted] mg dose and s[redacted] capsules for [redacted] mg dose). BGB-290 drug product is also supplied as a [redacted] mg strength in [redacted] capsules ([redacted] capsule shells).

Refer to the IB for more detailed information on the product description for pamiparib. [19]

6.2 Dosage and Administration

The treatments to be administered during the study are:

- Tislelizumab 10 mL single-use vial for IV infusion
- Pamiparib 10 mg, 20 mg, and 40 mg capsules for oral use

Tislelizumab will be administered as an IV infusion, every 3 weeks. Pamiparib will be administered orally twice daily, once in the morning and once in the evening 12 hours apart. The starting dose of each agent will not exceed the highest DL at which no DLT was reported during the first-in-human ongoing trials.

In both Parts A and B of the study, tislelizumab will be administered as an IV infusion on Day 1 of a 21-day cycle, and pamiparib will be taken orally twice daily starting from Day 1.

On the first day where both study drugs are administered, the morning dose of pamiparib should be given at least 30 minutes prior to the IV infusion of tislelizumab. Subsequently in the evening, pamiparib administration is repeated. On subsequent days of each cycle, twice daily dosing of pamiparib will continue in the morning and evening (at approximately the same time), as a 20-day period of continuous drug administration. During subsequent cycles, the treatment repeats every 21 days for 34 cycles (2 years) from Day 1 to Day 21.

If a dose of pamiparib is not taken at the scheduled time, it can be taken ASAP within 2 hours of the scheduled time and return to the normal schedule for the next dose. Extra dose of pamiparib should not be taken to make up for the missed dose. Patients will be instructed to swallow the capsules whole, in rapid succession, with water. Pamiparib can be administered with or without food.

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

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

The initial infusion (cycle 1, day 1) will be delivered over 60 minutes; if this is well tolerated, then the subsequent infusions may be administered over 30 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (refer to Section 7.0).

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of irAEs and infusion-related reactions are provided in detail in Section 10.13.4 and Appendix 10.

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

For management of toxicity refer to Section 5.1.4.

6.3 Patient Identification

Patients will be identified by a patient number. Each patient enrolled in this study will receive a unique patient number after signing the informed consent.

Each patient receiving concomitant tislelizumab and pamiparib will also receive a treatment allocation number. Patient and treatment numbers will be assigned in chronological order starting with the lowest number. Once a patient number and treatment number have been assigned to a patient, it cannot be reassigned to any other patient.

If a patient is replaced, the replacement patient will be assigned the next available patient number.

6.4 Packaging and Labeling

Tislelizumab has been aseptically filled in 20R glass vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial contains 10 mL of the drug solution. The vials are packaged in cartoon box.

The capsule supplies of pamiparib will be provided in a child-resistant closure and be open-labeled with space to enter the patient's treatment number and period number.

The primary labeling on the tislelizumab vials and pamiparib child-resistant closure contain following information: protocol number, content and quantity of study drugs, batch number, expiry date, storage instructions, and administration instructions. The contents of the label will be in accordance with all applicable regulatory requirements.

6.5 Handling and Storage

The investigational products will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures.

Investigational products must be dispensed or administered according to procedures described herein. Only patients enrolled in the study may receive investigational products, in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or administer investigational products. All investigational products must be stored in a secure area with access limited to the investigator and authorized study center personnel and under physical conditions that are consistent with investigational product-specific requirements. The investigational products, tislelizumab vials must be kept at 2ºC to 8ºC and pamiparib capsules must be kept at 15ºC to 30°C.

Tislelizumab does not contain a preservative. The diluted solutions of tislelizumab cannot be frozen, and must be stored at:

- Either room temperature at 20°C to 25°C (68°F to 77°F) for no more than 4 hours from the time of reconstitution. This includes room temperature storage of tislelizumab vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Or under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

6.6 Product Accountability

The investigator is responsible for investigational products accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain investigational products accountability records throughout the course of the study. This person(s) will document the amount of investigational products received from the sponsor, the amount supplied and/or administered to and returned by patients, if applicable.

After completion of the study, all unused investigational products will be inventoried and packaged for return shipment by the hospital unit pharmacist. The inventoried supplies will be returned to the sponsor or destroyed on site, after receiving written sponsor approval.

6.7 Assessment of Compliance

On all visits to the study center, patients will be questioned in regard to compliance with study instructions.

The investigator and/or study personnel will keep accurate records of the quantities of capsules dispensed and used by each patient. This information must be captured in the source document at the end of each cycle. The investigator is responsible for pamiparib accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain pamiparib accountability records throughout the course of the study. This person will document the amount of pamiparib received from the sponsor, the amount supplied, and/or administered to and returned by patients, if applicable.

6.8 Treatment of Investigational Product Overdose

Any overdose or incorrect administration of study drug 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 adverse event eCRF. If an overdose or incorrect administration of study treatment takes place, the sponsor or designee is required to be notified as soon as possible. Supportive care measures should be administered as appropriate.

6.9 Medical Care of Patients after the End of Trial

After a patient has discontinued from the study, other treatment options decided by the treating physician may be implemented, if required, in accordance with the investigational site's common medical practice and depending on the patient's individual medical needs.

6.10 Occupational Safety

The investigational products are not expected to pose significant occupational safety risk to the study center personnel under normal conditions of use and administration. A material safety data sheet describing occupational hazards and recommended handling precautions will be provided to the investigator, where this is required by local laws, or is available upon request from the sponsor.

7.0 CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

7.1 Permitted Medications

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications taken during the study will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal medicines, mushroom-containing products, dietary supplements and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date will also be included on the CRF.

All concomitant medications received within 30 days before the first dose of study medication and 30 days after the last dose of study medication should be recorded.

The eCRF entry must include the dose, regimen, route, tumor type, and start and stop dates of use of the prior and concomitant medication.

7.2 Prohibited Medications

Patients may receive other medications that the investigator deems to be medically necessary, with the specific exception of non-protocol specified chemotherapy, therapeutic radiotherapy, immunotherapy, anti-neoplastic biological therapy or investigational agents other than tislelizumab and pamiparib. External beam radiation therapy is allowed only for those patients who require radiation therapy for the treatment of pain secondary to bone metastases. Radiation therapy provided for therapeutic intent will be considered anticancer treatment. Patients who in the assessment by the investigator require the use of any of the aforementioned treatments for clinical management should be removed from the study. Bisphosphonate or denosumab use is permitted if the patient has already been on it for 3 or more months and on a stable dose.

Patients with active autoimmune disease or history of autoimmune disease that might recur, or who require immune suppressive treatment including systemic corticosteroids, should be excluded. These include but are not limited to patients with a history of immune-related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis, systemic lupus erythematosus, connective tissue diseases, scleroderma, inflammatory bowel disease, Crohn's, ulcerative colitis, hepatitis, TEN, Stevens-Johnson syndrome, or anti-phospholipid syndrome.

Patients are prohibited from receiving any live vaccines within 4 weeks (28 days) of initiation of study therapy. Patients are eligible if 28 days have elapsed since receipt of vaccine and

initiation of study treatment. (NOTE: seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines; and are not allowed.)

The primary metabolic pathway for pamiparib involves the cytochrome P450 (CYP)3A isoform. The compounds/substances presented in Appendix 12 are associated with possible interactions with pamiparib through the CYP3A metabolic pathway as well as other various metabolic interactions and are prohibited. [85]

Preliminary *in vitro* screening assays revealed pamiparib is not a strong inhibitor of human CYP isoenzymes tested. It is a moderate inhibitor of CYP2C9 (IC_{50} = 6.48 μM). Patients taking the medications presented in Appendix 13 need to be closely monitored for AEs. [85]

In addition to CYP3A and CYP2C9, pamiparib can also be metabolized by CYP2C8 in human liver microsomes, but to a lesser extent. The compounds/substances presented in Appendix 14 are associated with possible interactions with pamiparib through the CYP2C8 metabolic pathway and should also be used with caution. [85] The following website can be used as an alternate reference: medicine.iupui.edu/clinpharm/ddis

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

Section 5.2.2 of the protocol (Exclusion Criteria) describes other medications which are prohibited in this study.

7.2.1 Other Study Considerations

The following nondrug therapies must not be administered during the study (within 28 days before the start of study treatment):

- Major surgery (excluding prior diagnostic biopsy)
- Herbal remedies with immune-stimulating properties (ie, mistletoe extract) or known to potentially interfere with major organ function (ie, hypericin). Alternative medicines for cancer therapy or for altering the immune system.
- Drugs that are known to cause prolongation in QT/QTc interval and/or induce Torsades des Pointes (Appendix 17).
- Patients should avoid alcohol consumption and should avoid any other drugs or supplements during the study not prescribed by the attending physician.

8.0 STUDY ASSESSMENTS

8.1 Prescreening (Part B Only)

Patients in Arm 1 (ovarian cancer), Arm 2 (TNBC), and Arm 3 (mCRPC) in Part B of the study who have unknown biomarker status will be permitted to have a pre-screening period for HRD status. A separate pre-screening informed consent must be obtained for patients in these arms.

An archival tumor sample will be obtained for pre-screening purpose for patients in Arm 1 (ovarian cancer), Arm 2 (TNBC), and Arm 3 (mCRPC). If an archival tumor sample is not available, a fresh tumor biopsy of an accessible tumor lesion will be obtained for the pre-screening purpose.

The following will be performed during pre-screening tumor sample collection:

- Obtain written informed consent from the patient or the patient's legal representative to perform a tumor biopsy if it is required for the purpose of meeting the eligibility criteria of the study
- Prepare tumor samples and ship to the qualified central laboratory for mutation analysis as specified in the Laboratory Manual

Patients in Arm 1 (ovarian cancer) will proceed to the screening phase once they have signed the pre-screening informed consent and submitted their tumor tissue sample. Their biomarker status does not preclude their eligibility while both Arm 1a and Arm 1b remain open and enrolling. When either Arm 1a or Arm 1b is 50% enrolled, then biomarker status must be determined prior to patients proceeding to the screening phase to avoid over-enrollment to the cohort.

Patients in Arm 2 (TNBC) and Arm 3 (mCRPC) who submit archival tissue with proven mutational positivity are eligible for enrollment in Arm 2 or Arm 3. If a diagnostic test result on submitted archival tissue is HRD negative or is a failure, then the patient is **not** eligible for enrollment.

For patients in Arm 2 (TNBC) and Arm 3 (mCRPC) who submit a fresh tumor biopsy, their biomarker status will determine whether they will be eligible for enrollment in Arm 2 or Arm 3, respectively. If the pre-screening biopsy demonstrates germline or somatic *BRCA1/2* mutation or HRD positivity, then the patient would be eligible for enrollment in Arm 2 or Arm 3. If the results of the mutational test on the pre-screening biopsy is HRD negative or is a failure, then the patient is **not** eligible for enrollment.

8.2 Screening

A signed, written informed consent must be obtained prior to screening assessments and before any study-specific assessments are initiated. The study-specific assessments and procedures

are shown in the study assessments and procedures schedule in Table 3 and Table 5. The PK sampling time points are presented in Table 4 and Table 6.

The screening assessments are the same for Part A and Part B of the study.

Re-screening of laboratory parameters which do not meet the specified inclusion criteria will be allowed once per patient within the screening period window (Day -28 to Day -1).

Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer will undergo pulmonary function testing which may include but is not limited to spirometry and assessment of diffusion capacity done during the Screening period to assist the determination of suitability on the study (see Table 5).

8.2.1 Demographic and Baseline Assessments

Demographic and baseline assessments are the same for Part A and Part B.

Demographic data will include gender, age or date of birth, race, and ethnicity. This data will be captured in the eCRF.

