Clinical Study Protocol

Protocol Title:	**An Open Label, Multi-Center Phase I/II Study to Evaluate Efficacy and Safety of BGB-290 in Chinese Subjects with Advanced Ovarian Cancer, Fallopian Cancer, and Primary Peritoneal Cancer or Advanced Triple Negative Breast Cancer**
Protocol Number:	**BGB-290-102**
Date of Protocol:	**21 September 2018, Version 5.0**
Study Phase:	**1/2**
Sponsor:	**BeiGene (Beijing) Co., Ltd** **No. 30, Science Park Rd.** **Zhong-Guan-Cun Life Science Park** **Changping District 102206** **Beijing, China**
Sponsor Medical Monitor:	[redacted]

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FINAL PROTOCOL APPROVAL SHEET

An Open Label, Multi-Center Phase I/II Study to Evaluate Efficacy and Safety of BGB-290 in Chinese Subjects with Advanced Ovarian Cancer, Fallopian Cancer, and Primary Peritoneal Cancer, or Advanced Triple Negative Breast Cancer

BeiGene Approval:

_____ _____

[redacted] Date

Sponsor Medical Monitor

PROTOCOL AMENDMENT, VERSION 5.0, RATIONALE

The main purpose of this protocol amendment is to update the dose modification algorithm for anemia in the Phase 2 portion of this study. Meanwhile, content in the Note to Files to the last approved protocol amendment (version 4.0) were incorporated. In addition, some content was modified to improve the clarity of the document. Changes were made to the synopsis to match those in the protocol body.

This amendment version number is version 5.0.

Substantial changes from version 4.0 are summarized as below:

- Table 5 (Study Visit Schedule in Phase 1 Portion), changed column title "Cycle 4 and Subsequent Cycles (every 21 days for one Cycle)" to "Cycle 4 and Subsequent Cycles (every 21 days for 1 cycle in Year 1, every 12 weeks ± 7 days thereafter)"
- Section 4.1.2 (Phase 2 Portion), Table 5 Footnote 4, Table 7 Footnote 6 and Section 4.2.1 (Inclusion Criteria) #3-2)-a)-ii, updated the criteria to define platinum-sensitive from "if disease progression had occurred more than 6 months after their last dose of platinum treatment" to "≥ 6 months after their last dose of platinum treatment"
- Section 4.1.2.1 (Safety, Tolerability and Efficacy), added and specified "Dose interruption due to investigational drug-related anemia could be on hold for up to 56 days consecutively"
- Section 4.1.3 (Follow-up for Toxicities), updated "If the levels have not recovered to NCI-CTCAE ≤ Grade 1 or baseline after 4 weeks" to "If the levels have not recovered to NCI-CTCAE ≤ Grade 1 or baseline after 8 weeks"
- Section 4.2.4 (Patient Discontinuation and Withdrawal) and Table 7 (Study Visit Schedule in Phase 2 Portion) Footnote 3, added "If discontinuation is due to unresolved toxicities for more than 21 days (56 days for anemia), EOT visit should be conducted at the earliest day as possible within 5 days after permanent discontinuation is determined"
- Table 5 (Study Visit Schedule in Phase 1 Portion) and Table 7 (Study Visit Schedule in Phase 2 Portion)
  - Added pregnancy test to visits of Cycle 2 and subsequent cycles, EOT, and Safety Follow-up in the assessment table
  - Updated Table 5 Footnote 14 and Table 7 Footnote 15 to "For women of childbearing potential including those who have had a tubal ligation, urine or serum pregnancy test must be performed and documented as negative within 7 days prior to Cycle 1 Day 1, and urine pregnancy tests will be performed at each visit prior to dosing. A serum pregnancy test must be performed if urine pregnancy test is positive or equivocal"
- Table 7 (Study Visit Schedule in Phase 2 Portion),
  - Footnote 3 and Section 4.2.4.2 (End of Treatment Visit), clarified the rule for the assessment of CT/MRI at EOT by deleting "within 14 days of the EOT visit"
  - Footnote 4, added "If discontinuation is due to unresolved toxicities for more than 21 days, safety follow-up could be scheduled 30 ± 5 days after the last dose of

treatment. If discontinuation is due to unresolved toxicities for more than 56 days for anemia, safety follow-up could be scheduled at the earliest day possible within 5 days after permanent discontinuation is determined"

- Footnote 9, added "Weekly hematology test should be done for the first 3 cycles during the study"

- Table 8 (Pharmacokinetic Sampling in Phase 2 Portion) General note, added "For sparse PK sampling, the sequence of collection at a particular time point may be determined by the sites based on feasibility"
- Section 4.2.1 (Inclusion Criteria) #3-2)-a)-i, revised "patients must have received at least 2 lines of therapy in the advanced or metastatic setting" to "patients must have received at least 2 lines of standard chemotherapy"
- Section 4.2.2 (Exclusion Criteria)
  - #2, removed "surgical therapy"
  - #12, updated "a negative serum pregnancy test" to "a negative urine or serum pregnancy test"
- Section 5.2 (Dosage and Administration) Phase 2 Portion,
  - Clarified the dose administration interval from "The time difference between two consecutive doses should be at least 8 hours and generally not more than 12 hours" to "The time difference between two consecutive doses will be approximately 12 hours with a window of ± 4 hours"
  - Added "However, to reduce gastrointestinal irritation that parmiparib may cause, patients are encouraged to take parmiparib with food"
  - Revise "A dose of pamiparib should be skipped if it is not taken within 2 hours of the scheduled time" to "A dose of pamiparib should be skipped if it is not taken within the upper range of the scheduled time, ie, within 16 hours"
- Section 5.2.1 (Treatment interruption and treatment discontinuation), added "For reasons other than drug-related AEs, eg, safety concerns due to the poor health condition, if deemed necessary by the investigators, dose modifications could be applied after discussion with medical monitor"
- Table 9 (Criteria for interruption and re-initiation of Pamiparib due to treatment associated adverse event),
  - Revised the dose modification algorithm for anemia in the Phase 2 portion
  - Removed "Dosing of pamiparib can be withheld for up to 28 days consecutively" from the footnote
- Section 7.8 [redacted]."
- Section 9.1.4 (Follow-Up of Adverse Events),
  - Deleted "Once resolved, the appropriate AE or SAE eCRF page(s) will be updated"

  - Revised “new or updated information will be recorded on the originally completed SAE report/eCRF” to “New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in Section 9.6.1”

- Section 9.3 (Suspected Unexpected Serious Adverse Reaction), revised “meet the definition of an SAE” to “meets the definition of a serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the IB”
- Section 9.5.1 (Disease Progression), revised “event(s)” to “adverse event(s)”
- Section 9.6.1 (Timeframes for Submitting Serious Adverse Events), specified prompt reporting by adding “within 24 hours”
- Table 10 (Time Frame for Reporting Serious Adverse Events to the Sponsor or Designee), revised the table by updating the Documentation Method and adding Reporting Method
- Section 9.6.2 (Completion and Transmission of the Serious Adverse Event Report),
  - Replaced “SAE eCRF” with “SAE Report”
  - Removed “The data alert letter will automatically be submitted to sponsor or designee immediately after investigator signature”
  - Removed the content specifying the transmission rules of paper SAE forms under the situation when EDC is non-operational.
- Appendix 2 (Clinical Laboratory Assessments),
  - Updated “Blood urea nitrogen” to “Blood urea nitrogen or urea” in Clinical Chemistry
  - Removed “and a random urine sample for total protein and creatinine to determine a protein to creatinine ratio” from the footnote
- Appendix 8 (Prohibited Medications), updated the food products among moderate CYP3A inhibitors from “grapefruit juice (citrus paradisi fruit juice)” to “grapefruit and juice (*Citrus paradisi*), Seville orange and juice (*Citrus aurantium*)”

SYNOPSIS

Name of Sponsor/Company:	BeiGene (Beijing) Co., Ltd
Name of Finished Product:	Pamiparib (BGB-290) Capsules
Name of Active Ingredient:	Pamiparib (BGB-290)
Title of Study:	An Open Label, Multi-Center Phase I/II Study to Evaluate Efficacy and Safety of BGB-290 in Chinese Subjects with Advanced Ovarian Cancer, Fallopian Cancer, and Primary Peritoneal Cancer or Advanced Triple Negative Breast Cancer
Protocol No:	BGB-290-102
Study Centers:	Phase 1: in 2 study centers Phase 2: in 25 to 35 study centers

Study Duration: **Phase: 1/2**

For Phase 1: Screening (up to 21 days), treatment cycle of 23 days (Cycle 1 only) and repeated treatment cycles of 21 days, safety follow-up (30 ± 5 days after the last dose of pamiparib [also known as BGB-290]). Patients will continue treatment until confirmed disease progression, intolerable toxicity, withdrawal of consent, or deemed unacceptable for further treatment at the discretion of the investigators, whichever occurs first.

For Phase 2: Screening (up to 21 days), repeated treatment cycles of 21 days, safety follow-up (30 ± 5 days after the last dose of pamiparib). Patients will continue treatment until confirmed disease progression, intolerable toxicity, withdrawal of consent, or at the discretion of the investigators.

Objectives:

Phase 1

Primary:

- To evaluate the safety and tolerability of pamiparib for advanced cancer in Chinese patients
- To determine the recommended Phase 2 dose (RP2D) of pamiparib

Secondary:

- To characterize the pharmacokinetics (PK) of pamiparib in Chinese patients
- To evaluate the clinical anti-tumor activity of pamiparib in Chinese patients with triple negative breast cancer (TNBC) or high-grade epithelial, non-mucinous ovarian cancer (including fallopian cancer, or primary peritoneal cancer)
- To evaluate the relationship between pamiparib PK and clinical endpoints

Exploratory:

- [redacted]

Phase 2

Primary:

- To evaluate the efficacy of pamiparib as measured by objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (RECIST V 1.1), by independent radiology review (IRR) in patients with advanced platinum-sensitive or platinum-resistant high grade, non-mucinous, epithelial ovarian cancer (including fallopian cancer or primary peritoneal cancer), harboring germline breast cancer susceptibility gene 1/gene 2 (*BRCA1/2)* mutation

	Secondary: • To evaluate the efficacy of pamiparib as measured by progression free survival (PFS), duration of response (DOR) by both IRR and investigator review, and overall survival (OS) by investigator review • To evaluate the efficacy of pamiparib as measured by the objective response rate by investigator review • To evaluate the safety and tolerability of pamiparib • To evaluate the efficacy of pamiparib as measured by disease control rate (DCR), best overall response (BOR) and clinical benefit rate (CBR) by both IRR and investigator review • To evaluate the carcinoma antigen-125 (CA-125) response rate per Gynecological Cancer Intergroup (GCIG) criteria for CA-125 changes • To further characterize the PK of pamiparib Exploratory: • [redacted]
Methodology:	This is a Phase 1/2, open-label, multi-center study of pamiparib administered orally (PO) twice daily (BID) to adult Chinese patients with advanced solid tumors, which have progressed despite standard therapy, or for which no standard therapy exists. The Phase 1 portion of this study is designed to evaluate the safety, tolerability and PK profile of pamiparib in Chinese patients with advanced cancer and to determine the recommended Phase 2 dose (RP2D) of pamiparib for Chinese patients. In the Phase 2 portion of this study, approximately 100 evaluable Chinese patients will be evaluated for the efficacy, safety, tolerability, and PK profile of pamiparib: • Eighty (80) previously treated platinum-sensitive patients and 20 previously treated platinum-resistant patients with advanced high grade, non-mucinous, epithelial ovarian cancer (including fallopian cancer, or primary peritoneal cancer) with either known deleterious or suspected deleterious germline *BRCA1/2* mutation In the Phase 1 portion of the study, fresh blood samples at baseline for all patients must be collected for the purposes of retrospective germline *BRCA1/2* mutation testing. In the Phase 2 portion of the study, all patients, including those with known germline *BRCA1/2* mutation status need to undergo centralized germline *BRCA* mutation testing and have germline *BRCA1/2* mutation confirmed before being eligible for the study. Archival tumor tissues will be collected for all patients, if available. **Phase 1** Adult patients with advanced solid tumors which have progressed despite standard therapy or for which no standard therapy exists will be enrolled. Dose escalation will follow a modified 3+3 scheme: • If no dose limiting toxicity (DLT) is observed in a cohort of 3-6 patients at a given dose level, the next cohort of 3-6 new patients may be enrolled at the next higher dose level. • At least 3 patients will be enrolled into each cohort. Additional patient(s), up to a maximum of 6 patients in total, will be enrolled if more than 3 have been screened and are eligible for the cohort. The DLT assessment and dose escalation scheme will follow the same principle as stipulated for a standard 3+3 dose escalation design. For example, 3 additional patients will be enrolled if a DLT is observed in

	1 of 3 patients; an additional 2 patients will be enrolled if a DLT is observed in 1 of 4 patients; and an additional 1 patient will be enrolled if a DLT is observed in 1 of 5 patients. No additional patients are required if a DLT is observed in 1 of 6 patients. • If DLT occurs in 2 patients in a cohort of up to 6 patients at a given dose level, then this dose level will be defined as the DLT dose level. All investigators will be informed, no additional patient(s) will be enrolled at the DLT dose level, and dose escalation will stop. To be included in a dose-escalation decision, an evaluable patient is defined as one who either experienced a DLT during the first 23-day treatment cycle (Cycle 1) or has not experienced a DLT and has been administered for at least 18 days (ie, at least 75% of the dose) and completed all safety evaluations required in Cycle 1. Dose escalation will continue until RP2D or maximum tolerated dose (MTD), if any, is reached. <u>Starting dose and dose levels</u> The starting dose for pamiparib will be 20 mg BID which was based on the doses evaluated in the on-going first-in-human (FIH) Phase 1 study of pamiparib in Australia, and is significantly lower than the highest safe dose that has been identified to date. The dose escalation phase of the FIH study has been completed. Doses levels of 2.5, 5, 10, 20, 40, 60, 80 and 120 mg BID have been evaluated in 45 patients. Drug exposure is linear up to 80 mg BID. Therefore, 80 mg BID was determined to be the MTD and 60 mg BID is the RP2D for the dose expansion phase in that study. Three dose levels of 20, 40 and 60 mg BID are planned for the dose escalation phase. An intermediate, not pre-defined, and not previously-evaluated dose or a less frequent dosing schedule could be evaluated in dose escalation phase if necessary. <u>Dose-Limiting Toxicity</u> Adverse events (AEs) will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. A DLT is defined as an AE or abnormal laboratory value that occurs during the DLT assessment window and is assessed as unrelated to disease progression, intercurrent illness, or concomitant medications that meets one of the following criteria: *Hematologic:* • Grade 4 neutropenia lasting >7 days • Febrile neutropenia • Grade 3 neutropenic infection • Grade 3 thrombocytopenia with bleeding • Grade 4 thrombocytopenia • Grade 4 anemia *Non-hematologic:* • ≥ Grade 3 nausea, vomiting and diarrhea despite optimal supportive care • Any other clinically relevant ≥ Grade 3 non-hematologic toxicity (excluding asymptomatic biochemical abnormalities that are not clinically significant and resolve to ≤ Grade 2 in <7 days) • Any toxicity grade which in the judgment of the investigator or sponsor is dose limiting

Monitoring for DLT (SMC meetings)

Meetings or teleconferences between the sponsor or its designee and investigators (Safety Monitoring Committee [SMC]) will be held on a regular basis to review all safety data including DLTs. The dose for each new cohort will be determined by SMC at a dose-escalation meeting by evaluating all available safety (including AEs that are not DLTs), PK, pharmacodynamics, and efficacy data. The SMC consists of investigators, the sponsor's medical delegate, safety delegate, and the contract research organization's medical monitor. Ad hoc members will be consulted as needed and may include, but are not restricted to the biostatistician and pharmacokineticist. Whenever a DLT occurs (as defined below), the affected site must immediately inform the sponsor or its designee. The sponsor or its designee will then inform all other sites that a DLT has occurred and determine if a second DLT has occurred at any other site at the same dose. If two DLTs have occurred at the same dose level based on evaluation of the patients at all sites, further enrolment of new patients at that dose level will be suspended until a safety evaluation meeting takes place to determine if the MTD has been exceeded.

Once a DLT level has been established at a safety evaluation meeting, additional patients can be enrolled at a lower dose level (ie, the presumptive MTD) until a total of 6 patients have been treated at that dose level.

Maximum Tolerated Dose

MTD is the dose level at which 0/6 or 1/6 patients experiences DLT, provided that ≥ 33% of patients experienced DLT (eg, 2 of 3 or 2 of 6) at the next higher dose level. Even though an MTD may have been reached, a RP2D may still be selected which will take into account the MTD as well as available information on lower dose grade of AEs, AEs occurring in later cycles, PK, pharmacodynamics, and efficacy data. This decision will be made at a SMC meeting or teleconference at the time that the dose for the dose expansion phase is decided. At least 6, and up to 10 patients could be treated at RP2D.

Phase 2

Based upon the overall safety, efficacy, and PK profile of pamiparib, the dose of pamiparib 60 mg PO BID was confirmed as RP2D using available clinical data from study BGB-290-AU-002 and the Phase 1 portion of this study.

The following patients will be evaluated at 60 mg BID of pamiparib for efficacy, safety and tolerability in this Phase 2 portion:

- High grade (Grade 2 or Grade 3 endometrioid epithelial cancer is acceptable too), non-mucinous, epithelial ovarian cancer (including fallopian cancer, or primary peritoneal cancer), with either known deleterious or suspected deleterious germline *BRCA1/2* mutation: approximately 80 evaluable patients with platinum-sensitive high grade ovarian cancer (HGOC) and 20 evaluable patients with platinum-resistant HGOC

Study Plan

Only for the Phase 1 dose escalation portion, the patient will take a single dose of pamiparib on Cycle 1 Day1. On Day 3, after a one-day treatment-free period, patients will receive pamiparib BID continuously from Days 3 to 23, of Cycle 1 and in subsequent 21-day cycles. For Phase 2 portion, 21-day period of repeated drug administration (Days 1 to 21, BID) starts from Cycle 1.

Patients may continue treatment with pamiparib until the patient experiences disease progression or unacceptable toxicity that preclude any further treatment, or is discontinued from treatment at the discretion of investigator, or the patient withdraws consent from the study. An end of treatment (EOT) visit will be conducted at the earliest day possible within 5 days of the last dose of pamiparib, and a safety follow-up will be conducted approximately 30 days after the last dose of pamiparib. All patients will be followed for

	AEs, serious adverse events (SAEs) and concomitant medications (including any new cancer treatment) for 30 days following the last dose of pamiparib. **Assessment** All patients will be followed for safety, tolerability, and efficacy from the first dosing day to the 30 days after the last dose. Safety evaluation For the Phase 1 portion, safety evaluation (eg, AE, physical examinations, clinical laboratory assessments, vital signs) will be performed at the time points specified in Table 5. Electrocardiograms (ECGs) will be assessed with matching PK time points from Cycle 1 to Cycle 3. Subsequent ECG evaluations are outlined in Table 6 for the Phase 1 portion. For the Phase 2 portion, safety evaluation will be conducted at the clinical site on Day 1 of each cycle. Clinical laboratory evaluation should be conducted before dosing on visit days at the clinical sites. A 12-lead ECG will be performed as clinically indicated during treatment and at safety follow-up. For ECG test during the PK sample collection, follow instructions in Table 8 Efficacy assessment For the Phase 1 portion, tumor response will be assessed by investigators based on RECIST, version 1.1. For the Phase 2 portion, tumor response will be assessed separately by IRR and investigator's review based on RECIST, version 1.1. Tumor response will be evaluated once every 6 weeks ± 7 days for the first 18 weeks, thereafter once every 9 weeks ± 7 days for the remaining period in the first year, and then once every 12 weeks ± 7 days starting with the second year. For patients with a first response of complete response (CR) or partial response (PR), a response confirmation will need to be performed during the following 4-6 weeks, then patients will keep original tumor assessments schedule per protocol.
Planned Number of Patients:	Phase 1: Approximately 14-18 evaluable patients for the dose escalation until RP2D determination Phase 2: Approximately 100 evaluable HGOC patients.
Diagnosis and Main Criteria for Inclusion:	Patients may be enrolled in the study only if they meet all of the following criteria: 1. Patients have voluntarily agreed to participate by giving written informed consent. 2. Age 18 years (including 18 years) on the day of signing informed consent. 3. Patients meet the following eligibility criteria for the corresponding part of the study: 1) In Phase 1 portion: a) The patients must have a histologically or cytologically confirmed locally advanced or metastatic cancer, either TNBC or epithelial, non-mucinous, HGOC (including fallopian cancer, or primary peritoneal cancer), for which no effective standard therapy is available. b) *BRCA1* and *BRCA2* mutations are not required but enrichment of this patient population is preferred. c) Patients must agree to retrospective germline *BRCA* testing using blood samples. d) Archival tumor tissues will be collected, if available. 2) In Phase 2 portion: a) Patients who have histologically or cytologically confirmed high-grade (Grade 2 or Grade 3 endometrioid epithelial cancer is acceptable too),

	non-mucinous, epithelial ovarian cancer (including fallopian cancer or primary peritoneal cancer), harboring germline BRCA1/2 mutation and must meet the following criteria: i. Patients must have received at least 2 lines of standard chemotherapy, currently with relapsed/progressive disease or have withdrawn due to unacceptable toxicity from most recent standard treatment ii. Platinum-sensitive, or platinum-resistant patients (Patients are defined as platinum-sensitive if disease progression by RECIST, version 1.1 criteria, had occurred ≥ 6 months after their last platinum treatment, while platinum-resistant is defined if disease progression occurred < 6 months after the last platinum treatment) iii. If mixed histology, >50% of the primary tumor had to be confirmed to be high-grade (Grade 2 or Grade 3 endometrioid epithelial cancer is acceptable too), non-mucinous, epithelial ovarian cancer b) All patients will be required to undergo germline BRCA1/2 mutation testing using blood samples prior to enrolment. c) Archival tumor tissues will be collected from all patients, if available. 4. Patients must have measurable disease as defined per the RECIST, version 1.1. 5. Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 (Appendix 3) 6. Life expectancy ≥ 12 weeks 7. Patients must have adequate organ function as indicated by the following laboratory values: • Absolute neutrophil count (ANC) ≥ 1,500/mm^3 or 1.5 x 10^9/L • Platelets ≥ 75,000/mm^3 or 75 x 10^9/L • Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L (If transfusion is used, at least 14 days should pass before re-test for hematology is performed at the screening visit) • Estimated glomerular filtration rate (eGFR) ≥ 30 mL/1.73m^2 by Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI EQ; Appendix 6) • Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN) • Aspartate aminotransferase and alanine aminotransferase ≤ 3 x ULN 8. Females of childbearing potential and nonsterile males (only for Phase 1 portion), must practice highly effective method of birth control (Appendix 11) for the duration of the study and for at least 6 months after the last study drug administration
Main criteria for Exclusion:	Patients will not be entered in the study for any of the following reasons: 1. Patients who have been treated with chemotherapy, biologic therapy, immunotherapy, investigational agent, anti-cancer Chinese medicine, or anti-cancer herbal remedies ≤ 14 days (or ≤5 half-lives, whichever is shorter) prior to starting study drug, or who have not adequately recovered from the side effects of such therapy.