Having given consent, patients will be required to undergo a medical screen to determine whether they are eligible to participate in the study according to the criteria listed in Section 5.2. Screening assessments will be completed within 28 days prior to the first dose of the investigational product. If screening laboratory tests are completed within 14 days prior to first dose, pre-dose samples on Day 1 of Cycle 1 will not be repeated. The screening assessments will include:

- Baseline demographics
- Medical history including date of first cancer diagnosis, histology, prior anti-neoplastic therapy, and current sites of disease (Section 8.3.3)
- Concurrent medications, herbal medications, mushroom-containing products, and dietary supplements
- Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, temperature, and respiratory rate)
- Physical examinations, including height (in cm), body weight (in kg), and body mass index (in kg/m^2) (NOTE: Body Mass Index will be collected in Part A only)
- Ophthalmologic examination

- Evaluation of AEs (After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported)
- ECOG performance status (refer to Appendix 3)
- 12-lead electrocardiogram (ECG) within 14 days of Cycle 1 Day 1
- Laboratory tests: complete blood count (CBC), and serum chemistry, including serum testosterone for prostate cancer patients; urinalysis; pregnancy test (within 7 days of the first investigational product administration), and PT/aPTT
- Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb), HCV antibody, HIV 1/2 antibodies, and HBV DNA and/or HCV RNA if needed. Hepatitis E antibody or HEV RNA should be performed at baseline if testing is available.
- [redacted]
- CT/MRI scan will be performed within 28 days prior to the first administration of investigational product.
    - Bone scans will be performed within 56 days prior to the administration of investigational product.
    - Any patient with a history of CNS metastases will be required to undergo CT/MRI at baseline to ensure all sites of disease are evaluated per RECIST v1.1 criteria. Patients with newly diagnosed brain metastases on screening CT/MRI will be required to be treated for brain metastasis with standard of care treatments and be off corticosteroids prior to study entry.
    - All patients with SCLC are required to have CT/MRI of the brain at baseline
- A blood sample must be collected at screening stage for ovarian, fallopian tube, primary peritoneal, and breast cancer patients for germline *BRCA* and/or other mutations analysis for patients enrolled in Part A. All patients in Part B, regardless of tumor type, will have blood drawn for *BRCA* and/or other mutational analysis, even if it has been previously tested.
- Collection of archival tumor specimen or fresh tumor biopsy. If tumor samples have been collected at pre-screening stage, there is no need to collect it again during screening.

- [redacted]

The above-mentioned data will be captured in the source documents. Any results falling outside the normal range will be repeated at the discretion of the investigator.

8.2.2 Females of Childbearing Potential and Contraception

See Appendix 17 for The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials including the use of highly effective forms of birth control.

8.3 Assessments During Treatment

Safety assessments should be performed at all visits to the study center and throughout the study. The list of events and the time when they will be performed are presented in Table 3 for Part A and in Table 5 for Part B (if appropriate).

8.3.1 Laboratory Evaluation

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. Laboratory assessments need not be repeated on Day 1 if these assessments were completed for screening within 14 days of the first administration of the investigational product.

Routine laboratory tests (eg, CBC with differential; comprehensive serum chemistry panel; PT/INR and aPTT; immunoglobulins; urinalysis; urine and serum β-HCG) will be performed by the local study site laboratory or their contract laboratory. Patient treatment and overall management decisions will be based on local laboratory data. Details regarding the amount of blood drawn for laboratory testing are provided in a laboratory reference document.

Clinical chemistry, hematology, and urinalysis will be performed up to 14 days prior to Cycle 1 Day 1 and at the time points specified in Table 3 and Table 5 (for Parts A and B, respectively), and also at mandatory Safety Follow-up Visits.

PT/INR and aPTT should be collected at Screening and if a Grade 2 or higher hepatic AE occurs, as specified in Table 5. Coagulation parameters should be evaluated more frequently during the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.

In the event of neutropenia (ANC < 1000/mm^3), thrombocytopenia (platelets < 50,000/mm^3), or Grade 3 clinical chemistry toxicity, the relevant assessments will be conducted as frequent as the physician feels needed until toxicity resolves to ≤ Grade 2. If warranted, additional

testing can also be done, or the relevant tests done more frequently in accordance with institutional guidelines. All patients, who have any Grade 3 or Grade 4 laboratory abnormalities at the Safety Follow-up Visits, must be followed up until they have returned to ≤ Grade 2 or baseline, unless these are not likely to improve due to the underlying disease.

Thyroid function which includes T3, T4, and TSH will be assessed at pre-dose of Day 1 of every cycle and at the mandatory Safety Follow-up Visits. If feasible, early morning adrenocorticotropic hormone (ACTH) and cortisol will be obtained as part of the screening assessments and only repeated during the study if it is clinically indicated. Analysis will be performed by the local study site laboratory.

For Part B, thyroid function will be collected at screening, every 2 cycles, or more frequently as clinically indicated during treatment, and at the mandatory Safety Follow-up Visits.

Analysis of IgG and IgM will be performed at pre-dose of Day 1 every cycle in first 12 months, approximately every 2 months thereafter, and at Safety Follow-up Visits in Part A only. Analysis will be performed by the local study site laboratory.

[redacted]

A central laboratory may be used in this study. Investigators may use results from local laboratories for assessing eligibility, safety monitoring and dosing decision.

8.3.2 Physical Examination, Ophthalmologic Examinations and Vital Signs

A complete physical examination, vital signs, and weight as well as ophthalmologic examination will be performed at the time points specified in Table 3 and in Table 5. In Part B, a full physical examination will be performed at the Screening and Safety Follow-up visits, at all other times targeted or symptoms-directed physical examination, at the investigators discretion is permitted. A full physical examination includes: examination of general appearance; head, eyes, ears, nose and throat; neck; heart; chest (including lungs); abdomen; extremities; skin; lymph nodes; cardio-vascular; and neurological status.

ECOG performance status will be evaluated at time points specified in Table 3 and in Table 5.

Vital signs will include body temperature, heart rate, respiratory rate, and blood pressure. To the extent feasible, blood pressure will be taken on the same arm throughout the study. A large

cuff should be used for obese patients. Patients must be resting in a sitting position for 10 minutes prior to obtaining vital signs. If blood pressure is > 150/100 in a patient without a history of hypertension, or increased > 20 mmHg (diastolic) from baseline measurement in a patient with a previous history of hypertension, the assessment should be repeated in 10 minutes for confirmation.

Ophthalmologic Examination

Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed at the Screening Visit. Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of study entry may be used for the Screening evaluation. Patients will undergo repeat assessments approximately every 15 weeks (± 7 days) during study treatment and a final assessment < 30 days after the last dose of tislelizumab study treatment.

In addition, Investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance (see Appendix 10).

8.3.3 Medical History/ Prior Medications

The medical history and prior medications assessments are the same for Part A and Part B.

The medical history and current/ relevant prior medications (within the past 12 months) are recorded at Screening.

History of treatment for the primary diagnosis, including prior systemic, radiation treatment, and surgical treatment will be recorded. Radiographic studies performed prior to study entry may be collected for review by the investigator. Date and response to last platinum-containing chemotherapy treatment must be documented unless no platinum-containing treatment has been received. Date of disease progression after completing platinum-containing regimen must be documented.

8.3.4 Electrocardiogram

Part A:

Electrocardiograms will be obtained at the time points specified in Table 3 and Table 4 at Screening within 14 days of Cycle 1 Day 1 as baseline, and at the mandatory Safety Follow-up Visits. Additional ECGs may be obtained if clinically indicated.

Part B:

Electrocardiograms will be obtained at the time points specified in Table 5 and Table 6 at Screening within 14 days of Day 1 of study treatment as baseline, as clinically indicated during the treatment period, and at the mandatory Safety Follow-up Visits.

For both Part A and Part B:

Triplicate ECG recordings (3 readings in rapid succession and not more than 2 minutes apart) will be obtained locally at the site in conjunction with blood sampling for pamiparib pharmacokinetics at the times specified in Table 4 and Table 6. ECGs required at timepoints that do not include a PK sample do not need to be triplicate assessments.

Significant QTc prolongation will be defined as an interval ≥ 500 msec or an interval which increases by ≥ 60 msec over baseline. Either of these conditions should be documented on two or more ECG tracings separated by at least 5 minutes. The ECG tracing should be examined and a manual measurement by a trained physician should be performed to assess the accuracy of the equipment being used.

If a patient has significant QTc prolongation：

- He/she will be withdrawn from the investigational product administration if the investigator and/or the medical monitor determine the patient is at risk.
- The patient will be monitored, treated appropriately, and closely followed (ECGs at least three times per week) until the QT and QTc interval return to within 30 msec of baseline.
- The medical monitor will be consulted prior to administering further doses or re-challenging with pamiparib.
- The medical monitor will be consulted prior to administering further pamiparib.

8.3.5 Serum Tumor Markers

The serum tumor marker collection is to occur for Part A and Part B as per Table 3 and Table 5.

Standard tumor markers (as appropriate for a given tumor type) will be collected at [redacted]. Analysis will be performed by the local study site laboratory where feasible. If not feasible, tests will be performed by a certified central laboratory.

For both Part A and Part B:

PSA Measurements

Increases and decreases in PSA will be tracked to assess PSA responses by the PCWG3 criteria (refer to Appendix 6). PSA changes from baseline (either increment or decline) and maximal change in PSA will be recorded and responses assigned by PCWG3 criteria. PSA responses and progression must be confirmed 28 days later.

Although serial PSA will be measured on this study and PSA progression documented by the PCWG3 criteria, the PSA value on its own is not considered a reliable measure of clinical benefit and does not correlate tightly with survival. PSA flares may occur early in the treatment and may therefore confound response assessment. Additionally, there is emerging data that PARP-1 is implicated in multiple other essential cellular functions separate from DNA repair including ETS gene-mediated transcription regulation which may have a bearing on the response assessments by PSA. PSA reading should not be applied as the sole criteria to consider treatment discontinuation. In absence of evidence of radiological or clinical evidence of disease progression, patients with mCRPC should continue in the study despite an increment in PSA. Overall, therefore patients will not be taken off trial purely for rising PSA levels in the absence of worsening scans and symptoms since PARP inhibitors may impact tumor growth without impacting PSA secretion. PSA response and PSA progression will be defined according to the consensus guidelines of the PCWG3 criteria (refer to Appendix 6).

8.3.6 Computed Tomography

Tumor imaging is the same for Part A and Part B as per Table 3 and Table 5.

Tumor imaging (CT or MRI, with preference for CT) will be performed within 28 days prior to enrollment, and while on study approximately every 9 ± 1 weeks in the first 12 months and approximately every 12 ± 1 weeks thereafter and at the Safety Follow-up. Positron emission tomography (PET) imaging scans for treatment response evaluation are not allowed in this study.

A CT scan of the thorax, abdomen, and pelvis plus other relevant evaluations as appropriate, including bone scan for patients with bone metastasis, will be performed to assess all known disease. All known disease must be documented at baseline as target or non-target lesions using RECIST v1.1. The CT scan will be used for the evaluation of RECIST v1.1 by the investigator at each study center.

A baseline brain MRI is required for all patients in the SCLC cohort. Patients in other cohorts with a known history of brain metastases must have an MRI to document the status of existing, previously treated brain metastases. Brain metastases should be evaluated throughout the study

as part of the assessment of anti-tumor activity from the combination of tislelizumab and pamiparib.

Unless contraindicated, intravenous contrast product must be used to maximize visualization of all lesions. Five millimeter (mm) contiguous scans at baseline and subsequent scanning approximately every 9 ± 1 weeks in the first 12 months and approximately every 12 ± 1 weeks thereafter until progression, as calculated by the date of the first administration of the investigational product) until progression, with mandatory imaging coverage from thoracic inlet to symphysis pubis should be performed. Patients who are at increased risk of allergic reaction to iodinated contrast media should not have enhanced CT, but should instead be provided magnetic resonance imaging (MRI) with gadolinium enhancement patient to local protocol, with mandatory imaging coverage from thoracic inlet to symphysis pubis plus unenhanced CT scanning with coverage from the thoracic inlet to the inferior costophrenic recess. Patients with bone pain or biochemical changes suggestive of bony disease without other clear explanation should have a bone scan at baseline and if bone metastases are documented should then have bone scans or other appropriate imaging examinations as clinically indicated. New lesions on a bone scan should be assessed with caution and, unless otherwise explained, should be imaged by CT or focal radiographs.

The same imaging technique should be used in a patient throughout the study. After first documentation of response (CR or PR), imaging performed at the next regularly scheduled time point will be used for response confirmation. PD suspected as pseudo-progression needs to be confirmed in a subsequent imaging at least 4 weeks later or at the next regularly scheduled time point before discontinuation of study treatment as described in Section 8.8.1.

Technetium bone scans will be used to assess bone lesions. In patients with prostate cancer baseline bone scans will be performed during the screening window, and repeat bone scans will be performed approximately every 9 ± 1 weeks in the first 12 months and approximately every 12 ± 1 weeks thereafter until progression to keep with the schedule of the CT scans. Bone scan results will be reported as either no lesions or lesions present along with the number of bone lesions. Disease progression by bone scan will be defined per the PCWG3 (refer to Appendix 6); progression is defined as 2 new bone lesions at the first ‘progression’ scan, confirmed by a subsequent scan at least 6 weeks later with the presence of 2 additional lesions.

Patients who stop treatment prior to documentation of PD will undergo repeated imaging for tumor response assessments during the study approximately every 9 ± 1 weeks in the first 12 months and approximately every 12 ± 1 weeks thereafter until unequivocal PD is documented or the patient starts new anticancer therapies or patient withdraws consent from the trial. This imaging schedule will be maintained and will never be adjusted regardless of any intermediate unscheduled scans. Patients who withdraw from the study for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo

appropriate imaging to confirm PD. Every effort will be made to confirm a clinical diagnosis of PD by imaging.

8.3.7 Optional Tumor Biopsy

PART A and B:

For those patients who consent to fresh biopsy, an optional biopsy for biomarker analysis during the third week of the first cycle is recommended in order to assess pharmacodynamics effects and resistance mechanisms (Section 8.11). For the patients who have confirmed disease progression, an optional biopsy may be taken at the Safety Follow-up visit only if the lesion to be biopsied is at low risk for complications and the patient can safely undergo the procedure. The purpose of this biopsy sample is to evaluate mechanisms of resistance to study treatment (s). If feasible, any follow up biopsy should be ideally taken from the same anatomical location as the baseline biopsy. Additional written patient consent is required for optional fresh tumor biopsies.

8.3.8 Adverse Events

Adverse event collection is the same for Part A and Part B as per Table 3 and Table 5.

All AEs and SAEs, regardless of the relationship to the investigational product, will be collected from signing the informed consent form (ICF) and throughout the study until 30 days after the last study treatment or initiation of new anticancer therapy. The exception are irAEs, which will be recorded up to 90 days after the last dose of tislelizumab, regardless of initiation of subsequent anticancer therapy.

8.4 Safety Assessments

Overall safety assessment is the same for Part A and Part B as per Table 3 and Table 5.

Vital signs, weight, physical examinations, ophthalmologic examinations, ECOG performance status, ECGs and laboratory safety tests (eg, PT/aPTT, urinalysis, CBC, serum chemistries, autoantibodies, thyroid function, viral antigen reactions) will be obtained and assessed at designated intervals throughout the study (see Table 3 and Table 5). Special attention will be given to irAEs (eg, gut, skin, lung, liver, kidney, endocrine organs, others). If irAE of the liver occurs, a biopsy of the liver is strongly encouraged.

Adverse events will be graded and recorded throughout the study according to NCI-CTCAE, version 4.03. [86] Characterization of toxicities will include severity, duration, and time to onset. Safety endpoints will include all types of AEs, in addition to laboratory safety assessments, ECOG performance scale status, ECGs, and vital signs.

8.4.1 Safety Evaluation

The continuous safety evaluation will be performed by the sponsor, the coordinating investigator, and investigators. In Part A, a SMC is established for the determination of DLs to be administered during dose escalation phase and dose regimens in this study. Details of the safety monitoring process will be specified in a dedicated study management plan.

The SMC consists of the coordinating investigator, selected recruiting investigators, the sponsor's medical monitor, and the contract research organization's (CRO) medical monitor. Ad hoc members will be consulted as needed and may include, but are not restricted to the biostatistician and pharmacokinetic scientist.

The SMC will decide on DLTs relevant for the treatment and will decide by consensus on dose escalation, dose de-escalation, or suspension of enrollment based on safety and/or on PK data.

Before moving to the next dose level, the SMC will review all safety data available to determine whether recruitment to the next cohort should be initiated. The SMC will determine when no further dose escalation is appropriate and whether the MTD will be defined as a preceding dose or an intermediate dose.

The SMC will meet for cohort safety reviews after all patients in a dosing cohort have completed the first treatment cycle. All available safety data will also be provided for patients who discontinue prior to this time. Safety data from prior cohorts may also be presented. The decision to escalate dose and the determination of the MTD will be based on the cohort safety reviews. The SMC will review any protocol violations that may have impacted evaluation of potential DLT. The SMC may weigh collective evidence and may determine a DLT for reasons in addition to those explicitly stated in the final protocol.

Response from all SMC members, or their designees, shall be required for each escalation/review.

Adequate time for review of results will be given to SMC members (approximately 1 to 2 business days). Enrollment in subsequent DLs will be put "on hold" during each review period, pending the decision of the SMC.

The SMC decision points may fall into one of the categories detailed below:

- Escalate to a higher dose
- Recruit additional patients into existing dose level or expansion cohort
- Explore any other DLs; ie, an intermediate, not pre-defined, previously evaluated or not previously evaluated dose level below MTD
- Stop escalation and investigate lower dose(s)

- End part of the study
- End the overall study

Decisions will be made using the criteria defined within the protocol (see Section 5.1.1). The SMC will make the dose escalation decisions.

The SMC may decide to evaluate an intermediate, not pre-defined, previously evaluated or not previously-evaluated dose or a less frequent dosing schedule that will not exceed the MTD level, if evaluation of toxicity at such a dose or schedule is desired. If this approach is taken, up to 6 new patients should be enrolled at that dose or schedule.

In Part B of the study, the sponsor and its designees will review the safety (eg, related procedure adverse events and serious adverse events; disease related events do not need to be reported) on a routine basis and will discuss any significant safety findings with the investigators immediately. If necessary, an SMC including investigators treating patients in each disease-specific cohort may be convened for review of safety data and/or assessment of benefit/risk.

8.5 Follow-up Assessments

Generally, the overall follow-up strategy is the same for Part A and Part B as per Table 3 and Table 5.

All patients must be followed for at least 30 days after their last dose of study drug or until initiation of a new anticancer treatment, whichever occurs first.

Patients who are discontinued from the study due to an unacceptable drug-related AE will be followed until the resolution of the AE to ≤ Grade 1 or stabilization or non-laboratory toxicities to allow for re-treatment agreed by investigators and medical monitor or until beginning of a new therapy for their cancer, whichever occurs first.

In Part A, a mandatory Safety Follow-up Visit should be conducted 30 days (± 7 days) after the last dose of study drug administration or initiation of new anticancer therapy, whichever occurs first. Following completion or discontinuation of the treatment and/or Safety Follow-up phases of the study, every effort should be made to follow up all patients for their survival status until patient death.

In Part B, a mandatory Safety Follow-up Visit should be conducted 30 days (± 7 days) after the last dose of pamiparib administration and 90 days (± 14 days) after the last dose of tislelizumab or initiation of new anticancer therapy, whichever occurs first. With the exception of all irAEs, which will be recorded up to 90 days after the last dose of tislelizumab, regardless of initiation of subsequent anticancer therapy. Patients who have not demonstrated disease progression will have contrast CT of chest, abdomen (or MRI for patients who are allergic to

contrast) and pelvis conducted approximately every 9 ± 1 weeks in the first 12 months and approximately every 12 ± 1 weeks thereafter until unequivocal PD is documented or the patient starts new anticancer therapies or patient withdraws consent from the trial. The same methodology should be used throughout the study.

Patients who stop treatment prior to documentation of PD will undergo repeated imaging for tumor response assessments during the study approximately every 9 ± 1 weeks in the first 12 months and approximately every 12 ± 1 weeks thereafter until unequivocal PD is documented or the patient starts new anticancer therapies or patient withdraws consent from the trial. This imaging schedule will be maintained and will never be adjusted regardless of any intermediate unscheduled scans. Patients who withdraw from the study for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort will be made to confirm a clinical diagnosis of PD by imaging.

Following completion of the treatment and safety follow-up periods, all patients will be followed for survival and subsequent anticancer therapy information after the treatment termination. Survival follow-up and subsequent anticancer therapy information will be collected during telephone calls, through patients' medical records, and/or at clinic visit every 3 months until death, loss to follow-up or study termination by the sponsor. No other data (eg, subsequent therapies, performance status, etc.) beyond survival will be collected during these calls/visits. The study staff may use a public information source (eg, county records) to obtain information about survival status only.

8.6 Visit Windows

All visits must occur within the windows specified in Table 3 and Table 5. All assessments will be performed on the day of the specified visit unless an acceptable visit window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion/dose unless otherwise noted. Laboratory results are required to be reviewed prior to dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled on the nearest feasible date (the visit window is provided in Table 3 and Table 5), with subsequent dosing continued on the 21-day intervals accordingly, with a minimum of 14 days between tislelizumab dosing.

8.7 Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or 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 investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

8.8 Efficacy Assessment

This study includes preliminary assessments of efficacy (anti-tumor activity) as outlined in the sections below for both Part A and Part B.

Disease assessment by radiographic imaging (CT or MRI, with a preference for CT) will be performed and recorded at screening within 28 days before enrollment and while on study approximately every 9± 1 weeks in the first 12 months and approximately every 12 ± 1 weeks thereafter according to the RECIST v1.1 Guidelines as shown in Appendix 8. The same imaging technique as used at baseline must be used throughout the study. If any study patient discontinues study treatment for clinical progression, every attempt should be made to confirm PD using standard radiologic methods.

After first documentation of CR or PR, imaging performed at the next regularly scheduled time point will be used for response confirmation.

For patients with ovarian, fallopian tube, or primary peritoneal cancer, investigators may also incorporate GCIG CA-125 response criteria with RECIST Version 1.1 response criteria in assessing tumor response (refer to Appendix 4).

For patients with prostate cancer, PCWG3 criteria will also be used to evaluate PSA and modified RECIST responses.

8.8.1 Disease Progression and Treatment beyond Disease Progression

There is evidence that some patients treated with anti-PD-1 therapies such as tislelizumab may derive clinical benefit despite initial documentation of PD by RECIST Version 1.1. Pseudo-progression may occur due to immune cell infiltration and other mechanisms as manifested by apparent increase of existing tumor masses or appearance of new tumor lesions. [87] For PD suspected by the Investigator as pseudo-progression, treatment may continue until confirmation of PD with repeat imaging at least 4 weeks later or at the next regularly scheduled imaging time point, but not more than 12 weeks from the initial documentation of pseudo-progression. The criteria for pseudo-progression will not be satisfied if the only disease-specific finding is a change in tumor markers (eg, CA-125, PSA increases). It is the responsibility of the Investigator to determine if the patient should be considered for treatment

beyond progression due to clinical benefit. This decision should be considered carefully so as to permit patients who are likely to be benefiting to continue treatment while at the same time preventing prolonged exposure of a futile therapy in patients who may not be benefiting. The assessment of clinical benefit should take into account whether the patient is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be documented in the medical record, and agreed to by the sponsor medical monitor.

Patients will be permitted to continue study treatment beyond initial RECIST v1.1 defined PD for the time periods below and if they meet the following criteria:

- Investigator-assessed clinical benefit
- Patient is tolerating study drug and agrees to continued study treatment.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that necessitates urgent alternative medical intervention
- Patient agrees to continued treatment and is re-consented to continue study treatment

For mCRPC patients with only bone lesion(s), if there is ambiguity about the appearance of the bony lesions such as traumatic in nature or concern about the possibility of healing bone having the appearance of sclerosis (flare reaction), and the investigators assess that those patients could receive further clinical benefit from the treatment and should also meet the criteria listed above for treatment beyond PD defined by initial RECIST v1.1. Those patients will be permitted to continue study treatment beyond second confirmed PD by bone scan. These cases should be discussed with the sponsor or its designee.

8.9 Pharmacokinetics

Blood will be collected to characterize the PK of tislelizumab and pamiparib. In Part A of the study, PK parameters such as C_{max}, C_{trough} and T_{max} for pamiparib may be derived for each cycle at which pharmacokinetics are to be measured; C_{trough} may be derived for tislelizumab. In Part B of the study, PK parameters such as C_{trough} may be derived for both pamiparib and tislelizumab for each cycle at which pharmacokinetics are to be measured. Additional PK analyses will be conducted as appropriate in all patients for whom valid tislelizumab and pamiparib PK parameters can be estimated.

Blood taken for the PK analysis will be collected at the time points presented in Table 4 and Table 6. In addition, tislelizumab PK samples at pre-dose will be collected at the same time points as the ADA samples to assess the neutralizing capacity of ADA.

Details concerning handling of the PK serum and plasma samples, including labeling and shipping instructions will be provided in the Laboratory Manual. The actual time each sample was collected will be captured to the nearest minute in the eCRF and recorded in the database.

Samples will be shipped to the central laboratory where all samples will be analyzed for serum tislelizumab and plasma pamiparib concentrations using a validated method.

8.9.1 Blood Sample Collection and Handling

Cannulation for blood sampling for PK will be performed. PK samples should not be drawn from the infusion line or from the same arm of infusion. Blood will be collected via the intravenous cannula pre-dose and at the time points specified in Table 4 and Table 6. The actual time each sample was collected will be captured to the nearest minute in the eCRF.