	2. Patients who have undergone major surgery for any cause ≤ 4 weeks prior to starting study drug. Patients must have adequately recovered from the previous treatment and have a stable clinical condition before entering the study. 3. Patients who have undergone radiotherapy for any cause ≤ 14 days prior to starting study drug. Patients must have adequately recovered from the previous treatment and have a stable clinical condition before entering the study. 4. Untreated and/or active brain metastases. • A scan to confirm the absence of brain metastases is not required. • Patients with treated brain metastases must be off corticosteroids for ≥ 14 days and have no signs or symptoms of progressive brain metastases. 5. Prior therapies targeting poly (ADP-ribose) polymerase (PARP). 6. Inability to swallow oral medications (capsules and tablets) without chewing, breaking, crushing, opening or otherwise altering the product formulation. 7. Patients with any of the following cardiovascular criteria: • Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days prior to Day 1 • Evidence of symptomatic pulmonary embolism within 4 weeks prior to Day 1 • Acute myocardial infarction ≤ 6 months prior to Day 1 • Heart failure of New York Heart Association Classification III or IV (see Appendix 12) ≤ 6 months prior to Day 1 • ≥ Grade 2 ventricular arrhythmia ≤ 6 months prior to Day 1 • Cerebrovascular accident ≤ 6 months prior to Day 1 8. Patients with other malignant cancer • Except for surgically excised non-melanoma skin cancer, adequately treated carcinoma *in situ* of the cervix, adequately treated low-stage bladder cancer, ductal carcinoma *in situ* treated surgically with curative intent, or a malignancy diagnosed ≥ 5 years ago with no current evidence of disease and no therapy ≥ 5 years prior to Day 1 9. Diagnosis of myelodysplastic syndrome (MDS) 10. Known human immunodeficiency virus (HIV) infection, active viral hepatitis, or active tuberculosis 11. Use ≤ 10 days (or ≤ 5 half-lives, whichever is shorter), prior to Day 1, or anticipated need for food or drugs known to be strong or moderate cytochrome P450 (CYP) 3A inhibitors or strong CYP3A inducers (Appendix 8) 12. Pregnancy or nursing: • Females of childbearing potential require a negative urine or serum pregnancy test ≤ 7 days before Day 1. 13. Significant intercurrent illness that may result in the patient's death prior to death from HGOC, or TNBC (only for Phase 1 portion). 14. Known history of intolerance to the excipients of the pamiparib capsule 15. Previous complete gastric resection, chronic diarrhea, active inflammatory gastrointestinal disease, or any other disease-causing malabsorption syndrome.

	• Gastroesophageal reflux disease under treatment with proton pump inhibitors is allowed. 16. Active bleeding disorder, including gastrointestinal bleeding, as evidenced by hematemesis, significant hemoptysis, or melena ≤ 6 months before Day 1 17. Any illness that investigator thinks makes the patient unsuitable for entry into the study. 18. Unsolved acute effects of prior therapy of ≥ Grade 2 • Except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
Test Product, Dose, and Mode of Administration:	Pamiparib oral 10 mg and 40 mg capsules for Phase 1 Pamiparib oral 20 mg capsules for Phase 2 **Phase 1:** BID, except for single administration on Day 1 of Cycle 1 and treatment-free on Day 2 of Cycle 1 Level 1: pamiparib, 20 mg PO BID Level 2: pamiparib, 40 mg PO BID Level 3: pamiparib, 60 mg PO BID The proposed dose levels may be further modified and additional doses may be added based on the safety, tolerability, and efficacy observed during the dose escalation. **Phase 2:** 60 mg BID, once in the morning and once in the evening. The time difference between two consecutive doses will be approximately 12 hours with a window of ± 4 hours.
Endpoints:	**Phase 1** <u>Primary Endpoints:</u> • Incidence of AE, overall and by severity, and incidence of SAE according to NCI-CTCAE, version 4.03; laboratory abnormalities; changes in laboratory assessments, ECGs, and assessment of physical examinations <u>Secondary Endpoints:</u> • PK parameters of pamiparib and possibly its major metabolite(s) at selected time points: area under the plasma concentration-time curve from 0 to the last measurable concentration (AUC_{last}), maximum observed plasma concentration (C_{max}), and time to reach C_{max} (T_{max}); elimination half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution during terminal phase (V_z/F) • Efficacy assessment by investigator based on the RECIST, version 1.1: o ORR is defined as the proportion of patients who had confirmed CR or PR o DOR is defined as the time from the first determination of a confirmed overall response until the first documentation of progression or death, whichever comes first o DCR is defined as a BOR of CR, PR and stable disease (SD) o CBR is defined as a BOR of CR, PR and SD lasting ≥ 24 weeks

	○ PFS is defined as the time from first dose of study medication to the first documented disease progression or death due to any cause, whichever occurs first Exploratory Endpoints: • [redacted] **Phase 2** Primary Endpoint: • ORR as defined above in advanced HGOC patients by IRR Secondary Endpoints: • DOR is defined as the time from the first determination of a confirmed overall response until the first documentation of progression or death, whichever comes first • PFS is defined as the time from first dose of study medication to the first documented disease progression or death due to any cause, whichever occurs first • OS is defined as time from the first dose of study treatment to the date of death due to any cause • ORR as defined above in advanced HGOC patients by investigator review • CA-125 response rate per GCIG criteria for CA-125 changes • Incidence of AEs, overall and by severity, and incidence of SAEs; laboratory abnormalities; changes in laboratory assessments, ECGs, and assessment of physical examinations such as vital signs • PK parameters of pamiparib and possibly its major metabolite(s) at selected time points: AUC_{last}, C_{max}, and T_{max} • For patients participating in intensive PK sample collection: $AUC_{0\text{-}12h}$, C_{max}, C_{min}, and T_{max} • DCR and CBR as defined above Exploratory Endpoints: • [redacted]
Statistical methods:	**Populations** The Safety Population (SP) includes all patients who received at least one dose of pamiparib. The Efficacy Evaluable Population (EEP) includes all patients in the SP who had measurable disease at baseline per RECIST, version 1.1 and had at least one post baseline tumor assessment unless discontinued treatment due to clinical progression or death prior to tumor assessment. The DLT Population includes all patients who received at least 75% of pamiparib or who experienced a DLT event during the DLT observation period (Cycle 1). The PK Population includes all patients for whom valid pamiparib PK parameters can be estimated.

The Evaluable for CA-125 Response Population is defined as the subset of subjects in the SP with baseline CA-125 ≥ 2 x ULN (Rustin et al 2004). This will be the primary analysis set for the analysis of CA-125 response rate.

Statistical and Analytical Methods

Evaluation of safety and tolerability of pamiparib in Chinese patients is the primary objective of the Phase 1 portion of the trial. Descriptive statistics will be used to summarize the data according to the dose level tested. In Phase 2 portion, efficacy and safety of pamiparib will be evaluated in HGOC patients. The analysis methods described in this section are directed to Phase 2 portion of the study. However, they will be applied to Phase 1 portion of data analysis whenever appropriate.

Efficacy Analyses

Primary Efficacy Analyses (Phase 2)

Hypothesis testing of ORR will only be performed in the patients with platinum-sensitive ovarian cancer (PSOC). The primary analysis will be carried out using IRR data in EEP. Efficacy endpoints based on investigator assessed tumor response will be presented as the sensitivity analysis.

ORR of pamiparib per IRR is assumed as 52% in patients with recurrent PSOC. The historical rate in a similar population is estimated as 30%. The null and alternative hypotheses are set as follows:

H_0: ORR=30%

H_a: ORR > 30%

A binomial exact test will be performed for hypothesis testing in the recurrent PSOC EEP. If the obtained one-sided p-value is ≤ 0.025, it will be concluded that pamiparib monotherapy statistically significantly increases ORR compared with historical control. A two-sided binomial exact 95% confidence interval (CI) of ORR will be constructed to assess the precision of the rate estimate.

The primary efficacy analysis will be conducted when mature response rate data have been observed, estimated as no more than 12 months after the last patient received the first dose of study drug.

Sensitivity analysis of ORR will be carried out in the SP.

ORR in evaluable recurrent platinum-resistant ovarian cancer (PROC), as well as in all evaluable recurrent HGOC, will be summarized descriptively.

Secondary Efficacy Analyses (Phase 2)

Kaplan-Meier method will be used to estimate the key secondary endpoint, DOR, and corresponding quartiles (including the median) in the responders. A two-sided 95% CIs of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method.

The DOR censoring rule will follow Food and Drug Administration (FDA) *Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)* (FDA 2007).

Other time to event variables (PFS and OS) will be similarly analyzed in the SP using the Kaplan-Meier method as described above. The Kaplan-Meier estimates of PFS and OS will be plotted over time. The PFS time point estimates, defined as the percentages of patients in the analysis population who remain alive and progression-free at the specified time points (ie, 3 or 6 months), will be estimated using the Kaplan-Meier method along with the

corresponding 95% CI constructed using Greenwood's formula. The OS time point estimates will be calculated similarly.

BOR is defined as the best response recorded from the start of pamiparib until data cut off or start of new anti-neoplastic treatment. The proportion of each response category (CR, PR, SD, progressive disease [PD] and not evaluated [NE]) will be presented in the EEP and SP.

Data will be summarized by platinum status and overall. Data assessed by IRR and investigator will be summarized.

DCR and CBR and their 95% CIs will be summarized in the EEP and SP.

Exploratory Efficacy Analyses (Phase 2)

[redacted]

Safety

Pamiparib exposure will be summarized, including duration, dosage, and dose intensity.

Verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) terms and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.03. A treatment emergent adverse event (TEAE) is defined as an AE that had an onset date on or after the first dose of study drug up to 30 days following study drug discontinuation, or was worsening in severity from baseline (pre-treatment). All AEs will be included in the listings and only TEAEs will be included in the summary tables. SAEs, deaths, TEAEs Grade 3 or above, related TEAEs and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

DLT events will be summarized by dose level in Phase 1 dose escalation portion.

A patient will be counted only once by the highest grade according to NCI-CTCAE, version 4.03 within a system organ class (SOC) and preferred term (PT), even if the patient experienced more than 1 TEAE within a specific SOC and PT. Clinical laboratory data with values outside of the normal ranges will be identified. Selected laboratory data will be summarized by grade. Vital signs and physical examination will also be summarized by visit.

Sample Size

Approximately 14-18 evaluable patients will be enrolled in Phase 1 portion of the trial. In Phase 2 portion of the trial, approximately 100 evaluable patients will be enrolled.

In recurrent HGOC patients, it is assumed that ORR is 52% in previously treated platinum-sensitive patients with *BRCA* mutation. There is an 98% power of demonstrating a statistical difference versus a historical response rate of 30% using a binomial exact test at an alpha of 0.025 in 80 evaluable patients. The 2-sided exact 95% CI is (40.5%, 63.3%) when the observed ORR is 52%. Approximately 20 patients will be enrolled to the platinum-resistant HGOC patients.

Hence, approximately 118 patients will be enrolled to obtain 14-18 evaluable patients in Phase 1 and 100 evaluable patients in Phase 2.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	adverse event
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}inf}$	area under the plasma concentration time curve from zero extrapolated to infinity calculated using the linear up/log down trapezoidal method
$AUC_{0\text{-}12h}$	area under the plasma concentration-time curve from zero to 12 hours post-dose
AUC_{last}	area under the plasma concentration-time curve from zero to the last measurable concentration
BID	twice daily
BGB-290	study drug code
BOR	best overall response
BRCA	breast cancer susceptibility gene
BRCA1/2	breast cancer susceptibility gene 1/ gene 2
CA-125	carcinoma antigen-125
CBR	clinical benefit rate
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent clearance
C_{max}	maximum observed plasma concentration
CR	complete response
CT	computed tomography
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DOR	duration of response
EC_{50}	half maximal effective concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EEP	efficacy evaluable population
EOT	End of Treatment
FDA	Food and Drug Administration
FIH	first-in-human
GCIG	Gynecological Cancer Intergroup
GCP	Good Clinical Practice

Abbreviation	Definition
HGOC	high grade ovarian cancer
HIV	Human immunodeficiency virus
HR	hazard ratio
HRD	homologous recombination defects
IB	Investigator's Brochure
IC_{50}	half inhibitory concentration
ICF	informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRR	independent radiology review
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NE	not evaluated
ORR	objective response rate
OS	overall survival
pamiparib	BGB-290
PAR	poly(ADP-ribose)
PARP	poly(ADP-ribose) polymerase
PBMCs	peripheral blood mononuclear cells
PD	progressive disease
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetic(s)
PO	Orally
PROC	platinum-resistant ovarian cancer
PR	partial response
PT	preferred term
PSOC	platinum-sensitive ovarian cancer
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SMC	Safety Monitoring Committee
SOC	system organ class
SOP	standard operating procedure
SP	safety population

Abbreviation	Definition
TEAE	treatment emergent adverse event
TNBC	Triple negative breast cancer
$t_{1/2}$	elimination half-life
T_{max}	time of maximum observed plasma concentration
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal phase

1 INTRODUCTION

1.1 Background and Pharmacology

Poly (ADP-ribose) polymerase (PARP) proteins are involved in DNA replication, transcriptional regulation, and DNA damage repair. Inhibition of PARP converts common single-strand DNA breaks into double-strand breaks during DNA replication. 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.