Blood samples for PK analysis will be collected according to the Laboratory Manual. Plasma (for pamiparib) and serum (for tislelizumab) will be separated and immediately frozen. Samples must remain frozen. Temperatures and tissue handling during shipment are specified in the Laboratory Manual.

Samples will be shipped to a central laboratory where they will be analyzed for serum tislelizumab and plasma pamiparib concentrations using a validated method.

Other Blood Samples

Blood samples should be obtained, when possible, for analysis of serum tislelizumab and plasma pamiparib per time-point, in the event of a DLT. The investigator must record the time points the blood samples obtained and the time of the previous administration in the eCRF.

Should a DDI between tislelizumab and/or pamiparib, and a concomitant medication be suspected, further blood samples for PK analyses may be taken to characterize the extent of the potential interaction.

8.10 Anti-Drug Antibody

Immunogenic responses to tislelizumab will be assessed to determine occurrence of anti-tislelizumab antibody. For Part A, as specified in Table 4, blood for anti-tislelizumab antibodies should be collected within 24 hours before the start of infusion on Day 1 and one sample between Day 7 through 10 of Cycle 1, and before the start of infusion on Day 1 of Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 9 in the first 6 months, approximately every 8 cycles thereafter (Cycle 17). For Part B, as specified in Table 6, blood for anti-tislelizumab antibodies should be collected within 24 hours before the start of infusion on Day 1 and one sample between Day 7 through 10 of Cycle 1, and before the start of infusion on Day 1 of Cycle 2,

Cycle 3, Cycle 4, Cycle 5, Cycle 9 in the first 6 months, approximately every 8 cycles thereafter (Cycle 17).

In patients who discontinue study therapy before 6 months, every effort should be made to analyze anti-tislelizumab antibodies approximately 6 months after the first dose. tislelizumab PK samples at pre-dose will be collected at the same time points as the ADA samples to assess the neutralizing capacity of ADA. Samples will be processed according to the Laboratory Manual and shipped to a central laboratory for analysis using a validated method.

8.11 Biomarker Assessments

A blood sample at screening stage will be collected for ovarian, fallopian tube, primary peritoneal, and breast cancer patients enrolled in Part A and in all patients in Part B for germline *BRCA* and/or other mutations analysis, even if it has been tested previously. Blood samples will be prepared as indicated in the Laboratory Manual.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.12 Appropriateness of Measurements

All safety and PK assessments used in this study are standard, ie, widely used and generally recognized as reliable, accurate, and relevant.

9.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the Good Clinical Practice (GCP) guidelines [88], the sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s)
- Certified local laboratories for laboratory measurements and ECGs
- Study center initiation visit
- Early study center visits post-enrollment
- Routine study center monitoring
- Ongoing study center communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final clinical study report

In addition, the sponsor and/or the CRO's clinical quality assurance department may conduct periodic audits of the study processes, including, but not limited to the study center, study center visits, PK laboratories, local laboratories, vendors, clinical database, and the final clinical study reports. When audits are conducted, access must be authorized for all study-related documents including medical history and concomitant medication documentation to authorized sponsor's representatives and regulatory authorities.

9.1 Monitoring

In accordance with applicable regulations, GCP, and sponsor procedures, the sponsor has engaged the services of a CRO to perform all monitoring functions within this clinical study. Monitors will work in accordance with the sponsor or CRO SOPs and have the same rights and responsibilities as monitors from the sponsor's organization. Monitors will establish and maintain regular contact between the investigator and the sponsor.

During these contacts, the monitor will:

- Check the progress of the study.

- Review study data collected.
- Conduct source document verification.
- Identify any issues and address their resolution.

This will be done to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of patients are being protected.
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the monitor to discuss findings and any relevant issues.

At study closure, monitors will also conduct all activities described in Section 13.1.

9.2 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of the sponsor or the delegated CRO.

An electronic data capture (EDC) system will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center personnel designated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorized study center personnel prior to the study being initiated and any data being entered into the system for any patients.

The eCRFs should always reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed ASAP during or after the patient's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all safety evaluations. The investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the investigator should indicate this in the eCRF. The investigator will be required to electronically sign off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the responsible

investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the study center personnel responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate study center personnel will answer queries sent to the investigator.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the investigator or hospital that relate to the patient's medical history, that verify the existence of the patient, the inclusion and exclusion criteria and all records covering the patient's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, patient files, etc.

The investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The investigator must submit a completed eCRF for each patient who receives the investigational product, regardless of the duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and patient number. Any personal information, including patient name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic CRF records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records will be electronically signed by the investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the investigator's unique UserID and password; date and time stamps will be added automatically at the time of the electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0 or higher versions. Concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO-DD). Concomitant diseases/medical history will be coded using the MedDRA Version 17.0 or higher versions.

9.3 Quality Assurance Audit

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.

10.0 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.

10.1 Risks Associated with Tislelizumab

Tislelizumab is an investigational agent that is currently in clinical development. Limited safety data are available in patients and the full safety profile has not been characterized. The following information is based on results from nonclinical and clinical studies with tislelizumab and published data on other molecules within the same biologic class.

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of irAEs, specifically the induction or enhancement of autoimmune conditions. Immune-related AEs commonly associated with anti-PD-1 therapy are presented in Table 9.

Although most irAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Guidance for evaluation and management for suspected irAEs are provided in Section 10.13.4 and Appendix 10.

10.2 General Plan to Manage Safety Concerns

10.2.1 Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this trial. Results from the nonclinical toxicology studies and clinical data with tislelizumab and pamiparib, as well as the nonclinical/clinical data from other PD-L1/PD-1/PARP inhibitors, were taken into account. Specifically, patients at risk for study-emergent active autoimmune diseases or history of autoimmune diseases that may relapse, and patients who have received a live viral vaccine within 28 days before study entry are excluded from the study.

10.2.2 Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events, defined and graded according to NCI-CTCAE v4.03. Patients will be assessed for safety (including laboratory values) according to the schedule in Table 3 and Table 5. Clinical laboratory results must be reviewed prior to the start of each cycle.

In this study, all enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs, physical examinations, laboratory measurements (eg, hematology, chemistry) and other assessments. In addition, patients will be

closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

Serum samples will be drawn from patients for the determination of ADAs to tislelizumab. Administration of tislelizumab will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available.

All AEs will be recorded during the trial (AEs from the time of the first dose and SAEs from the time of signing of informed consent) and for up to 30 days after last dose of pamiparib and up to 90 days after tislelizumab study treatment or initiation of new anticancer therapy, whichever occurs first. At the end of treatment, ongoing AEs considered related to study treatment will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the Investigator as stable, the patient is lost to follow-up, the patient withdraws consent.

All irAEs will be recorded up to 90 days after the last dose of tislelizumab, regardless of initiation of subsequent anticancer therapy. All drug-related SAEs will be recorded by the Investigator after treatment discontinuation until patient death or loss to follow-up, whichever occurs first.

Investigators are instructed to report all events (including AEs and pregnancy-related AEs). The potential safety issues anticipated in this trial, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

10.3 Adverse Events

10.3.1 Definition and Reporting of an Adverse Event

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

Examples of an AE include:

- Worsening of a chronic or intermittent pre-existing condition including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study drug administration even though it 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 prior to submission to the sponsor.

For the purposes of this study, all events of MDS and AML that occur while on study should be reported as an SAE because these events are clinically significant (see Section 0).

10.3.1.1 Assessment of Severity

The investigator will make an assessment of severity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the National Cancer Institute (NCI) CTCAE v4.03.

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 (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 10.4.

10.3.1.2 Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship. 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 will be considered and investigated. The investigator will also consult the IB and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes assessment of causality for every SAE prior to transmission of the SAE report/eCRF to the sponsor since the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE report/eCRF accordingly.

The causality of each AE should be assessed and classified by the Investigator as "related" or "not related". An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study 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

An AE should be considered 'related' to study drug if any of the following are met:

- 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).

10.3.1.3 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, the patient withdraws consent, or starts a new anticancer therapy. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. 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, 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 post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE report/eCRF, with all changes signed and dated by the investigator. The updated SAE report/eCRF should be resent to the sponsor within the time frames outlined in Section 10.8.1.

10.3.1.4 Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, 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 if they meet the definition of an AE (as defined in Section 10.3.1) or an SAE (as defined in Section 10.4). Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the patient's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs. They should be reported as AEs or SAEs if they induce clinical signs or symptoms, need active intervention, need dose interruption or discontinuation or are clinically significant in the opinion of the investigator.

Abnormalities in liver function tests (ALT, AST, total bilirubin) that are Grade 3 or higher need to be reported to the sponsor with 24 hours of occurrence. Repeat LFT testing should be performed according to the schedule in Appendix 10.

The investigator will exercise his/her medical and scientific judgment in deciding whether other abnormal laboratory finding or other abnormal assessment is clinically significant.

10.4 Definition of a Serious Adverse Event

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

- Results in death
- Is life-threatening

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

- Requires hospitalization or prolongation of existing hospitalization

  NOTE: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the AE is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Results in disability/incapacity

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

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

The following are NOT considered SAEs:

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

10.5 Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

10.5.1 Adverse Event Reporting Period

During the pre-screening stage, no adverse events will be reported. Only serious adverse events will be reported during the pre-screening stage if the serious adverse event is related to the pre-screening procedure.

After informed consent has been signed but prior to 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 30 days after the last study treatment or initiation of new anticancer therapy. After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment. Immune-related adverse events should be reported if they occur within 90 days after the last dose of tislelizumab, regardless of initiation of subsequent anticancer therapy.

10.5.2 Eliciting Adverse Events

The investigator or designee will ask 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?

10.6 Specific Instructions for Recording Adverse Events and Serious Adverse Events

10.6.1 Disease Progression

Disease progression (including fatal disease progression), which is expected in this study population and measured as an efficacy endpoint, should not be reported as an AE term. Instead, the symptoms, signs or clinical sequelae that result from disease progression should be reported as the AE term(s).
For instance, a patient presents with pleural effusion resulting from disease progression of metastasis to lungs. The event term should be reported as “pleural effusion” instead of disease progression. If a patient experienced a fatal multi-organ failure due to disease progression, the term “multi-organ failure” should be reported as the SAE with death as outcome instead of reporting “fatal disease progression” or “death due to disease progression”.

10.6.2 Death

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

10.7 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 Investigator’s Brochure.

10.8 Prompt Reporting of Serious Adverse Events

10.8.1 Timeframes for Submitting 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 to the sponsor or designee as described in Table 7.

Table 7: Time Frame for Reporting Serious Adverse Events to the Sponsor or Designee

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

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

Abnormalities in liver function tests (ALT, AST, total bilirubin) that are Grade 3 or higher need to be reported to the sponsor with 24 hours of occurrence. Repeat LFT testing should be performed according to the schedule in Appendix 10.

10.8.2 Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she will report the information to the sponsor within 24 hours as outlined in Section 10.8.1. The SAE Report will always be completed as thoroughly as possible with all available details of the SAE, 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 will not wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 10.3.1.2.

The sponsor will provide contact information for SAE receipt.

10.8.3 Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 10.8.2. 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

This protocol is being conducted under an Investigational New Drug (IND) with the US FDA. All IND safety reports submitted to the FDA will also be sent to all investigators conducting studies under this IND.

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

10.9 Pregnancy Reporting

If a female patient or the partner of a male patient becomes pregnant while receiving investigational therapy or within 6 months after the completion of the last dose of study drug, a pregnancy report form should 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 or SAE, 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.

10.10 Post-study Adverse Event

A post-study AE or SAE is defined as any AE that occurs outside of the AE/SAE reporting period, defined in Section 10.5.1.

Investigators are not obligated to actively seek AEs or SAEs in former patients. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the SAE related to the study drug, the investigator will notify the sponsor.

10.11 Assessing and Recording Immune-Related Adverse Events

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune-related (see Section 10.13.4) should be classified as irAEs and identified as such in the eCRF AE page until up to 90 days after the last dose of tislelizumab, regardless of initiation of subsequent anticancer therapy.

Investigators should consult the guidance on diagnostic evaluation and management of irAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 10.

An extensive list of potential irAEs appears in Section 10.13.4, Table 8. All conditions similar to those listed should be evaluated to determine whether they are irAEs, based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 10.