Small molecule inhibitors of PARP1/2 represent a class of anticancer agents that exert their cytotoxic effect by modulating the PARylation activity of PARP1/2 and trap PARP proteins on damaged DNA. Since the discovery of synthetic lethality of PARP inhibitors in breast cancer susceptibility gene (*BRCA*)-deficient cells and, more broadly, cells with homologous recombination defects (HRD), accumulation of unrepaired single-strand DNA breaks 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 single-strand DNA breaks (Pommier et al 2016; O'Connor 2015; Lord and Ashworth 2017). In the clinic, PARP inhibitors, including olaparib, rucaparib, niraparib, and talazolparib, have demonstrated sustained anti-tumor responses as a single agent in patients with *BRCA1*- or *BRCA2*-mutant tumors, while still achieving a favorable safety profile. Olaparib (FDA Summary Review for Regulatory Action: Olaparib) and rucaparib (NDA 209115 Rubraca) are two PARP inhibitors that are approved as a single agent for patients with advanced ovarian cancer who have a germline mutation in the *BRCA* gene.

Pamiparib (also known as BGB-290) is a potent and selective inhibitor of PARP1 and PARP2 (BGB-290 Investigator's Brochure). It showed potent PARP-trapping activity and anti-proliferative activity against a number of cell lines harboring *BRCA* gene mutations or HRDs. In combination studies, pamiparib demonstrated strong synergism with temozolomide in a number of small cell lung cancer and glioblastoma cell lines.

1.2 PARP Inhibitors in the Treatment of Breast Cancer and Ovarian Cancer

Breast Cancer

Breast cancer is a clinically and biologically heterogenous disease characterized by diverse genomic signatures and protein expression patterns. Up to 10% of breast cancers can be linked to germline mutations in *BRCA1* and/or *BRCA2* genes (Welsch et al 1998). Both *BRCA1* and *BRCA2* are tumor suppressor genes, and when mutated, can lead to a higher risk of cancer by disabling DNA repair processes called homologous reconstitution or homology directed repair. (Yoshida and Miki 2004; O'Sullivan 2014) Many investigations have shown that HRD is critical in response to platinum and PARP inhibitor therapy.

Triple negative breast cancer (TNBC) is considered an aggressive disease, characterized by absence of the estrogen, progesterone and human epidermal growth factor 2 receptors, with frequent association with *BRCA1* mutations.

Clinical studies support the use of platinum compounds in *BRCA1/2* mutated breast cancer in the neo-adjuvant and advanced disease treatment setting including metastatic TNBC (Gronwald et al 2009; Arun et al 2011; Telli 2014; Tutt et al 2015). The TNT study (Tutt et al 2015) demonstrated no difference in overall tumor response rates or progression-free survival (PFS) with carboplatin treatment compared to docetaxel for an unselected population of patients with TNBC; however, carboplatin was associated with improved objective response rate (ORR) and PFS in the subgroup of patients with germline *BRCA1/2* mutated breast cancer. When added to either docetaxel (Fan et al 2013) or gemcitabine, (Hu et al 2015) Hu-13 clinical outcomes were superior in the combination treatment arms containing cisplatin over the comparator monotherapy arms.

It has been hypothesized that inhibition of PARP, in combination with DNA-damaging chemotherapeutics, would be highly effective in tumors lacking *BRCA* function. (Tutt et al 2010; Bryant et al 2005; Farmer et al 2005; O'Shaughnessy et al 2009)

PARP inhibitors have been tested clinically in breast cancer patients with *BRCA1/2.* In a single-arm, open-label study, olaparib (400 mg or 100 mg orally twice daily [PO BID]) was administered to women with *BRCA1*- and/or *BRCA2*-mutant, advanced breast cancer (of which >50 percent were triple-negative). (Tutt et al 2009) Patients in the 400 mg BID treatment group had an ORR of 41% and PFS of 5.7 months. The most commonly reported Grade 3 adverse events (AEs) were fatigue, nausea, and vomiting.

Other Phase 3 studies investigating single-agent PARP inhibitors in patients with germline *BRCA1/2* mutated breast cancer are ongoing (olaparib, niraparib, and talazoparib).

Ovarian Cancer

Currently two PARP inhibitors, olaparib and rucaparib, have been approved by the Food and Drug Administration (FDA) for women with advanced ovarian cancer with *BRCA1/2* mutation. In addition, olaparib and niraparib were approved by the FDA and European Medicines Agency for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who achieved a CR or PR with platinum-based chemotherapy.

Data from clinical studies support the use of PARP inhibitors as monotherapy in patients with *BRCA* mutation and treated with multiple lines of chemotherapy. The effectiveness of rucaparib was demonstrated in 106 patients with deleterious *BRCA* mutation associated advanced ovarian cancer who had been treated with two or more chemotherapies on two single-arm open-label trials. All 106 patients received rucaparib 600 mg PO BID as monotherapy until disease progression or unacceptable toxicity. Objective response rate (ORR) as assessed by the investigator was 54% (95% CI: 44, 64) with 9% complete responses (CRs) and 45% partial responses (PR). Median duration of response (DOR) was

9.2 months (95% CI 6.6, 11.6). Investigator-assessed ORR was 66% (52/79; 95% CI [54, 76]) in platinum-sensitive patients, 25% (5/20; 95% CI [9, 49]) in platinum-resistant patients, and 0% (0/7; 95% CI [0, 41]) in platinum-refractory patients (NDA 209115 Rubraca).

Olaparib (Study 42), was a single-arm, open-label, multi-center study assessing the response rate of olaparib in patients with advanced cancers who have a deleterious germline *BRCA* mutation (FDA Summary Review for Regulatory Action: Olaparib). Of the 193 patients with ovarian cancer on this trial, 137 patients with measurable, germline *BRCA* mutation-associated ovarian cancer treated with three or more prior lines of chemotherapy who were enrolled to this trial were assessed. The overall response and DOR in patients with germline *BRCA* mutation advanced ovarian cancer who received 3 or more prior lines of chemotherapy in Study 42 are summarized in below (Table 1).

Table 1. Summary of Patient Response Rate with Olaparib

Response	**N=137**
Objective Response Rate (95% CI)	34% (26, 42)
Complete Response	2%
Partial Response	32%
Median Duration of Response in months (95% CI)	7.9 (5.6, 9.6)

Adapted from: https://www.accessdata fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000SumR.pdf

In a randomized study with approximately 300 women with platinum-sensitive high-grade recurrent epithelial ovarian cancer (EOC), patients were randomly assigned to maintenance treatment with the PARP inhibitor, olaparib, or placebo (Ledermann et al 2014). Results from this study showed a significant improvement in progression free survival (PFS) in patients treated with olaparib compared with placebo (8 versus 5 months, hazard ratio [HR] for progression or death 0.35, 95% CI 0.25-0.49), although interim analysis found no overall survival (OS) benefit (30 months in both, HR 0.94, 95% confidence interval [CI] 0.63-1.39). A subanalysis of data from this study showed a significant benefit in PFS with olaparib compared with placebo among patients with a known *BRCA* mutation (median, 11 versus 4 months, HR 0.18, 95% CI 0.10-0.31), with a trend towards improved OS (HR 0.73, 95% CI 0.45-1.17), which became more pronounced at a longer follow-up (>5 years) (Ledermann et al 2012; Ledermann, et al 2016). In a recent double-blind Phase 3 study (NOVA), 553 patients with platinum-sensitive, recurrent ovarian cancer were randomized 2:1 to receive a PARP inhibitor, niraparib or placebo (Mirza et al 2016). Patients were stratified according to presence or absence of a germline *BRCA* mutation. The non-germline *BRCA* cohort was further classified by HRD status, and patients with somatic *BRCA* mutations were also included. Patients treated with niraparib had an increased PFS in all cohorts compared with placebo. In the germline *BRCA* group, PFS was 21.0 versus 5.5 months (HR 0.27, 95% CI 0.17-0.41); in the overall non-germline *BRCA* cohort, PFS was 9.3 versus 3.9 months (HR 0.45, 95% CI 0.34-0.61); and in the HRD-positive subgroup of the non-germline *BRCA*

cohort, PFS was 12.9 versus 3.8 months (HR 0.38, 95% CI 0.24-0.59). The most common Grade 3 or 4 toxicities associated with niraparib were thrombocytopenia (34%), anemia (25%), and neutropenia (20%). Myelodysplastic syndrome (MDS) occurred in 5 of 367 patients (1.4%) who received niraparib.

Another PARP inhibitor, veliparib, was evaluated in a Phase 2 study in 50 women with a known *BRCA* mutation. Veliparib treatment resulted in a 26% ORR and the median PFS and OS were 8 and 20 months, respectively (Coleman et al 2015).

1.3 Nonclinical Data on Pamiparib

Pamiparib is a highly potent and selective inhibitor of PARP1 and PARP2 and is unique from other PARP inhibitors by combining potent PARP-trapping activity with good brain penetrance. In addition, pamiparib has shown anti-tumor activity against a number of cell lines harboring *BRCA* gene mutations or HRD, as well as *in vivo* models.

1.3.1 Nonclinical Safety Data for Pamiparib

The nonclinical toxicity and toxicokinetic profile of pamiparib was characterized in single and up to 91-day repeat-oral-dose studies in rats and dogs, and in a core battery of genotoxicity tests, including in vitro Ames and chromosomal aberration assays, and in vivo bone marrow micronucleus assays in rats. Safety pharmacology assessments included in vitro human ether-a-go-go related gene channel activity assays and in vivo studies of cardiovascular function in dogs, as well as central nervous system and respiratory system function tests in rats.

The main toxicity findings were bone marrow inhibition that correlated with clinical pathology changes, and gastrointestinal toxicity that presented as emesis, decreased food consumption, and decreased body weight. The systemic exposure increased dose-proportionally without apparent sex differences or accumulation. The maximum tolerated dose (MTD) was considered to be 6 mg/kg in rats and 3 mg/kg in dogs for both 28-day and 91-day toxicity studies.

Pamiparib was not mutagenic in the in vitro Ames (bacterial reverse mutation) assay, but clastogenic in the in vitro chromosomal aberration assay in mammalian Chinese hamster ovary cells, and in the in vivo bone marrow micronucleus assay in rats, which is consistent with its mechanism of action. PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and DNA damage repair. Pamiparib interacts with and inhibits the enzymatic repair machinery that carries out detection and repair of single-stranded binding proteins.

In the general toxicity studies in rats and dogs with pamiparib, no gross lesions or histopathological changes were noted in male and female reproductive organs. No embryo-fetal toxicity studies were conducted or planned as it was not considered essential because of its genotoxicity and bone marrow inhibition.

There was no apparent inhibition of pamiparib on human ether-a-go-go related gene channel as the half inhibitory concentration (IC_{50}) was 12.4 µM; for comparison, the IC_{50} of the positive control amitriptyline was 1.9 µM. No effects on blood pressure, heart rate, or electrocardiograms (ECGs) were noted in telemetry-instrumented conscious dogs. No effects on central nervous system, or respiratory functions were noted in Sprague Dawley rats. No abnormal changes in the cardiovascular, central nervous system, and respiratory systems were identified in single- or repeat-dose toxicity studies in both rats and dogs. No QT interval prolongation was noted in cardiovascular function studies in conscious dogs and in 28-day and 91-day repeat-dose toxicity studies in dogs. Embryo-fetal toxicity studies were not conducted because of the already established genotoxicity of and bone marrow inhibition by pamiparib.

In summary, all available toxicological studies and data are adequate to support clinical development of pamiparib for treatment of patients with advanced cancer.

Please refer to the Investigator's Brochure (IB) for additional information (BGB-290 Investigator's Brochure).

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Please refer to the BGB-290 Investigator's Brochure for additional information.

1.4 Clinical Data for Pamiparib

Pamiparib is currently being studied in two Phase 1a studies: BGB-290-AU-002 in Australia, n=56 (as of 27 January 2017) and BGB-290-102 in China, n=15 (as of 25 September 2017). There is one Phase 1b study, BGB A317/BGB-290_Study_001, for the combination of pamiparib with BGB-A317, an anti-PD 1 antibody (n= 42; as of 27 January 2017). The study data from BGB-290-AU-002 are the most mature, and key interim results are summarized below. Preliminary results for BGB-290-102 Phase 1 study in China are also summarized below.