10.12 Expedited Reporting to Health Authorities, Ethics Committees and Investigators

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

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

- Pamiparib Investigator's Brochure
- Tislelizumab Investigator's Brochure

10.13 Special Precautions

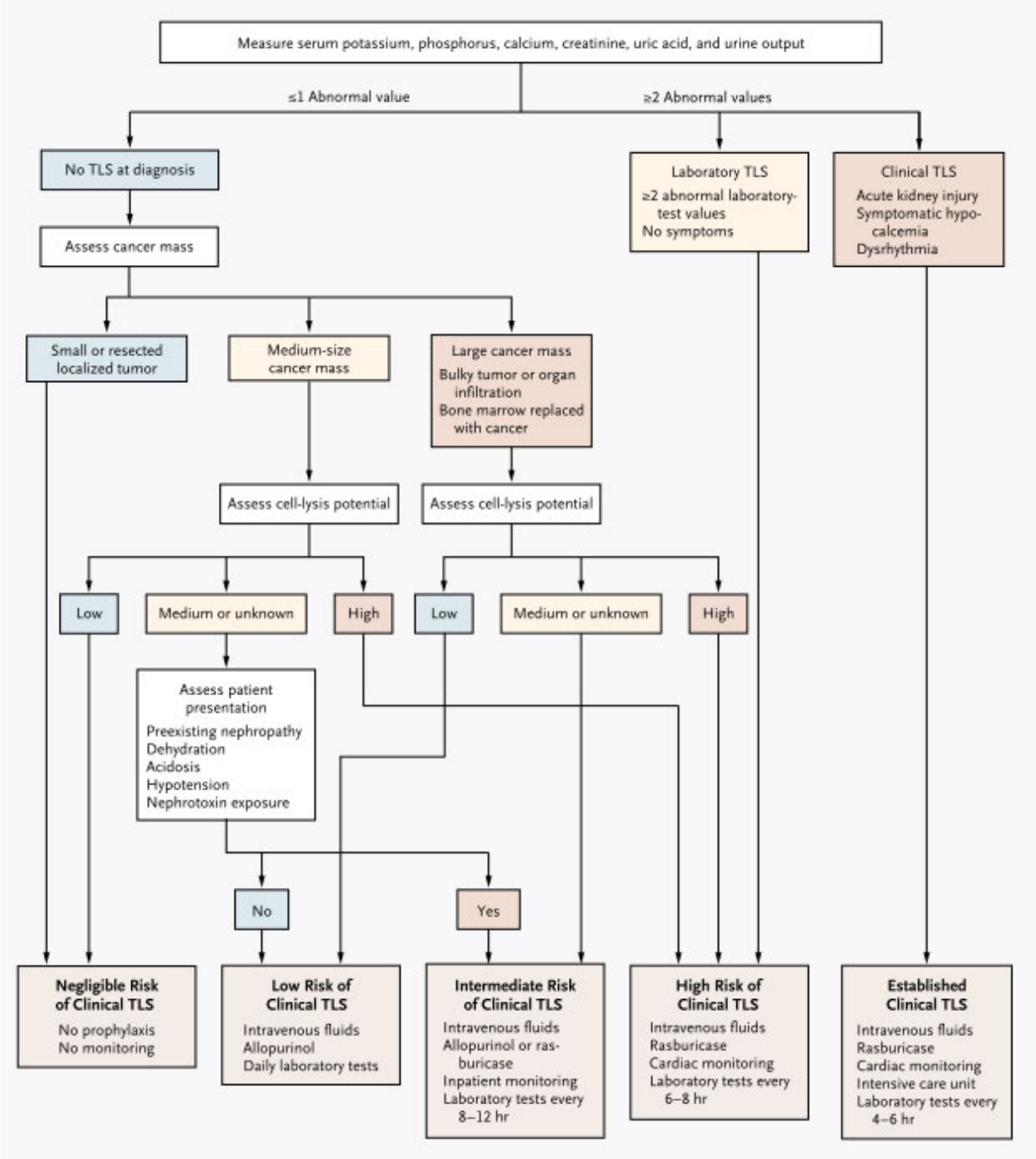
As a routine precaution, after infusion of tislelizumab on day 1 of cycle 1 and cycle 2, patients must be monitored for at least 1 hour afterwards in an area with resuscitation equipment and emergency agents. From cycle 3 onward, a minimum of a 30-minute monitoring period is required in an area with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

The management for tumor lysis syndrome, infusion-related reactions, severe hypersensitivity reactions, irAEs, and renal function abnormalities according to the NCI-CTCAE criteria are outlined in Sections 10.13.1, 10.13.2, 10.13.3, 10.13.4, and 10.13.5 respectively.

10.13.1 Tumor Lysis Syndrome

A potential risk of tumor lysis syndrome (TLS) exists since tislelizumab can induce cytotoxicity. As recommended by Howard et al. [89], once TLS occurs, patients should be treated as per the local guidelines and the management algorithm (Figure 3).

Figure 3: Assessment and Initial Management of Tumor Lysis Syndrome



10.13.2 Infusion-Related Reaction

The symptoms of infusion-related reactions include 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, and cardiogenic shock. Patients should be closely monitored for such reactions. Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modification for symptoms of infusion-related reactions due to study drug(s) is provided in Table 8.

Table 8: Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

NCI-CTCAE Grade	Treatment Modification for Tislelizumab
Grade 1 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 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions has resolved or decreased to at least 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: IV, intravenous; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Event; NSAIDs, nonsteroidal anti-inflammatory drugs.

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

CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted, as indicated per type of the reaction. This includes but is not limited to an anti-histamine (eg, diphenhydramine or equivalent), anti-pyretic (eg, paracetamol or equivalent), and if considered indicated oral or IV 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.

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 IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

10.13.3 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). [90, 91] Patients should be instructed to report any delayed reactions to the investigator immediately.

In the event of a systemic anaphylactic/anaphylactoid reaction (typically manifested within minutes following administration of the drug/antigen, and 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 infusion must be immediately stopped and the patient discontinued from the study.

The patients will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed and then the patient should 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 h before and 8 h after the start of each dose of study drugs(s) infusion.

Alternative treatments for fever (ie, paracetamol) may be given to patients at the discretion of the investigator.

10.13.4 Immune-Related Adverse Events (irAE)

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

A list of potential irAEs is shown below in Table 9. All conditions similar to those listed should be evaluated in patients receiving tislelizumab to determine whether they are immune-related.

Recommendation for diagnostic evaluation and management of irAEs is based on a recent ESMO guideline [92] and common immune-related toxicities are detailed in Appendix 10. For any adverse events not included in Appendix 10, please refer to the recent ESMO guideline [92] for further guidance on diagnostic evaluation and management of immune-related toxicities.

Table 9: Immune-Related Adverse Events

Body System Affected	Events
Skin (mild-common)	pruritus or maculopapular rash; vitiligo
Skin (moderate)	follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet's syndrome
Skin (severe-rare)	full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation
Endocrine	thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism, eg, fatigue, weakness, weight gain; insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	pneumonitis/diffuse alveolitis
Eye	episcleritis; conjunctivitis; iritis/uveitis

Neuromuscular	arthritis; arthralgia; myalgia; neuropathy; Guillain-Barre syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis, meningoencephalitis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure

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 with rechallenge should permanently discontinue treatment unless the guidance in Appendices 10 and 11 allow continued treatment.

For dose modifications of tislelizumab see Section 5.1.4. Please refer to Appendix 10 for guidance on managing immune-related adverse events. For dose interruption and/or modification of pamiparib, please refer to Appendix 11.

10.13.5 Renal Function Abnormalities

Patients with moderate renal dysfunction (estimated glomerular filtration rate > 30 mL/min and < 60 mL/min by Chronic Kidney Disease Epidemiology Collaboration equation) may be enrolled into the study. The following algorithm is proposed for the use of steroid treatment in the management of irAEs:

- If the serum creatinine is normal at baseline, please see Section 10.13.4 and refer to Appendix 10 for diagnosis and management of patients with abnormal renal laboratory values.
- If the serum creatinine is Grade 1 at baseline and increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 2 after starting treatment with tislelizumab, refer to Appendix 10 for diagnosis and management of patients with abnormal renal laboratory values. Check the estimated GFR using Appendix 18 and the eGFR calculator link. In the setting of a Grade 2 serum creatinine increase only, study treatment can continue unless the serum creatinine increases by at least 50% from the baseline value OR the eGFR falls below 20 mL/min.
- If the serum creatinine is Grade 2 at baseline and increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 3 after starting treatment with tislelizumab, refer to Appendix 10 for diagnosis and management of patients with abnormal renal laboratory values. In the setting of a Grade 3 serum creatinine increase only, study treatment will be held until serum creatinine improves to baseline and treatment may resume only after discussion with the sponsor medical monitor.

11.0 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

11.1 Sample Size Considerations

In Part A, the number of DLs examined and the emerging tislelizumab and pamiparib toxicities will determine the sample size. Five DLs are planned, and it is anticipated that up to 50 patients will be required to establish the RP2D of the combination.

Part B will include expansion arms of specific tumor types. Up to approximately 200 patients may be enrolled. The purpose of these expansion arms is to explore signals of clinical efficacy as well as to confirm the safety and tolerability of the combination in each selected tumor type. Anti-tumor activity will be evaluated in Part B. A decision can be made to stop an arm early due to suboptimal clinical anti-tumor activity. All Arms will enroll approximately 20 patients. The sample size (n = 20) is determined such that the probability of observing at least one responder is approximately 88% in an expansion arm (n = 20) when the underlying ORR is as low as 10%. Each arm in Part B: 1a, 1b, 2, 3, 4, 5, 6, 7, 8, and 9 will be analyzed independently. All Arms will enroll approximately 20 patients with an option to increase each cohort to 40 patients to confirm outcomes observed in the first 20 patients.

Twenty additional patients may be enrolled in any disease cohort to evaluate further the anti-tumor activity if evidence of activity is observed in the first 20 patients. Since a precise estimate of objective response rate is difficult to predict due to the heterogeneity of patients enrolled within each arm, a Bayesian predictive probability, which evaluates the statistical strength of the pamiparib plus tislelizumab combination regimen vs the standard chemotherapy, will be used to provide a guidance to decide whether to enroll additional 20 patients. For example, for an arm with historical response rate 10%, within the initial 20 patients, at least 2 responders should be observed to have a predictive probability of > 10% superiority over the 10% historical rate in a total of 50 patients; however, for an arm with higher response rate expected (eg, > 30% ORR in arm 1a), at least 6 responders are required to have a > 10% predictive probability in order to expand the arm beyond the initial 20 patients.

11.2 General Considerations for Data Analysis

Data will be listed and summarized using SAS® Version 9.3 or higher (SAS Institute, Inc., Cary, North Carolina) according to sponsor agreed reporting standards, where applicable. Complete details will be documented in the reporting and analysis plan.

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

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

All data will be presented by part, then by dose level in Part A or by arm in Part B. Further description of the statistical methods and analyses will be provided in the statistical analysis plan.

11.2.1 Analysis Populations

All Patients Enrolled Set (ENR)

The all patients (both parts) enrolled (ENR) set will include all patients who provide informed consent for this study.

Safety Analysis Set (SAF)

The safety analysis set (SAF) will include all patients (both parts) who received at least one dose of tislelizumab and/or pamiparib. The SAF analysis set will be used for all summaries (except DLTs).

Efficacy Evaluable Set (EFF)

The efficacy evaluable set (EFF) includes patients in the SAF who had measurable or evaluable disease at baseline including patients in the mCRPC aim whose disease progression can be evaluated by PSA and had at least one post baseline tumor assessment unless discontinued treatment due to clinical progression or death prior to tumor assessment.

DLT Analysis Set (DLT)

The DLT Analysis Set includes all patients who received at least 90% of tislelizumab and 75% of pamiparib or who experienced a DLT event during the DLT observation period (Cycle 1).

PK Analysis Set (PKS)

The PK Analysis Set will include patients in the Safety Analysis Set for whom at least one PK parameter can be derived for either pamiparib or tislelizumab.

Exploratory Analyses

[redacted]

11.2.2 Data Analysis

This study is a dose escalation and schedule expansion study. Safety, PK and pharmacodynamic, and efficacy data will be evaluated on an ongoing basis.

11.2.3 Patient Disposition

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

Major protocol deviations will be summarized and listed by each category (major or minor).

11.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the safety analysis set using descriptive statistics. Continuous variables include age, weight, vital signs and time since initial and metastatic cancer diagnosis; categorical variables include, gender, ECOG, race, smoking status, TNM staging, metastatic site, and site of primary tumor.

11.2.5 Prior and Concomitant Medication

Concomitant medications will be assigned an 11-digit code 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 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. A listing of prior and concomitant medications will be included in the CSR of this protocol.