1.4.1 Pharmacokinetics of BGB-290-AU-002 and BGB-290-102 Phase 1 studies

Pharmacokinetics for BGB-290-AU-002 study

In the first-in-human (FIH) Phase 1 study, interim PK data of pamiparib showed that pamiparib is rapidly absorbed and eliminated after oral administration. The maximum observed serum concentration (C_{max}) and the drug exposure (the area under the plasma concentration time curve [AUC]) increased in a nearly dose-proportional manner from 2.5 mg twice daily (BID) to 120 mg BID 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 5.4 to 34 hours. At the steady state, from 2.5 mg BID to 120 mg BID, drug exposure was increased in a dose-dependent manner, with an approximately 2-fold accumulation.

Further, in 6 patients that received 60 mg BID of pamiparib, the AUC_{last} at high-fat fed status is 85% of it at fast status; the C_{max} at high-fat fed status is 63% of it at fast status, while the T_{max} was prolonged. With the inter- patient variability of 54%, coefficient of variation (CV) observed at 45 patients in Phase 1a, the food effect results suggest that AUC of pamiparib was not altered by food. Based on the overall consistent AUC with high fat meal, pamiparib may be administered with or without food.

Pharmacokinetics for BGB-290-102 Phase 1 study

In this Phase 1 study, the PK data were extracted based on samples obtained from 15 enrolled patients. PK samples were taken on Cycle 1 Day 1 and Cycle 1 Day 10. On Cycle 1 Day 1, samples were collected within 1 hour predose, and at 0.5, 1, 2, 4, 6, 9, 12, 24, and 48 hours postdose. On Cycle 1 Day 10, samples were collected within 1 hour predose, and at 0.5, 1, 2, 4, 6, 9, and 12 hours postdose. Preliminary PK showed that pamiparib plasma drug exposure (AUC) increased in a nearly dose proportional manner, with a plasma half-life of about 12 hours. In the 20-mg BID cohort, pamiparib steady state plasma maximum concentration

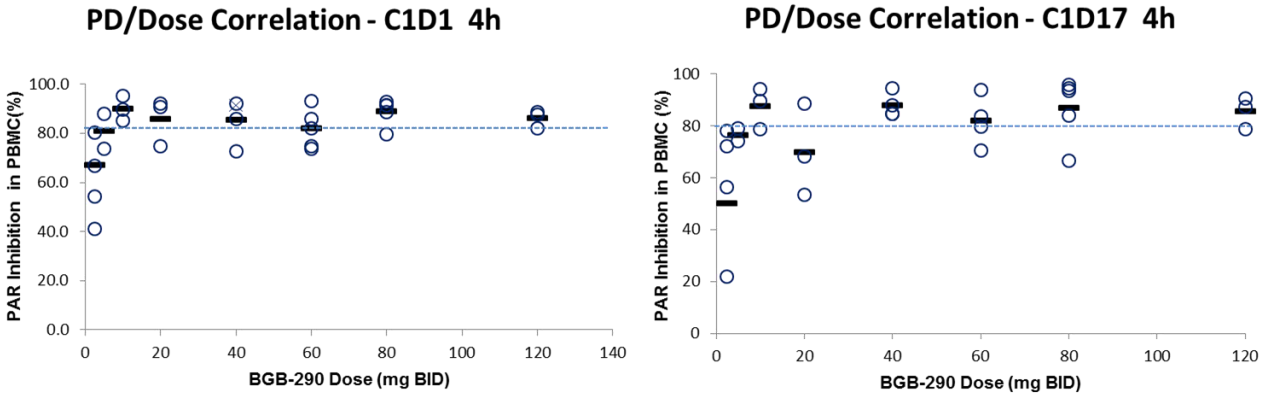
(C_{max}) and drug exposure (area under the plasma concentration-time curve from 0 to 9 hours postdose [AUC_{0-9}]) were 1450 ng/mL and 9361 ng/mL•h, respectively. In the 40-mg BID cohort, pamiparib steady state C_{max} and AUC_{0-9} were 5340 ng/ml and 33545 ng/mL•h, respectively. In the 60-mg BID cohort, pamiparib steady state plasma C_{max} and AUC_{0-9} were 6048 ng/ml and 39657ng/mL•h, respectively. pamiparib steady state C_{max} and AUC_{0-9} in the Phase 1 portion of the BGB-290-102 study were about 35% higher than that in BGB-290-AU-002 study. Given the limited sample size in this study (n=4 each at 20 and 40 mg BID, n=7 at 60 mg BID) and approximately 50% between-subject variability in PK, these differences represent a very preliminary result and need to be interpreted with caution. Importantly, as described in Section 1.4.3, there were no dose limiting toxicities in this study at 60 mg BID

[redacted]

1.4.2 [redacted]

[redacted]

Figure 1. Correlation of PAR Inhibition in Peripheral-blood Mononuclear Cells with Pamiparib Dose



Abbreviations: BID, twice daily; C1D1, Cycle 1 Day 1; C1D17, Cycle 1 Day 17; PBMC, peripheral blood mononuclear cell; PD, pharmacodynamics

1.4.3 Clinical Safety and Preliminary Efficacy for BGB-290-AU-002 and BGB-290-102 Phase 1 study

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

BGB-290-AU-002 is a FIH study 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 (PO) BID up to 120 mg PO BID.

The study is being conducted in 3 Australian study centers, and preliminary data for 45 patients are available (cut-off date of 30 September 2016).

The preliminary safety data indicates the most frequent adverse events (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).

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).

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).

Serious adverse events (SAEs) 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 a fatal AE ≤ 28 days after the last pamiparib dose. All deaths were due to complications of the underlying malignancy, and none was considered related to pamiparib.

Four patients experienced AEs that were considered dose limiting toxicities (DLTs): 2 patients experienced Grade 2 nausea that persisted despite optimal standard medical therapy; 1 patient experienced Grade 2 anorexia and Grade 2 nausea, and 1 patient experienced Grade 2 nausea and Grade 2 paresthesia. Based on the encountered DLTs and the overall safety profile of pamiparib, the MTD of pamiparib was determined to be 80 mg PO BID (160 mg/day).

MDS or acute myeloid leukemia (AML) are recognized AEs in patients receiving PARP inhibitors (Ricks et al 2015). 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.

Clinical Safety and Preliminary Efficacy for BGB-290-102 Phase 1 study

The Phase 1 portion of study BGB-290-102 evaluated the safety, tolerability, PK, and preliminary efficacy of pamiparib in Chinese patients with advanced high-grade, non-mucinous, epithelial ovarian cancer, including fallopian and primary peritoneal cancer, or TNBC. Three cohorts with BID dosing (20, 40, and 60 mg) were evaluated in the dose-escalation phase. Preliminary data for 15 patients are available (HGOC: n=9; TNBC: n=6; as of 25 September 2017): n=4 for 20 mg, n=4 for 40 mg and n=7 for 60 mg.

The most common related AEs were asthenia (n=12), nausea (n=12), decreased appetite (n=9), white blood cell count decreased (n=9), anemia (n=8) and neutrophil count decreased (n=7). Treatment-related Grade 3 AEs in ≥ 2 patients were anemia (n=5), decreased neutrophil count and decreased white blood cell count (n=2 each). No ≥ Grade 4 AEs were reported. All SAEs were not related to pamiparib (1 each of abdominal infection, ileus, and pleural effusion). No dose-limiting toxicities were reported; and the recommended Phase 2 dose was confirmed as 60 mg PO BID.

Available preliminary efficacy data for 8 HGOC patients (all platinum-resistant/refractory) showed 2 patients with partial response (on treatment: n=2; *BRCA1/2* mutation: n=1) and 4 with stable disease (on treatment: n=4; *BRCA1/2* mutation: n=2). Median duration of treatment for 9 HGOC patients was 133 days (range: 8–260). Available preliminary efficacy data for 5 TNBC patients showed progressive disease (PD) for all 5 (*BRCA1/2* mutation: n=1).

1.5 Study Rationale

The study will be conducted in compliance with the protocol, good clinical practice (GCP), The Declaration of Helsinki and the applicable regulatory requirement(s).

This is a two-phase study. Phase 1 (dose escalation) of this study will evaluate the safety and tolerability, as well as determine the recommended Phase 2 Dose (RP2D) of pamiparib. The PK profile, and the preliminary anti-tumor activity of the pamiparib will also be studied. Phase 2 of this study will further evaluate the anti-tumor activity of the pamiparib, its safety and PK profile [redacted]

The study population used for Phase 2 consists of patients with advanced high grade, non-mucinous, epithelial ovarian cancer of either known deleterious or suspected deleterious germline *BRCA1/2* mutations susceptible to treatment with PARP inhibitor.

Pamiparib is a potent and selective inhibitor of PARP1 and PARP2. It showed potent PARP-trapping activity and anti-proliferative activity against a number of cell lines harboring *BRCA* gene mutations or HRD. Mutations of *BRCA1* and *BRCA2* predispose cells to increased risk of malignancies, particularly breast and ovarian cancer.

The reported prevalence of *BRCA1/2* mutations in patients with ovarian cancer varies in different studies, ranging from 10% to 20%. To date, there have been two major epidemiological researches about *BRCA1/2* mutations in China. One study included 916 patients with unselected consecutive EOC from Eastern China, with an overall mutation incidence of 16.7%, which is consistent with pervious global data (Shi et al 2017). The other study included 826 patients from 3 top cancer hospitals and 2 major tertiary hospitals in China; the prevalence rate or *gBRCA*m was determined to be 28.5% (Wu et al 2017).

Rationale for Dose Selection in Phase 1

Pamiparib has demonstrated a favorable toxicology and safety pharmacology profile in clinical and non-clinical experiments.

The starting dose for pamiparib will be 20 mg BID in this study, which is 1/3 of RP2D (60 mg BID) and 1/4 of MTD (80 mg BID) determined from the on-going FIH Phase 1 study of pamiparib in Australia.

Three dose levels of 20, 40 and 60 mg BID are planned for this dose escalation portion (Phase 1). An intermediate, not pre-defined, and not previously-evaluated dose or a less frequent dosing schedule could be evaluated in the dose escalation portion if necessary.

Rationale for Phase 2

Pamiparib is a particularly promising PARP inhibitor to study in solid tumors as it has a unique combination of attributes. It is a potent and selective inhibitor of PARP1 and PARP2. It has excellent PARP-trapping activity that is likely to be more important for anti-tumor activity than catalytic PARP inhibition. In the clinic, pamiparib has shown favorable PK properties, has been well-tolerated and achieved maximum pharmacodynamic target modulation in PBMCs at a dose level well below the RP2D (10 mg versus 60 mg BID). PK modeling predicts that the RP2D of pamiparib can achieve brain concentrations required for anti-tumor activity.

Rationale for Selection of pamiparib Dose in Phase 2

Based upon the overall safety, efficacy, and PK profile of pamiparib, the dose of pamiparib 60 mg PO BID was confirmed as RP2D using available clinical data from study BGB-290-AU-002 and the Phase 1 portion of this study. Study BGB-290-AU-002 determined the maximum tolerated dose of pamiparib to be 80 mg PO BID (160 mg/day). The dose of 60 mg BID was selected for further evaluation based on the following findings (refer to BGB-290 Investigator's Brochure):

- A linear PK profile observed up to 80 mg BID
- Similar toxicity profiles at 60 and 80 mg BID with the following exceptions:
  - Fewer patients at 60 mg BID experienced treatment-related AEs of anemia and neutropenia
  - There was a slightly higher rate of dose interruptions at 80 versus 60 mg BID for anemia and nausea
- Responses were observed across the dose range evaluated

BGB-290-102 Phase 1 study confirmed that the recommended dose for further investigation in Chinese patients was also 60 mg PO BID based on the following findings:

- AE profile observed from 15 female Chinese patients in BGB-290-102 study was generally consistent with that from BGB-290-AU-002 (Australia) study, and AEs could be managed clinically
- No DLTs and drug-related SAEs were observed across the dose range evaluated
- Average steady-state pamiparib plasma exposure (Cmax, AUC) at 60 mg BID in Chinese patients was approximately 35% higher than for Australian patients (AU-002). In summary, pamiparib is an excellent candidate to determine the effects of PARP inhibition in advanced cancers.