11.3 Efficacy Analyses

Response based on investigators' judgment will be collected at screening and while on study approximately every 9 ± 1 weeks in the first 12 months and approximately 12 ± 1 weeks

thereafter in the simple form of four categories: PD, SD, CR, and PR (according to RECIST v1.1).

For patients with ovarian, fallopian tube, or primary peritoneal cancer, investigators may also incorporate GCIG CA-125 response criteria [93], with RECIST Version 1.1 response criteria in assessing tumor response (refer to Appendix 4).

For patients with prostate cancer, PCWG3 criteria [94] will also be used to evaluate PSA and modified RECIST responses (refer to Appendix 6).

Anti-tumor activity of the combination therapy will be evaluated separately in each part in the safety analysis set. In Part B, efficacy variables (ie, ORR, DCR, CBR, PFS, DOR and OS) will be summarized by expansion arm using RECIST v1.1 when applicable. ORR, along with its 95% confidence interval using exact method will be summarized. PFS will be summarized using Kaplan-Meier method. Kaplan-Meier curves will be shown by expansion arm. A waterfall plot of maximum tumor shrinkage from baseline will also be displayed.

DCR, CBR, DOR and OS will be summarized using the methods as described above in the SAF. Efficacy endpoints will also be summarized in the efficacy evaluable set.

To limit the number of patients who might be exposed to a less efficacious treatment, continuous monitoring of efficacy and safety will be implemented whenever possible during the trial. ORR in each arm will be calculated and compared to a historical rate. The enrollment of an expansion arm will be stopped early in case of low ORR such that any improvement over historical rate of single agent is unlikely. Due to the exploratory nature of the efficacy analysis, any early futility boundaries/criteria are advisory; and are to be used to aid the data interpretation only. Any decision made towards a particular arm during the Part B enrollment will be based on the totality of the data.

11.4 Safety Analyses

All patients who are exposed to (or started receiving) tislelizumab and/or pamiparib will be evaluated for safety. Safety data will be summarized by dose level.

11.4.1 Dose Limited Toxicity

For Part A, the number and proportion of patients experiencing DLTs will be reported by dose level, based on DLT observations during the first cycle. The DLT Analysis Set will be used for this analysis. There is no DLT analysis in Part B.

11.4.2 Maximum Tolerated Dose

The MTD is defined as the dose that produces an “acceptable” level of toxicity or that, if exceeded, would put patients at “unacceptable” risk for toxicity. The MTD for this study is

defined as the highest dose studied at which more than 2 in 3 to 6 patients has experienced a DLT in Cycle 1. If a MTD is identified, a dose level lower than MTD will be selected by SMC.

11.4.3 Adverse Events

In this protocol, a TEAE is defined as any AE or SAE with either an onset date or a date of worsening in severity from baseline (ie, pretreatment) occurring after first dose of study drug and up to either 30 days following discontinuation from study drugs or start of new anticancer therapy, whichever occurs first. The TEAE classification also applies to irAEs that are recorded up to 90 days after discontinuation from tislelizumab, regardless of initiation of subsequent anticancer therapy. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class (SOC) and Preferred Term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v4.03 [86] within an SOC and Preferred Term, even if the patient experienced more than 1 TEAE within a specific SOC and Preferred Term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug.

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

11.4.4 Laboratory Assessments

Clinical laboratory (eg, hematology, serum chemistry) values will be evaluated for each laboratory parameter as appropriate. Abnormal laboratory values will be flagged as high or low relative to the normal range, where applicable. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst post-baseline visit.

Laboratory parameters that are graded in CTCAE v.4.03 will be summarized by CTCAE grade. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

11.4.5 Electrocardiogram

All ECG parameters including the QT interval corrected for heart rate (QTc) will be listed for each patient and summarized by dose level and assessment time. If sufficient data are available,

change from baseline will also be summarized. Relationship between dose level and QTc changes may be explored by graphs. QTc will be calculated using Fridericia's formulae.

11.4.6 Vital Signs

Blood pressure, pulse, respiratory, temperature and weight will be summarized and listed. The change from baseline will also be displayed.

11.4.7 Extent of Exposure

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

The number (percentage) of patients requiring dose reduction, 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.

11.4.8 Physical Examination

Physical examination results will be listed and summarized.

11.4.9 Ophthalmologic Examination

Ophthalmologic examination results will be listed and summarized.

11.5 Pharmacokinetic Analyses

In Part A of the study, PK parameters such as C_{max}, C_{trough} and T_{max} for pamiparib may be derived for each cycle at which pharmacokinetics are to be measured; C_{trough} may be derived for tislelizumab, where applicable (as specified in Table 4). In Part B of the study, PK parameters such as C_{trough} may be derived for both pamiparib and tislelizumab for each cycle at which pharmacokinetics are to be measured, where applicable (as specified in Table 6).

Additional PK analyses will be conducted as appropriate in all patients for whom valid tislelizumab and pamiparib PK parameters can be estimated. Nominal sampling times will be used for interim PK parameter calculations, while actual sampling times will be used in the final PK parameter calculations.

Summary statistics of the calculated PK parameters will be provided. Graphical, non-compartmental and [redacted].

Possible DDIs between tislelizumab and pamiparib may be evaluated by comparison of the pharmacokinetic data generated in the present study and historical data. Significant differences in pharmacokinetic outcomes may be assessed for clinical relevance in consultation with the SMC (See Section 8.4.1)

11.6 Biomarker Analyses

12.0 ETHICS

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 Ethical Conduct of the Study and Ethics Approval

This study will be conducted 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 individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/IEC by the principal investigator 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.

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

12.3 Informed Consent

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

The ICFs must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records

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

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

12.4 Handling of Clinically Significant Findings of Genomic Studies

Any clinically significant results with familial implications (eg, a germline pathogenic mutation which confers an increased risk of developing disease) will be verified but the central laboratory and these results will be conveyed back to the treating investigator. The treating investigator will then contact the patient. The patient will not be informed of the result specifically but encouraged to contact the Familial Cancer Centre (FCC) for formal genetic counseling. The cancer genetics counseling service will facilitate a discussion regarding the potential implications of such genetic results to both participants and their families, allowing participants to make an informed choice to either (a) receive the results or (b) to opt not to receive any further information. The FCC will manage the participants with confirmed mutations and their families as per established clinical guidelines, or as deemed appropriate by the involved staff. If there are any areas which require additional clarification, the principle investigator, will approach the central Human Research Ethics Committee (HREC) to seek further guidance.

Participants will be asked at the time of informed consent to nominate a next of kin to receive information regarding clinically meaningful results in the instance that the participant is no longer contactable, or deceased. Only germline research results that may be significant for family members will be returned to the next of kin.

12.5 Investigator Reporting Requirements

As indicated in Section 10.12, the investigator (or sponsor, where applicable) is responsible for reporting SAEs to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

13.0 STUDY ADMINISTRATION

13.1 Study and Study Center Closure

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

- Return of all study data to the sponsor
- Resolve and close all data queries
- Accountability, reconciliation, and arrangements for unused investigational product(s)
- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of PK and biomarker samples to assay laboratories

In addition, the sponsor reserves the right to suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

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

If the study is prematurely discontinued, all study data must be returned to the sponsor. In addition, arrangements will be made for all unused investigational product(s) in accordance with the applicable sponsor procedures for the study.

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

13.2 Records Retention

[redacted]

[redacted]

13.3 Provision of Study Results and Information to Investigators

[redacted]

13.4 Information Disclosure and Inventions

[redacted]

[redacted]

[redacted]

13.4.1 Publication and Data Sharing Policy

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
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15.0 APPENDICES

APPENDIX 1: SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Phase 1/1b, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activity of the anti-PD-1 Monoclonal Antibody BGB-A317 in combination with the PARP inhibitor BGB-290 in Subjects with Advanced Solid Tumors

PROTOCOL NO: BGB-A317/BGB-290_Study_001

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

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to BeiGene.

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

APPENDIX 2: CLINICAL LABORATORY ASSESSMENTS

Clinical Chemistry	Hematology	Coagulation	Urinalysis
Alkaline phosphatase Alanine aminotransferase Amylase Aspartate aminotransferase Albumin Total bilirubin Blood urea nitrogen or urea Creatine Kinase (CK, including CK-MB)[2] Creatinine Glucose Lactate dehydrogenase Lipase Total protein Potassium Sodium Testosterone[1]	Hematocrit Hemoglobin Platelet counts WBC count with differential Neutrophil count Lymphocyte count	Prothrombin time Activated Partial thromboplastin time International Normalized Ratio	Glucose Protein Ketones Blood

Abbreviations: WBC: white blood cell.

[1] Testosterone test is only applied for patients with mCRPC. However, the testosterone levels do not need to be checked if the patient has undergone surgical castration for > 4 months. Patients receiving chemical castration should have testosterone levels checked at baseline and confirmed to be in the castrate levels (< 0.5 ng/mL or 1.735 nM).

[2] Include cardiac troponin I and T if CK-MB testing is not available

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

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work). (Karnofsky 70-80)
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. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)
5	Dead (Karnofsky 0)

APPENDIX 4: EVALUATION OF RESPONSE ACCORDING TO CA-125

The text below was obtained from the following reference: Rustin GJ, Vergote I, Eisenhauer E, et al. Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG). *Int J Gynecology Cancer*. 2011; 21(2): 419-423. [93]

Definition of Response:

A CA-125 response is defined as at least a 50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Subjects can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

To calculate CA-125 responses accurately, the following rules apply:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the reference range of CA-125 levels will not interfere with the response definition.
- For each subject, the same assay method must be used, and the assay must be tested in a quality control scheme.
- Subjects are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human anti-mouse antibody4, 5) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (eg, paracentesis). If assessing therapy that includes 2 treatment modalities for relapse (eg, surgery and chemotherapy), any CA-125 response results from both treatment modalities. CA-125 cannot distinguish between the effects of the 2 treatments.

The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response. To calculate response, an intent-to-treat analysis should be used that includes all subjects with an initial CA-125 level of at least twice the upper limit of the reference range as eligible and evaluable. In addition, as a separate analysis, those subjects who have a CA-125 response and whose CA-125 level falls to within the reference range can be classified as CA-125 complete responders. In Table 3, Table 4, Table 5, and Table 6 where CA-125 is stated as normalized or normal, this refers to being within the reference range. Subjects who have a decrease in CA-125 to within the reference range, but whose initial CA-125 was less than twice the upper limit of

the reference range, are not considered to have had a CA-125 response and cannot therefore be classified as a CA-125 complete responder.

Reporting of Response According to Both RECIST v1.1 and CA-125 Criteria

Responses should be reported separately for both RECIST v1.1 and CA-125 response, as shown in the hypothetical example in below table:

Example of Reporting RECIST, CA-125, and Combined Response

RECIST	CA-125 Response			
	Yes	**No or PD**	**N/E**	**Total RECIST**
CR[1]	***4***	0	0	*4*[2]
PR	***3***	*1*	*1*	*5*[2]
SD	**3**	12	1	16
PD	0	8	2	10
NE	**3**	5	2	10
Total CA-125	**13**	26	6	Total entered = 45

1. *RECIST v1.1 includes normalization of CA-125 to achieve CR (Table 4 of this reference).
2. In the above example, the RECIST v1.1 response rate is 9 (25.7%) of 35 RECIST v1.1 evaluable subjects, the CA-125 response rate is 13 (33%) of 39 CA125 evaluable subjects, and the combined overall response rate (either RECIST or CA-125 response) is 15 (35%) of 43.

Note: Bolded numbers, CA-125 responders; bolded and italicized numbers, both RECIST and CA-125 responders; italicized numbers, RECIST responders.

APPENDIX 5: EVIDENCE OF PROGRESSIVE DISEASE TO DETERMINE TRIAL ENTRY ELIGIBILITY IN PATIENTS WITH PROSTATE CANCER

Patients being considered for trial entry should have evidence of disease progression by PSA, modified RECIST or bone scan to be eligible.

PSA: PSA evidence of disease progression based on the prostate cancer working group (PCWG) 3 criteria consist of a minimum PSA level 2.0 ng/ml that has risen on at least 2 successive occasions, at least 1 weeks apart. As shown in Figure below, the reference value # 1 is the last value before the rise in PSA was observed. If the confirmatory PSA value (# 3A) is greater than the screening value then progression by PSA is met and the patient is eligible for trial enrollment on the basis of PSA alone. If the confirmatory PSA (#3B) value is less than the screening PSA (#2) value, then an additional test for rising PSA (#4) will be required to document progression before the patient can be enrolled.