1.6 Benefit-Risk Assessment

Pamiparib is the investigational product with safety data gathered from non-clinical and Phase 1 clinical studies. Preliminary safety results of pamiparib from the ongoing Phase 1a clinical trial were summarized above. Patients enrolled in this clinical study using pamiparib must be closely monitored by means of reporting AEs, recording vital signs and ECGs, and conducting clinical laboratory safety tests on blood and urine, with particular attention paid to the safety profile of what is currently known. Pamiparib and other PARP inhibitors (eg, olaparib) in clinical trials have shown some side effects including fatigue, somnolence, nausea, loss of appetite, anemia and thrombocytopenia (NDA 209115 Rubraca; FDA Summary Review for Regulatory Action: Olaparib; Weil and Chen 2011). MDS and AML have been reported in a small number (<1%) of patients treated with PARP inhibitors, especially in patients harboring a germline *BRCA* mutation (FDA Summary Review for Regulatory Action: Olaparib). Patients who develop MDS and AML while on PARP inhibition therapy typically had a history of extensive previous chemotherapy and some had a history of previous cancer or bone marrow abnormalities. Patients in this study will be

monitored monthly for hematological toxicities and reports of MDS and AML will be reported as SAEs.

In Phase 1 (dose escalation), high grade non-mucinous ovarian cancer (including fallopian cancer, or primary peritoneal cancer), or TNBC, will be recruited. Even though *BRCA1* and *BRCA2* mutations are not required, enrichment of this patient population is encouraged. In Phase 2, HGOC (including fallopian cancer, or primary peritoneal cancer) patients with germline *BRCA1/2* mutation will be recruited. The PARP inhibitors, including pamiparib in clinical development, have shown clinical benefit in these patient populations.

1.7 Study Conduct

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

2 STUDY OBJECTIVES

2.1 Phase 1 Portion

2.1.1 Primary Objectives

- To evaluate the safety and tolerability of pamiparib for advanced cancer in Chinese patients
- To determine the recommended Phase 2 dose of pamiparib

2.1.2 Secondary Objectives

- To characterize the pharmacokinetics of pamiparib in Chinese patients
- To evaluate the clinical anti-tumor activity of pamiparib in Chinese patients with TNBC or high-grade epithelial, non-mucinous ovarian cancer (including fallopian cancer, or primary peritoneal cancer)
- To evaluate the relationship between pamiparib PK and clinical endpoints

2.1.3 Exploratory Objectives

- [redacted]

2.2 Phase 2 Portion

2.2.1 Primary Objectives

- To evaluate the efficacy of pamiparib as measured by objective response rate according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (RECIST V 1.1), by independent radiology review (IRR) in patients with advanced platinum-sensitive or platinum-resistant high grade, non-mucinous, epithelial ovarian cancer (including fallopian or primary peritoneal cancer), harboring germline *BRCA1/2* mutations

2.2.2 Secondary Objectives

- To evaluate the efficacy of pamiparib as measured by progression free survival, duration of response by both IRR and investigator review, and overall survival by investigator review
- To evaluate the efficacy of pamiparib as measured by the ORR by investigator review
- To evaluate the safety and tolerability of pamiparib
- To evaluate the efficacy of pamiparib as measured by disease control rate (DCR), best overall response (BOR) and clinical benefit rate (CBR) by both IRR and investigator review
- To evaluate the carcinoma antigen-125 (CA-125) response rate per Gynecological Cancer Intergroup (GCIG) for CA-125 changes
- To further characterize the PK of pamiparib

2.2.3 Exploratory Objectives

- [redacted]

3 STUDY ENDPOINTS

3.1 Phase 1 Portion

3.1.1 Primary Endpoint

- Incidence of adverse events, overall and by severity, and incidence of SAEs according to National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.03 (NCI-CTCAE); laboratory abnormalities; changes in laboratory assessments, ECGs, and assessment of physical examinations.

3.1.2 Secondary Endpoints

- PK parameters of pamiparib and possibly its major metabolite(s) at selected time points: area under the plasma concentration-time curve from 0 to the last measurable concentration (AUC_{last}), maximum observed plasma concentration (C_{max}), and time to reach C_{max} (T_{max}); elimination half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution during terminal phase (V_z/F) and other applicable parameters.
- Efficacy assessment by the investigator based on the RECIST, version 1.1:
  - ORR is defined as the proportion of patients who had confirmed CR or PR
  - DOR is defined as the time from the first determination of a confirmed overall response until the first documentation of progression or death, whichever comes first
  - DCR is defined as a BOR of CR, PR and stable disease (SD)
  - CBR is defined as a BOR of CR, PR and SD lasting ≥24 weeks
  - PFS is defined as the time from first dose of study medication to the first documented disease progression or death due to any cause, whichever occurs first

3.1.3 Exploratory Endpoint

- [redacted]

3.2 Phase 2 Portion

3.2.1 Primary Endpoints

- ORR as defined above in advanced HGOC patients by IRR

3.2.2 Secondary Endpoints

- DOR and PFS as defined above
- OS is defined as time from the first dose of study medication to the date of death due to any cause
- ORR as defined above in advanced HGOC patients by investigator review
- CA-125 response rate per GCIG criteria for CA-125 changes
- Incidence of AEs, overall and by severity, and incidence of SAEs; laboratory abnormalities; changes in laboratory assessments, ECGs, and assessment of physical examinations such as vital signs

- PK parameters of pamiparib and possibly its major metabolite(s) at selected time points: AUC_{last}, C_{max}, and T_{max}
- For patients participating in intensive PK sample collection: $AUC_{0\text{-}12h}$, C_{max}, C_{min}, and T_{max}
- DCR and CBR as defined above

3.2.3 Exploratory Endpoints

- [redacted]

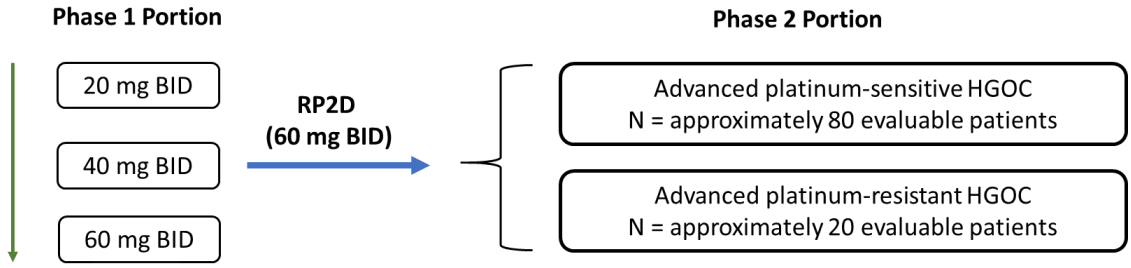
4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a Phase 1/2, open-label, multi-center study of pamiparib administered PO BID to adult Chinese patients with advanced solid tumors which have progressed despite standard therapy or for which no standard therapy exists.

The study will continue until the last patient has died, becomes lost to follow up, or withdraws from study, or until sponsor decides to terminate the study.

Figure 2. Schema of overall study design of Phase 1/2 study Pamiparib-102



Abbreviations: HGOC, high grade ovarian cancer; BID, twice daily

4.1.1 Phase 1 Portion

The Phase 1 portion of this study is designed to evaluate the safety, tolerability and PK profile of pamiparib in Chinese advanced cancer patients and to determine RP2D of pamiparib for Chinese patients. In the FIH study of pamiparib in Australia, the RP2D and MTD were determined to be 60 mg BID and 80 mg BID, respectively. In this study, three dose levels, 20 mg, 40 mg, and 60 mg BID, will be evaluated. The purpose of this study is to determine the RP2D and MTD, if any, of pamiparib in Chinese cancer patients. Dose escalation will follow a modified 3+3 dose escalation design.

Patients will be screened for eligibility up to 21 days prior to the first dose of pamiparib. The starting dose will be 40 mg/day (20 mg BID; see Section 1.5 for the justification of the starting dose level). The 23-day initial treatment cycle (Cycle 1) of each dose level will consist of a single administration of pamiparib (20 mg) on the morning of Day 1, followed by one day treatment-free period (Day 2) and a 21-day period of repeated drug administration (BID, once in the morning and once in the evening 12 hours ± 2 hour apart, Days 3 to 23).

Safety evaluation of at least 3 patients completing one cycle of treatment at that dose level is required prior to determining the next dose level and dose regimen for the next cohort.

If a patient wishes to continue study treatment upon completion of Cycle 1, the patient can continue study treatment in 21-day Cycle 2 (with no treatment-free or rest period) and subsequent cycles, at the discretion of the investigator.

After the first patient in the first dose level receives the Cycle 1, Day 1 dose, subsequent patients in that cohort will not be dosed until the first patient has been observed for at least 24 hours to exclude unexpected acute toxicity. The continuous safety evaluation will be

performed by the sponsor, the coordinating investigator, and investigators. A Safety Monitoring Committee (SMC) will be established to determine the dose levels to be administered and dose regimen during dose escalation, and their decision will depend on the data available from the previous dose levels. The suggested dose escalation scheme is presented in Table 3.

Table 3. Suggested Dose Escalation Scheme

Step	Daily dose (mg)[1]
1	20 BID
2	40 BID
3	60 BID

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.

4.1.1.1 Dose Escalation

Safety evaluation of at least 3 patients completing one cycle of treatment at that dose level and dose regimen is required prior to determining the next dose level and dose regimen for the next cohort.

The study will follow a modified 3+3 dose escalation scheme. At least 3 patients will be enrolled into each cohort, up to a maximum of 6 patients in total. The DLT assessment and dose escalation scheme will follow the same principles as stipulated for a standard 3+3 dose escalation design. For example, 3 additional patients will be enrolled if a DLT is observed in 1 of 3 patients; an additional 2 patients will be enrolled if a DLT is observed in 1 of 4 patients; and an additional 1 patient will be enrolled if a DLT is observed in 1 of 5 patients. No additional patients are required if a DLT is observed in 1 of 6 patients. In this case, it will move to the next cohort.

If none of the patients in the cohort experience DLT by the end of Cycle 1, the dose to be administered in the next cohort will be increased by up to 100%, as determined by the SMC.

If 1 out of 6 patients experience a DLT by the end of Cycle 1, the dose to be administered in the next cohort will be increased by up to 50%, as determined by the SMC. However, due to the capsule sizes available (10 mg and 40 mg), if a 50% dose increase is not possible, the SMC will select the most appropriate dose level that utilizes whole capsules.

No additional patients will be treated at a given dose level if 2 or more of the patients in a cohort develop a DLT in Cycle 1. In this instance, the MTD is considered to have been exceeded. If the MTD is exceeded, the lower dose level previously evaluated will be deemed as MTD or the next lower intermediate dose level will be explored, as determined by the SMC.

The SMC will also determine the dose level and dose regimen for each cohort. The dose regimen chosen will be dependent on the available PK data and various dose regimens may be explored (eg, daily dosing, etc.). The dose level and dose regimen selected will be communicated to IRB/ IEC.

MTD is the dose level at which 0 or 1 out of 6 patients experience DLT, provided that ≥ 33% of patients experienced DLT (eg, 2 or 3 out of 6 patients) at the next higher dose level. RP2D is smaller or equal to MTD. Even though an MTD may have been reached, a RP2D may still be selected which will take into account the MTD as well as available information on lower dose level of AEs, AEs occurring in later cycles, PK, pharmacodynamics and efficacy data. This decision will be made at a SMC meeting where the dose for the dose expansion phase is decided. At least 6, and up to 10 patients could be accrued at RP2D to further assess safety.

Dose escalation will continue until RP2D or MTD, if any, is reached.

4.1.1.2 Dose-Limiting Toxicity

All AEs will be evaluated according to the NCI-CTCAE Version 4.03. A DLT is defined as an AE, or abnormal laboratory value that occurs during the DLT assessment window, is assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and meets one of the following criteria (Table 4):

Table 4. Dose-Limiting Toxicity Assessment Criteria

Hematologic:	• Grade 4 neutropenia lasting >7 days • Febrile neutropenia • Grade 3 neutropenic infection • Grade 3 thrombocytopenia with bleeding • Grade 4 thrombocytopenia • Grade 4 anemia
Non-hematologic:	• ≥ Grade 3 nausea, vomiting and diarrhea despite optimal supportive care • Any other clinically relevant ≥ Grade 3 non-hematologic toxicity (excluding asymptomatic biochemical abnormalities that are not clinically significant and resolve to ≤ Grade 2 in <7 days) • Any toxicity grade which in the judgment of the investigator or sponsor is dose limiting.