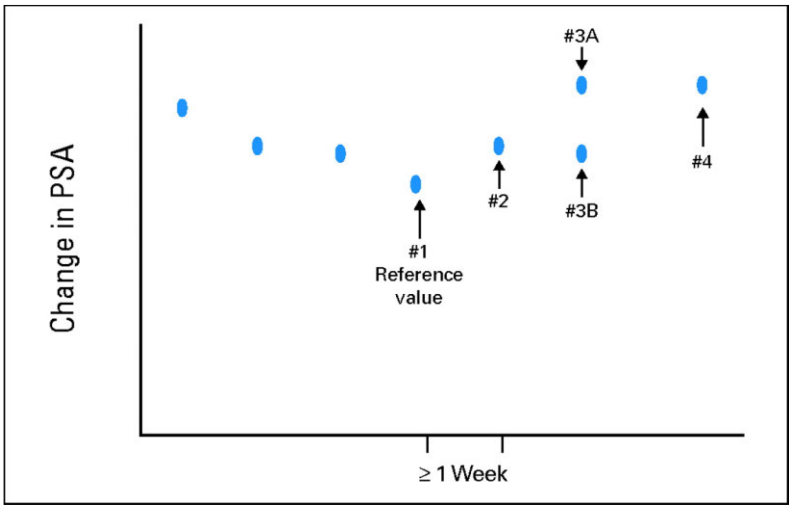

Figure 1: Eligibility Based on PSA

Target lesion/measurable disease: Patients are not required to have evidence of disease progression by measurable disease if they meet the criteria for disease progression on the basis of PSA or bone scan. Evidence of nodal or visceral disease progression however is sufficient for trial entry independent of PSA readings. Because lymph nodes may be enlarged due to benign pathology, only lymph nodes that are ≥ 2 cm should be used for disease evaluation.

Bone scan: Evidence of disease progression based on bone scan appearance is sufficient for trial entry independent of PSA readings. If the appearance of the bone scan is the only indicator of progression then there must be ≥ 2 new bone lesions compared with the prior

bone scans. If there is ambiguity about the appearance of the bony lesions such as traumatic in nature or secondary to a flare reaction then it is recommended that an alternative imaging modality such as MRI or fine-cut CT be used to evaluate these lesions further.

APPENDIX 6: PROSTATE CANCER CLINICAL TRIALS WORKING GROUP 3 (PCWG3) CRITERIA TO GUIDE ASCRIBING DISEASE RESPONSE

The table below is modified from the following reference: Scher HI, Morris MJ, Stadler WM, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. *J ClinOncol*. 2016 34:12, 1402-1418. [94]

Variable	PCWG3 (2016)
PSA	On this study serial PSA measurements will be done every 9 weeks on day 1 of every 4th cycle. Increases and decreases will be tracked in order to assess disease response. The PSA readings on its own will not be used to define progression in this protocol. PSA response and PSA progression will be defined according to the consensus guidelines of the PCWG 3: • PSA partial response is defined as a ≥ 50% decline in PSA from Cycle1 Day1 (baseline) PSA value. This PSA decline much be confirmed to be sustained by a second PSA value obtained 4 or more weeks later. • PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained four or more weeks later. The first PSA reading will be obtained at week 12. **Duration of PSA Response:** Duration of PSA response is calculated from the time the PSA value first declines by at least 50% of the Cycle 1 Day 1 (baseline) value that has been confirmed by a second value until the time there is an increase of 25% of PSA nadir, provided the absolute increase is at least 2 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 25% above the nadir. If the PSA never shows a 25% increase over the nadir value, then the subject will be assessed at the last PSA measurement.

Target Lesions	Nodal or visceral progression sufficient for trial entry independent of PSA Measurable lesions not required for entry Use RECIST to record soft-tissue (nodal and visceral) lesions as target or non-target Only lymph nodes ≥ 2 cm in diameter should be used to assess for a change in size Record presence of nodal and/or visceral disease separately. Progression at any scheduled reassessment ≥ 12 weeks does not need to be confirmed
Bone	≥ 2 new lesions at the first scheduled reassessment from Cycle 1 Day 1 compared with baseline must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should show an additional 2 new lesions compared to the first post-treatment scan (ie, a total of ≥ 4 new lesions compared with the baseline bone scan). Confirm ambiguous results by other imaging modalities (eg, CT or MRI). Investigators are highly encouraged to maintain the subject's treatment with study medication unless progression is confirmed.

Abbreviations: PCWG3: Prostate Cancer Clinical Trials Working Group 3; PSA: prostate-specific antigen; PSA-DT: PSA doubling-time; RECIST: Response Evaluation Criteria in Solid Tumors; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography

APPENDIX 7: DRUG DILUTION CALCULATION FOR BGB-A317

Dose Level: 2 mg/kg

Body Weight (kg)	Total Administered Drug (mg)	Total Dose Volume (mL)	Drug Product Volume (mL)	Drug Product Volume (vial)	Aspirated 0.9% NaCl Volume (mL)	Target Final Concentration (mg/mL)
40	80	50	8.0	1	8.0	1.60
42	84	50	8.4	1	8.4	1.68
44	88	50	8.8	1	8.8	1.76
46	92	50	9.2	1	9.2	1.84
48	96	50	9.6	1	9.6	1.92
50	100	50	10.0	1	10.0	2.00
52	104	50	10.4	2	10.4	2.08
54	108	50	10.8	2	10.8	2.16
56	112	50	11.2	2	11.2	2.24
58	116	50	11.6	2	11.6	2.32
60	120	50	12.0	2	12.0	2.40
62	124	50	12.4	2	12.4	2.48
64	128	50	12.8	2	12.8	2.56
66	132	50	13.2	2	13.2	2.64
68	136	50	13.6	2	13.6	2.72
70	140	50	14.0	2	14.0	2.80
72	144	50	14.4	2	14.4	2.88
74	148	50	14.8	2	14.8	2.96
76	152	50	15.2	2	15.2	3.04
78	156	50	15.6	2	15.6	3.12
80	160	50	16.0	2	16.0	3.20
82	164	50	16.4	2	16.4	3.28
84	168	50	16.8	2	16.8	3.36
86	172	50	17.2	2	17.2	3.44
88	176	50	17.6	2	17.6	3.52
90	180	50	18.0	2	18.0	3.60
92	184	50	18.4	2	18.4	3.68
94	188	50	18.8	2	18.8	3.76
96	192	50	19.2	2	19.2	3.84
98	196	50	19.6	2	19.6	3.92
100	200	50	20.0	2	20.0	4.00

APPENDIX 8: THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES

The text below was obtained from the following reference: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). *Eur J Cancer* 2009;45: 228-247. [96]

DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

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

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

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

Non-measurable Disease

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

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

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

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT 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, saggital, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm× 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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

Non-target Lesions

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

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new

lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following 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 subject 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 PSA 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.

Histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors).

RESPONSE CRITERIA

Evaluation of Target Lesions

CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

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

Lesions that split or coalesce on treatment: When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion

sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of Non-target Lesions

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

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions.

When the subject also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the subject has only non-measurable disease: This circumstance arises in some Phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen, the subject should be considered to have had overall PD at that point. While it would be ideal

to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

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

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The subject'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 FDG-PET (PET scanning with the tracer fluorine-18 [F-18]fluorodeoxyglucose [FDG]) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The 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 subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

The best overall response is determined once all the data for the subject 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 subject 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 subject's best response depends on the subsequent assessments. For example, a subject 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 subject lost to follow-up after the first SD assessment would be considered unevaluable.

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

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

Note: 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 subjects with CR may not have a total sum of "zero" on the eCRF.

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

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

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

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

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

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also

permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (Phase 2 or 3) or trials where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

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

Duration of Overall Response

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

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

Duration of Stable Disease

Stable disease is measured from the start of the treatment (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 subjects 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 two measurements for determination of stable disease.

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

APPENDIX 9: GUIDELINES FOR SUPPORTIVE CARE

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- Diarrhea: Subjects should be monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or sever, endoscopic evaluation should be considered.
    - In subjects with severe enterocolitis, BGB-A317 will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
    - In subjects with moderate enterocolitis, BGB-A317 should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with BGB-A317 see Protocol Section 5.1.4.
- All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.
- Anemia: Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.
- Neutropenia: Prophylactic use of colony-stimulating factors including granulocyte colony-stimulating factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) is not allowed in this study. Therapeutic use of G-CSF is allowed in subjects with Grade 3-4 febrile neutropenia.

- Thrombocytopenia: Transfusion of platelets may be used if clinically indicated. Idiopathic thrombocytopenic purpura (ITP) should be ruled out before initiation of platelet transfusion.

- Anti-infective: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

- Immune-related AEs: Subjects who develop a Grade 2 or higher irAEs (eg, colitis, skin rash, hepatitis, uveitis, hypo- or hyperthyroidism, hypophysitis, or any other), should be discussed immediately with the sponsor. Depending on the type and severity of an irAE, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition.

- Infusion reaction: Infusion reactions may consist of 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, and cardiogenic shock. Subjects should be closely monitored for an infusion reaction during and immediately following drug infusion.

    - In the event of a Grade 1 or 2 infusion reaction, reduce the infusion rate by 50% for the entire remaining duration of that infusion. Proper medical management should be instituted, as indicated per type of the reaction. This includes but is not limited to an anti-histamine (eg, diphenhydramine or equivalent), anti-pyretic (eg, paracetamol or equivalent), and if considered indicated oral or IV glucocorticoids, epinephrine, brochodilators, and oxygen.

    - In the event of a Grade 3 or 4 infusion reaction, immediately stop the infusion. 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 IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

    - Regarding continuation of study therapy after an infusion reaction has occurred; see the guidelines in Protocol Section 10.13.2.

APPENDIX 10: IMMUNE-RELATED ADVERSE EVENTS MANAGEMENT GUIDANCE FOR INVESTIGATORS

The recommendations below for the diagnosis and management of any irAE 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 irAEs 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 irAE diagnosis:

- What was the temporal relationship between initiation of BGB-A317 and the adverse event?
- How did the patient respond to withdrawal of BGB-A317?
- Did the event recur when BGB-A317 was reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is disease progression or an alternative diagnosis a more likely explanation?

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

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

Immune-related Toxicity	**Diagnostic Evaluation Guideline**
Thyroid Disorders	Scheduled and repeat thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including *D*LCO.

Immune-related Toxicity	Diagnostic Evaluation Guideline
	Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen, and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
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, 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 patients experience new onset, acute or worsening eye inflammation, blurred vision or other visual disturbance, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3-4; every 2-3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol and drug 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. A liver biopsy is strongly encouraged for patient with Grade 3 or higher events.
Renal toxicity	Review hydration status, and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination, consider dermatology referral for skin biopsy.
Rheumatology	Conduct musculoskeletal history and perform complete rheumatology 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.

Immune-related Toxicity	Diagnostic Evaluation Guideline
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 T analysis, and refer to a cardiologist.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; *D*LCO, diffusing capacity for carbon monoxide; 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.