The evaluable patient population for the determination of RP2D will consist of patients who have met the minimum safety evaluation requirements of the study. The minimum safety evaluation requirements will have been met if, in Cycle 1, the patient has been treated with at least 75% of the expected dose of pamiparib, (ie, completed at least 18 days of treatment), and observed for ≥ 23 days following the first dose, and has completed all required safety evaluations or the patient experiences DLT during Cycle 1. Patients who do not meet these minimum safety evaluation requirements will be regarded as ineligible for the RP2D-determining population and will be replaced.

4.1.1.3 Dose Continuation, Intra-patient Dose Escalation and Dose De-escalation

In the absence of unacceptable toxicity, disease progression, or patient withdrawal, patients may continue with BID administrations of pamiparib at the discretion of the investigator. The sponsor may consider to roll over those patients who are still on treatment and derive clinical benefit to a new study to continue receiving pamiparib treatment and follow for safety and other clinical relevant information if this study has been ended.

Intra-patient dose escalation is not allowed in this study.

In the event of a DLT, treatment will be stopped and supportive therapy administered as required. If the toxicity resolves or subsides to Grade 0, Grade 1 or Grade 2 (Grade 2 is only applicable to neutropenia) within 14 days and interruption or delay of treatment for no more than 21 days of the onset of the DLT and the patient is showing clinical benefit in the investigator's opinion, resumption of treatment after resolution of a DLT will be at the next lower dose level tested (or 50% lower if the DLT occurs with the first dose level). If the toxicity does not resolve to Grade 0, Grade 1 or Grade 2 (Grade 2 is only applicable to neutropenia) within 14 days of onset, the patient must be withdrawn from the study. Any exception to this must be agreed upon by the investigator and the medical monitor.

The visit schedule for Phase 1 portion is presented in Table 5.

Table 5. Study Visit Schedule in Phase 1 Portion

Assessments[6]	**Screening**[1]	**Cycle 1 (23 days)**					**Cycle 2 (21 days)**	**Cycle 3 (21 days)**	**Cycle 4 and Subsequent Cycles (every 21 days for 1 cycle in Year 1, every 12 weeks ± 7 days thereafter)**	**EOT Visit**[2]	**Safety Follow-up**[3]
Day of Study	**D -21 to -1**	**D1**	**D2**	**D3**	**D10**	**D17**	**D24**	**D45**	**D66~**	**Within 5 days after last dose**	**30 ± 5 days after last dose**
Allowed time window							**±2 days**	**±2 days**			
Informed consent	X										
Baseline demographics	X										
Medical history/treatment[4]	X										
Concurrent medications	X	X			X	X	X	X	X	X	X
Physical examination[5]	X	X			X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X			X	X	X	X	X	X	
ECOG performance status	X	X					X	X	X	X	
Hematology[7]	X	X			X	X	X	X	X	X	
Clinical chemistry[7]	X	X			X	X	X	X	X	X	
CA-125[8]	X	EVERY 6 WEEKS ± 7 DAYS in the First Year EVERY 12 WEEKS ± 7 DAYS starting with the Second Year									
Coagulation		X			X	X	X	X	X	X	
Urinalysis[9]	X						X	X	X	X	

Assessments[6]	**Screening[1]**	**Cycle 1 (23 days)**					**Cycle 2 (21 days)**	**Cycle 3 (21 days)**	**Cycle 4 and Subsequent Cycles (every 21 days for 1 cycle in Year 1, every 12 weeks ± 7 days thereafter)**	**EOT Visit[2]**	**Safety Follow-up[3]**
Day of Study	**D -21 to -1**	**D1**	**D2**	**D3**	**D10**	**D17**	**D24**	**D45**	**D66~**	**Within 5 days after last dose**	**30 ± 5 days after last dose**
Allowed time window							**±2 days**	**±2 days**			
12-lead electrocardiogram[10]	X	X			X		X	X	X	X	
Disease assessment[11]	-28 to -1 X	EVERY 6 WEEKS ± 7 DAYS in the First Year EVERY 12 WEEKS ± 7 DAYS starting with the Second Year									
Adverse events (including serious) [12]	X	X	X	X	X	X	X	X	X	X	X
CT or MRI[13]	X	EVERY 6 WEEKS ± 7 DAYS in the First Year EVERY 12 WEEKS ± 7 DAYS starting with the Second Year									
Pregnancy test[14]	X						X	X	X	X	X
Blood sample collection for *BRCA1/2* mutation testing[15]	X										
Archival tissue[15] (additional consent required)	X										
Pharmacokinetic blood sampling[17]		X	X	X	X		X	X			

Assessments[6]	**Screening**[1]	**Cycle 1 (23 days)**					**Cycle 2 (21 days)**	**Cycle 3 (21 days)**	**Cycle 4 and Subsequent Cycles (every 21 days for 1 cycle in Year 1, every 12 weeks ± 7 days thereafter)**	**EOT Visit**[2]	**Safety Follow-up**[3]
Day of Study	**D -21 to -1**	**D1**	**D2**	**D3**	**D10**	**D17**	**D24**	**D45**	**D66~**	**Within 5 days after last dose**	**30 ± 5 days after last dose**
Allowed time window							**±2 days**	**±2 days**			
Investigational product administration[18]		CONTINUOUS									
Bone ECT Scan[19]	-28 to -1 X										

Abbreviations: CA-125, carcinoma antigen -125; CT: computed tomography; D, Day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; PK, pharmacokinetic; X, to be performed; EOT, end of treatment; ECT, emission computed tomography

1. Screening assessments will be completed within 21 days prior to the first dose of pamiparib, with the exception of disease assessment (see footnote 11 and 18).
2. EOT visit will be conducted at the earliest day possible within 5 days of the last dose of pamiparib if possible
3. Safety follow-up visit should occur 30 ± 5 days after the last dose of pamiparib
4. Date of and response to last platinum treatment must be documented unless no platinum treatment has been received before. Patients are defined as platinum-sensitive if disease progression by RECIST or CA-125 criteria had occurred ≥ 6 months after their last platinum treatment while platinum-resistant is defined as disease progression that occurred < 6 months after the last platinum treatment
5. Full physical exam 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; and 11) neurological status. Only at baseline and EOT visit is the full physical examination required. In other visits (or as clinically indicated), limited symptom-directed physical examinations will be performed
6. All assessments, unless stated otherwise, must be performed before investigational product administration in each cycle
7. In the event of neutropenia (absolute neutrophil count <1000/mm^3), thrombocytopenia (platelets of less than 50,000/mm^3), or ≥ Grade 3 clinical chemistry toxicity, these assessments will be conducted as frequently as the physician feels needed until toxicity resolves to ≤ Grade 2
8. Patients with high grade epithelial tumor, non-mucinous ovarian cancer, fallopian cancer, or primary peritoneal cancer will have CA-125 tested in local laboratory within 2 weeks before the dose of pamiparib, every 6 weeks ± 7 days after the first dose of the study drug in the first year, then every 12 weeks ± 7 days thereafter. The CA-125 responses must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of reference range and within 2 weeks before starting the treatment
9. If urine protein is ≥ 2+, a 24-hour urine sample for total protein will be obtained and evaluated
10. Three electrocardiograms (12-lead ECGs) will be performed at screening after at least a 10-minute rest. If there is any clinically meaningful abnormality observed based on the investigators judgment for the first ECG test, the other 2 additional ECG tests will be requested at least 5 minutes apart and all 3 test results should be recorded. If the clinically meaningful abnormality was observed in 2 of 3 ECG tests, the patient is not eligible for this study. It is not required to conduct 3 ECG tests for all patients at

screening. The ECG time points for pharmacokinetic sampling in conjunction with PK will be obtained as per Table 6. Patients should be in the semi-recumbent or supine position. If prolongation of QT or QT interval corrected for heart rate (QTc) is noted during the first 15 days, 12-lead ECGs will be performed weekly during Week 3 to Week 6, and then once every 3 weeks, on Day 1 of every cycle from Cycle 3 onwards, for the remaining duration of treatment

11. Disease assessment during the screening may be completed up to 28 days prior to the first dose of pamiparib. Afterwards, disease assessments will be performed once every 6 weeks ± 7 days after the first dose of pamiparib in the first year, then every 12 weeks ± 7 days thereafter to assess all known disease. For patients with treatment terminated prior to documentation of disease progression, they shall be subjected to CT/MRI radiographic assessment according to the previous visit assessment scheme, until 1) commencement of new treatment, 2) disease progression, 3) death or 4) termination of the study
12. After informed consent has been signed, but prior to study treatment, only SAEs should be reported
13. A CT scan or MRI scan of the chest, abdomen, and pelvis will be performed once every 6 weeks ± 7 days in the first year, then every 12 weeks ± 7 days thereafter to assess all known disease
14. For women of childbearing potential including those who have had a tubal ligation, urine or serum pregnancy test must be performed and documented as negative within 7 days prior to Cycle 1 Day 1, and urine pregnancy tests will be performed at each visit prior to dosing. A serum pregnancy test must be performed if urine pregnancy test is positive or equivocal
15. Baseline blood samples for all patients should be collected for retrospective germline *BRCA1/2* mutation testing. Blood sample will be taken from each patient.
16. Archival tumor tissues will be collected, if available
17. The pharmacokinetic blood samples will be collected at the time points specified in Table 6
18. A single dose of pamiparib will be administered on the morning of Day 1 of Cycle 1. Multiple administrations will start on Day 3 (Cycle 1 only) or on Day 1 (Cycle 2 and onwards) and continue throughout for each cycle
19. Bone ECT scan at baseline is required if the patient has known bone metastases or has symptoms that could be due to bone metastases. The bone ECT test window duration could be expanded to -28 days from -21 days at baseline. In the subsequent visits, whether to conduct bone ECT scan depends on the clinical indication and investigator's decision. Only bone lesion confirmed by CT/MRI or X ray could be recorded as non-target lesion and should be followed with the same method of examination

Table 6. Pharmacokinetic Sampling in Phase 1 Portion

Procedure	**Cycle 1**																		**Cycle 2**		**Cycle 3**	
	Day 1								**Day 2**	**Day 3**	**Day 10**								**Day 1±2**		**Day 1±2**	
Hours	**Pre-dose[4]**	**0.5**	**1**	**2**	**4**	**6**	**9**	**12[3]**	**24**	**48[1]**	**Pre-dose[4]**	**0.5**	**1**	**2**	**4**	**6**	**9**	**12[3]**	**Pre-dose[4]**	**2**	**Pre-dose[4]**	**2**
12-lead ECG for PK sampling	X			X[2]							X		X	X	X				X	X	X	X
Vital signs	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X	X[1]	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X	X[2]	X	X[2]
PK sampling	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X	X[1]	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X	X[2]	X	X[2]

Abbreviations: ECG, electrocardiogram; PK, pharmacokinetics

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) vital sign measurements; 3) PK blood samples (to be performed at the precise protocol scheduled time); and 4) any other scheduled or unscheduled measurements at that time point.

1. On Day 3, within 1h before the morning dose
2. For all procedures, a window period of ±10 minutes exists within 0.5-1h, ±20 min within 2-4h, ±30 min within 6-24h after the study drug is taken
3. It should be pre-evening dose
4. The window period is within 1h before morning dose

4.1.2 Phase 2 Portion

Approximately 100 evaluable patients (80 previously treated platinum-sensitive and 20 previously treated platinum-resistant) with advanced high grade (Grade 2 or Grade 3 endometriod epithelial cancer is acceptable too), non-mucinous, epithelial ovarian cancer (including fallopian cancer, or primary peritoneal cancer) of either known deleterious or suspected deleterious *BRCA1/2* mutations who have received at least two lines of prior therapies will be enrolled.

Patients are defined as platinum-sensitive if disease progression by RECIST, version 1.1, had occurred ≥ 6 months after their last dose of platinum treatment, while platinum-resistant is defined as disease progression that occurred < 6 months after the last dose of platinum.