Treatment of Immune-related Adverse Events

- Immune-related AEs can escalate quickly; study treatment interruption, close monitoring, timely diagnostic work-up and treatment intervention, as appropriate, with patients is required
- Immune-related AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice and contact the study medical monitor
- For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study medical monitor
- Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory irAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil [MMF])
- Budesonide may be substituted for prednisolone if considered standard of care. Prednisolone is preferred over prednisone, in the event that hepatic metabolic activity may be affected by the adverse event.
- Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy

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

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to hospital and initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological Toxicity	**1** Mild symptoms		Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening	Initiate treatment with oral prednisolone or IV methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 1 month. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours	Discontinue study treatment.
Colitis / Diarrhea	**1** Mild symptoms: < 3 liquid stool per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days manage as a Grade 2 event	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks. Consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline Grade.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.
	4 Life-threatening symptoms		Discontinue study treatment.
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice daily) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: • For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. • For severe symptoms: IV methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Retreat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to hospital and seek urgent dermatology consultation	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3X ULN	Check LFTs within 1 week; and before the next dose, check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST 3-5X ULN	Recheck LFTs every 48-72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over at least 4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold all study treatment and, treatment may be resumed when resolved/improved to baseline grade and prednisolone tapered to ≤ 10 mg. Restart tislelizumab at 200 mg IV Q3Weeks when transaminase levels return to baseline. Pamiparib may be started after 2 cycles of tislelizumab is tolerable. Restart pamiparib at 20 mg orally twice daily. Dose increases to 40 mg orally twice daily may occur only if LFTs remain stable after 2 cycles of treatment at 20 mg dosing.
	3 ALT or AST 5-20X ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at	Permanently discontinue tislelizumab. Hold pamiparib until transaminase levels

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		least 4 weeks. Recheck LFTs every 2 days until improved. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate IV (methyl)prednisolone 2 mg/kg/day. Check LFTs every day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	return to baseline levels; reintroduce pamiparib only after discussion with the study medical monitor at a dose of 20 mg orally twice daily. Dose escalation to 40 mg orally twice daily may occur only if the LFTs remain stable after 2 cycles of treatment at 20 mg dosing.
	4 ALT or AST > 20X ULN	Initiate IV methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: · If on oral prednisolone, change to pulsed IV methylprednisolone · If on IV, add mycophenolate mofetil (MMF) 500-1000 mg twice daily · If worsens on MMF, consider addition of tacrolimus Duration and dose of steroid required will depend on severity of event		
Nephritis	**1** Creatinine 1.5X baseline or > ULN to 1.5X ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5-3X baseline or > 1.5-3X ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to Grade 0-1: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3X baseline or > 3-6X ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg.	Hold study treatment until the cause is investigated.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		Taper corticosteroids over at least 1 month.	If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6X ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Checks for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended	Continue Study Treatment.
	2 Fasting glucose value 160 - 250 mg/dL; 8.9 - 13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue Study Treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250 - 500 mg/dL; 13.9 - 27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
Ocular Toxicity	**1** Asymptomatic eye exam/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue Study Treatment
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue Study Treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance
	3 Posterior uveitis/ panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks	Discontinue study treatment

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	Blindness (at least 20/200) in the affected eyes		
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes	Continue study treatment
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment, manage as a Grade 3 event.	Continue treatment or, if symptoms continue worsens, hold study treatment until symptoms improve to baseline or Grade 0-1
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline	Continue study treatment
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guideline, treat with analgesics, topical treatments and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as Grade 3.	Continue study treatment
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms	Hold study treatment until improved to Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		improved to Grade 2 and taper over at least 4 weeks	
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider IV corticosteroids if not contraindicated by infection	Discontinue study treatment
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 X ULN or worse initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks	Hold study treatment until improved to Grade 0-1
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks	Hold study treatment until improved to Grade 0-1. Discontinue if any evidence of myocardial involvement
Myocarditis	**1** Asymptomatic but abnormal CK-MB, cardiac troponin or intraventricular conduction delay	Admit to hospital and refer to a cardiologist. Transfer all patients with moderate/severe cardiac symptoms or any increase in cardiac serum markers to the coronary care unit. Initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab or anti-thymocyte globulin	Hold study treatment until completely resolved or myocarditis has been ruled out.
	2 Symptoms on mild-moderate exertion		Discontinue study treatment unless cardiac involvement has been excluded and symptoms have completely resolved
	3-4 Severe symptoms with exertion		

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

APPENDIX 11: CRITERIA FOR INTERRUPTION AND RE-INITIATION OF PAMIPARIB

Criteria for treatment modifications and suggested guidelines for the management of some toxicities related to pamiparib are summarized below. These general guidelines may be modified at the discretion of the investigator based on best clinical judgment at that time. Any toxicities related to pamiparib should be managed according to standard medical practice.

Dosing of pamiparib can be withheld for up to 28 days consecutively. If drug is planned to be held > 28 days, the medical monitor should be contacted before permanent patient discontinuation from the study drug.

Criteria for treatment modifications and suggested guidelines for the management of some toxicities related to pamiparib are summarized below. These general guidelines may be modified at the discretion of the investigator based on discussions with the medical monitor and the best clinical judgment at that time; any decisions should be documented. Any toxicities related to pamiparib should be managed according to standard medical practice.

A maximum of one dose reduction is allowed before the patient is permanently withdrawn from pamiparib administration. Dose levels for pamiparib are in 20 mg increments and are summarized in the Table below.

Dose Levels for Pamiparib

Dose Level	Pamiparib	
1	40 mg orally twice daily or	60 mg orally twice daily
-1	20 mg orally twice daily	40 mg orally twice daily

After discussions with the medical monitor, pamiparib may be dose-reduced for a maximum of 2 dose reductions.

A dose reduction will be made in a 20 mg increment. For example, pamiparib 40 mg orally twice daily will be dose reduced to 20 mg orally twice daily for any NCI CTCAE Grade ≥2 hematologic toxicity. If pamiparib 20 mg orally twice daily is not tolerable, then pamiparib should be discontinued.

Specific guidance for the treatment of anemia includes:

Adverse events of anemia with NCI CTCAE Grade 1 or 2 (Hb ≥ 8 g/dL) should be investigated and managed as deemed appropriate by the investigator with or without interruption of study drug or change in dose, taking into account previous history of anemia. Common treatable causes of anemia (eg, iron, vitamin B12, or folate deficiencies, and

hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions.

If a patient develops anemia with CTCAE Grade 3 (Hb < 8g/dL) or worse, study treatment should be interrupted for up to maximum of 3 weeks.

Study treatment can be restarted at the same dose if Hb has recovered to Grade 2 or better, ie, ≥ 8 g/dL. Any subsequently required anemia-related interruptions, considered likely to be dose related, or coexistent with newly developed neutropenia, and or thrombocytopenia, will require pamiparib dose reductions to 20 mg orally twice daily.

If a patient has been treated for anemia with multiple blood transfusions and becomes blood transfusion dependent as judged by investigator, pamiparib study treatment should be discontinued.

Pamiparib will be dose-modified as outlined in the Table below.

Recommended dose modifications for Pamiparib

Toxicity	Recommended Dose Modification[a]
Hematologic	
Anemia (Hgb)	
Grade 2 (Hgb < 10 - 8 g/dL) *Only applies to patients with ≤ Grade 1 at baseline*	First occurrence: continue dosing at current dose level Second and subsequent occurrences: hold pamiparib until resolved to ≤ Grade 1 or baseline • If resolved ≤ 14 days, then maintain dose levels • If resolved > 14 days, then ↓ pamiparib by 1 dose level
Grade 3 (Hgb < 8 g/dL)	Hold pamiparib until resolved to ≤ Grade 1 or baseline • If resolved ≤ 14 days, then maintain dose levels • If resolved > 14 days, then ↓ pamiparib by 1 dose level
Grade 4 (life-threatening consequences; urgent intervention indicated)	Hold pamiparib until resolved to ≤ Grade 1 or baseline and ↓ pamiparib by 1 dose level
Neutropenia (ANC)	
Grade 3 (ANC < 1.0 - 0.5 × 10^9/L)	Hold pamiparib until resolved to ≤ Grade 2 or baseline • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ pamiparib by 1 dose level
Grade 4 (ANC < 0.5 × 10^9/L)	Hold pamiparib until resolved to ≤ Grade 1 or baseline and ↓ pamiparib by 1 dose level
Febrile neutropenia (ANC < 1.0 × 10^9/L with single temperature of > 38.3°C or sustained temperature of ≥ 38°C for > 1 hour)	Hold pamiparib until resolved and ↓ pamiparib by 1 dose level

Toxicity	Recommended Dose Modification[a]
Thrombocytopenia (PLT)	
Grade 3 (PLT < 50 - 25 × 10^9/L)	Hold pamiparib until resolved to ≤ Grade 1 or baseline • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ pamiparib by 1 dose level
Grade 4 (PLT < 25 × 10^9/L)	Hold pamiparib until resolved to ≤ Grade 1 or baseline and ↓ pamiparib by 1 dose level
Renal	
Serum creatinine	
2-3 × ULN	Hold pamiparib until resolved to ≤ Grade 1 or baseline • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ pamiparib by 1 dose level
Grade 3 (> 3.0 - 6.0 × ULN) and Grade 4 (> 6.0 × ULN)	Permanently discontinue pamiparib
Hepatic	
Bilirubin	
Grade 2 (> 1.5 - 3.0 × ULN) and Grade 3 (> 3.0 - 10.0 × ULN)	Hold pamiparib until resolved to ≤ Grade 1 or baseline • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ pamiparib by 1 dose level
Grade 4 (> 10.0 × ULN)	Permanently discontinue pamiparib Note: If Grade 3 or 4 hyperbilirubinemia is due to the indirect (unconjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (eg, review of peripheral blood smear and haptoglobin determination), then ↓ pamiparib by 1 dose level and continue treatment at the discretion of the investigator in discussion with the medical monitor
AST and/or ALT	
Grade 3 (> 5 and ≤ 20 × ULN)	• Hold pamiparib until transaminase levels have resolved and the prednisolone doses are consistent with replacement corticosteroid doses (< 10 mg). Restart pamiparib only after discussion with medical monitor at a dose of 20 mg orally twice daily.
Grade 4 (> 20 × ULN)	Permanently discontinue pamiparib
Pancreatic	
Pancreatitis	
Grade 3 or 4	Permanently discontinue pamiparib
Cardiac	
Cardiac - Prolonged QTc interval	

Toxicity	Recommended Dose Modification[a]
QTcF > 500 msec	• Obtain triplicate ECGs (2 to 3 minutes apart) ~1 hour after initial ECG • If mean QTcF > 500 ms, hold pamiparib until evaluation of ECGs by cardiologist o Cardiology evaluation as soon as practical but within 7 days of initial abnormal ECG • If mean QTcF > 500 ms confirmed by cardiologist, permanently discontinue pamiparib
Cardiac - General	
Grade 3	Hold pamiparib until resolved to ≤ Grade 1 or baseline and ↓ pamiparib 1 dose level
Grade 4	Permanently discontinue pamiparib
Other adverse events	
Grade 3	Hold pamiparib until resolved to ≤ Grade 1 or baseline and ↓ pamiparib by 1 dose level No dose reduction required for asymptomatic laboratory abnormalities
Grade 4	Permanently discontinue pamiparib

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ECG, electrocardiogram; Hgb, hemoglobin; PD, progressive disease; PLT, platelet (count); QTcF, QT interval corrected for heart rate using Fridericia's formula; ULN, upper limit of normal.

a. Dosing of pamiparib can be withheld for up to 28 days consecutively.

APPENDIX 12: PROHIBITED MEDICATIONS (STRONG AND MODERATE CYP3A INHIBITORS AND STRONG CYP3A INDUCERS

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Strong CYP3A Inducers
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (*Hypericum perforatum*)
Moderate CYP3A Inhibitors
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole
Protease inhibitors: amprenavir, atazanavir, darunavir, fosamprenavir
Calcium channel blockers: diltiazem, verapamil
Tyrosine kinase inhibitors (anticancer): imatinib
Food products: grapefruit and juice (*Citrus paradisi*), Seville orange and juice (*Citrus aurantium*)
Herbal medications: *Schisandra sphenanthera*
Others: aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam

Data compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;"
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664 htm

from the Indiana University School of Medicine's "Clinically Relevant" Table
http://medicine.iupui.edu/flockhart/table.htm;

from the University of Washington's Drug Interaction Database
www.druginteractioninfo.org

APPENDIX 13: MEDICATIONS TO BE USED WITH CAUTION (SENSITIVE CYP2C9 SUBSTRATES OR CYP2C9 SUBSTRATES WITH NARROW THERAPEUTIC INDEX)

Celecoxib[1]
Phenytoin[2]
Warfarin[2]

[1] Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor, where AUCi is the AUC of the substrate when coadministered with a known potent inhibitor and AUC is the AUC of substrate alone.
[2] Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (eg, Torsade de Pointes).

APPENDIX 14: MEDICATIONS TO BE USED WITH CAUTION (STRONG CYP2C8 INHIBITORS)

Gemfibrozil

APPENDIX 15: PRE-EXISITING 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 sponsor medical monitor regarding any uncertainty about immune deficiency/autoimmune disease exclusions.

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

APPENDIX 16: NEW YORK HEART ASSOCIATION CLASSIFICATION

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, eg, no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

APPENDIX 17: CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL", "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

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

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
    - Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized male partner
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment).
  NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

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

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

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

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

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
    - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
    - < 55 years of age with no spontaneous menses for ≥ 12 months AND with postmenopausal follicle-stimulating hormone concentration > 30 IU/mL

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

APPENDIX 18: CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION EQUATION

In adults, the most widely-used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the Modification of Diet in Renal Disease (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. Read more about creatinine standardization.
This CKD-EPI equation calculator should be used when S_{Cr} reported in mg/dL. This equation is recommended when eGFR values above 60 mL/min/1.73 m^2 are desired.

The source of the equation shown below is as follows:

- Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.

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

where:
Scr 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.

Abbreviations: eGFR = estimated glomerular filtration rate; S_{Cr} = standardized serum creatinine; max = indicates the maximum of S_{Cr}/κ or 1min = indicates the minimum 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