Patients will be screened for eligibility up to 21 days prior to the first dose of pamiparib and will take pamiparib at 60 mg BID on Day 1 of Cycle 1 (21-day cycle) and continuously in all subsequent cycles. Patients will be instructed to swallow the capsules whole, in rapid succession, with water. Pamiparib can be administered with or without food.

The visit schedule for Phase 2 portion is presented in Table 7.

Rescreening under limited condition may be allowed after consultation with BeiGene, and it is allowed only once. Repeating screening assessments within the original screening window is allowed if the patient did not previously meet certain eligibility criteria.

4.1.2.1 Safety, Tolerability and Efficacy

Phase 2 portion will investigate efficacy in patients with selected tumor types and further evaluate safety and tolerability of pamiparib at 60 mg BID.

Patients will be monitored for safety, tolerability, and efficacy throughout the study. Radiological assessment of tumor response status should be performed approximately once every 6 weeks ± 7 days for the first 18 weeks, thereafter once every 9 weeks ± 7 days for the remaining period in the first year, and then once every 12 weeks ± 7 days starting with the second year. For patients with first a response as complete response (CR) or partial response (PR), a response confirmation will need to be performed during the following 4-6 weeks, then patients will keep original tumor assessments schedule per protocol.

Tumor response will be assessed by IRR and investigators separately based on RECIST, version 1.1.

Patients will continue treatment until occurrence of unacceptable toxicities, disease progression, withdrawal of consent, investigator discretion, or delay of treatment due to unresolved toxicities for more than 21 days. Dose interruption due to investigational drug-related anemia could be on hold for up to 56 days consecutively.

Table 7. Study Visit Schedule in Phase 2 Portion

Assessments[7]	Pre-screening[1]	Screening[1]	Cycle 1 (21 days)	Cycle 2 (21 days)	Cycle 3 and subsequent Cycles (every 21 days for one cycle)	Unscheduled Visit[2]	EOT Visit[3]	Safety Follow-up[4]	Survival Follow-up[5]
Day of Study	**Before screening**	**D -21 to -1**	**D1**	**D22**	**D43~**	**Varies**	**Within 5 days after last dose**	**30 ± 5 days after last dose**	**Every 12 weeks ± 7 days**
Allowed time window				**±3 days**	**±3 days**				
Informed consent	X	X							
Baseline demographics		X							
Medical history/treatment history[6]		X							
Concurrent medications		X	X	X	X	X	X	X	
Physical examination[8]		X	X	X	X	X	X		
Vital signs		X	X	X	X	X	X		
Height		X							
Weight		X				X	X		
ECOG performance status		X	X	X	X	X	X		
Hematology[9]		-7 to -1 X	X	X	X	X	X		
Clinical chemistry[9]		-7 to -1 X	X	X	X	X	X		

Assessments[7]	**Pre-screening**[1]	**Screening**[1]	**Cycle 1 (21 days)**	**Cycle 2 (21 days)**	**Cycle 3 and subsequent Cycles (every 21 days for one cycle)**	**Unscheduled Visit**[2]	**EOT Visit**[3]	**Safety Follow-up**[4]	**Survival Follow-up**[5]
Day of Study	**Before screening**	**D -21 to -1**	**D1**	**D22**	**D43~**	**Varies**	**Within 5 days after last dose**	**30 ± 5 days after last dose**	**Every 12 weeks ± 7 days**
Allowed time window				**±3 days**	**±3 days**				
CA-125[10]		-14 to -1 X	EVERY 6 WEEKS ± 7 DAYS for the first 18 weeks, thereafter EVERY 9 WEEKS ± 7 DAYS for the remaining period in first year EVERY 12 WEEKS ± 7 DAYS starting with the second year						
Urinalysis[11]		-14 to -1 X	X			X	X	X	
12-lead electrocardiogram[12]		-14 to -1 X				X	X	X	
Disease assessment[13]		X	EVERY 6 WEEKS ± 7 DAYS for the first 18 weeks, thereafter EVERY 9 WEEKS± 7 DAYS for the remaining period in first year EVERY 12 WEEKS ± 7 DAYS starting with the second year[13]						
Adverse events (including serious)[14]		X	X	X	X	X	X	X	
Pregnancy test[15]		-7 to -1 X		X	X	X	X	X	

Assessments[7]	**Pre-screening**[1]	**Screening**[1]	**Cycle 1 (21 days)**	**Cycle 2 (21 days)**	**Cycle 3 and subsequent Cycles (every 21 days for one cycle)**	**Unscheduled Visit**[2]	**EOT Visit**[3]	**Safety Follow-up**[4]	**Survival Follow-up**[5]
Day of Study	**Before screening**	**D -21 to -1**	**D1**	**D22**	**D43~**	**Varies**	**Within 5 days after last dose**	**30 ± 5 days after last dose**	**Every 12 weeks ± 7 days**
Allowed time window				**±3 days**	**±3 days**				
Blood sample collection for *BRCA1/2* mutation testing[16]	X								
Pharmacokinetic blood sampling[17]			X	X					
Tumor Tissues[18]		X							
Investigational product administration [19]			CONTINUOUS			X			
Bone ECT Scan[20]		-28 to -1 X				X			
Survival follow-up visit									X

Abbreviations: CA-125, carcinoma antigen-125; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End of Treatment; MRI, magnetic resonance imaging; PBMCs, peripheral blood mononuclear cells; PD, progression disease; PK, pharmacokinetic; X, to be performed.

1. Screening assessments will be completed within 21 days prior to the first dose of pamiparib, with the exception of disease assessment. Pre-screening for germline *BRCA* mutation test (blood sample) can be completed prior to the study eligibility screening. A separate pre-screening informed consent must be obtained
2. Unscheduled visits may occur any time as necessary as per investigator decision or patient's request for reasons such as assessment or follow-up of adverse events. Study activities, as indicated by 'X,' should be performed based on the reason for the unscheduled visit. If PD is suspected, imaging studies should be performed and [redacted]
3. EOT visit should be conducted at the earliest day as possible within 5 days of the last dose of pamiparib, if possible. If discontinuation is due to unresolved toxicities for more than 21 days (56 days for anemia), EOT visit should be conducted at the earliest day as possible within 5 days after permanent discontinuation is determined. The CT/MRI does not have to be repeated if it was performed at a prior response evaluation that documented progressive disease. CA-125 and ECG do not have to be repeated if it was performed within 14 days of the EOT visit, For the other required assessment, if they were performed within 4 days of the EOT visit, they do not need to be repeated on EOT visit

4. Approximately 30 days after the last day of pamiparib, a safety follow-up visit will occur with the outlined safety assessments. If a new anti-cancer therapy is initiated before this safety follow-up, a safety follow-up should be scheduled as soon as possible ideally before other anti-cancer treatment starts. For patients who do not want to or cannot return to the clinic for the safety follow-up, the patient should be contacted by phone for a review of AEs. If discontinuation is due to unresolved toxicities for more than 21 days, safety follow-up could be scheduled 30 ± 5 days after the last dose of treatment. If discontinuation is due to unresolved toxicities for more than 56 days for anemia, safety follow-up could be scheduled at the earliest day possible within 5 days after permanent discontinuation is determined
5. Patients will be followed for survival via phone contact approximately every 12 weeks ± 7 days or as otherwise directed by the sponsor
6. Date of and response to last platinum treatment must be documented (unless no platinum treatment has been received). Patients are defined as platinum-sensitive if disease progression by RECIST or CA-125 criteria had occurred ≥ 6 months after their last dose of platinum treatment while platinum-resistant is defined as disease progression that occurred < 6 months after the last dose of platinum
7. All assessments, unless stated otherwise, must be performed before investigational product administration in each cycle
8. 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; and 11) neurological status. Only at baseline and EOT visit is full physical examination required. In other visits (or as clinically indicated), limited symptom-directed physical examinations will be performed
9. If the assessments were performed within 4 days of Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1. Weekly hematology test should be done for the first 3 cycles during the study. In the event of neutropenia (absolute neutrophil count < 1000/mm^3), thrombocytopenia (platelets of < 50,000/mm^3), or Grade ≥ 3 clinical chemistry toxicity (per NCI-CTCAE, version 4.03), these assessments will be conducted as frequently as needed until toxicity resolves to Grade ≤ 2
10. Patients will have CA-125 tested in local laboratory within 2 weeks before the dose of pamiparib, once every 6 weeks ± 7 days after the first dose of pamiparib for the first 18 weeks, thereafter once every 9 weeks± 7 days for the remaining period in the first year, and then every 12 weeks ± 7 days starting with the second year. The CA-125 responses must be confirmed and maintained for at least 28 days. Patients 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
11. Screening urine tests must be performed within 14 days of Cycle 1 Day1 and at the EOT visit. If they were performed within 4 days of Day 1 they do not need to be repeated on Cycle 1 Day 1. Urine tests will be performed as clinically indicated during treatment and at safety follow-up. If urine protein is ≥ 2+, a 24-hour urine sample for total protein will be obtained and evaluated
12. A single 12-lead ECG will be performed during screening within 14 days of Cycle 1 Day1 and at the EOT visit. A 12-lead ECG will be performed as clinically indicated during treatment and at safety follow-up. For ECG test during the PK sample collection, follow instructions in Table 8
13. Disease assessment during the screening may be completed up to 28 days prior to pamiparib administration. Afterwards, disease assessments will be performed once every 6 weeks ± 7 days after the first dose of pamiparib for the first 18 weeks and thereafter every 9 weeks± 7 days for the remaining period in the first year, then every 12 weeks ± 7 days afterwards. For patients with first response as complete response or partial response, a response confirmation will be needed to be performed at following 4-6 weeks, then patients will keep original disease assessments schedule per protocol. A CT scan or MRI scan of the chest, abdomen, and pelvis will be performed. Patients with treatment terminated prior to documentation of PD, shall be subjected to CT/MRI radiographic assessment according to the previous visit assessment scheme, until 1) commencement of new treatment, 2) disease progression, 3) death or 4) termination of the study
14. After informed consent has been signed, but prior to study treatment, only SAEs should be reported
15. For women of childbearing potential including those who have had a tubal ligation, urine or serum pregnancy test must be performed and documented as negative within 7 days prior to Cycle 1 Day 1, and urine pregnancy tests will be performed at each visit prior to dosing. A serum pregnancy test must be performed if urine pregnancy test is positive or equivocal
16. Patients with unknown mutation status must undergo germline BRCA1/2 testing in pre-screening phase prior to screening. Patients with known germline BRCA1/2 mutation can proceed to the screening phase once they have signed the pre-screening informed consent and submitted their blood samples for confirmatory germline BRCA1/2 mutation testing, but patients need to have germline BRCA1/2 mutation confirmed before being eligible for the study. Blood sample will be taken from each patient
17. The PK blood samples will be collected at the time points specified in Table 8
18. Archival tumor tissues will be collected, if available
19. BID dosing of pamiparib starts from Cycle 1 Day 1
20. Bone ECT scan at baseline is required if the patient has known bone metastases or has symptoms that could be due to bone metastases. The bone emission computed tomography (ECT) test window duration could be expanded to -28 days from -21 days at baseline. Only bone lesion confirmed by CT/MRI or X ray should be recorded as non-target lesion and should be followed with the same method of examination. If bone metastases are present at screening or if clinically indicated, bone ECT scans should be repeated when a complete response is identified in target lesion or when progression in bone is suspected

Table 8. Pharmacokinetic Sampling in Phase 2 Portion

Procedure	**Cycle 1**								**Cycle 2**							
Days	**Day 1**								**Day 1±3**							
Hours	**Pre- dose**	**0.5**	**1**	**2**	**4**	**6**	**9**	**12**	**Pre-dose**	**0.5**	**1**	**2**	**4**	**6**	**9**	**12**
ECGs[2]	X[1]			X[1]					X[1]			X[1]				
Vital signs	X[1]			X[1]					X[1]			X[1]				
Serial PK sampling[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sparse PK sampling[4]	X[1]			X[1]					X[1]			X[1]				

Abbreviations: ECG, electrocardiogram, PK, pharmacokinetic.

General note: It is important that 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 for serial PK group is: 1) vital sign measurements; 2) scheduled triplicate ECGs; 3) PK blood samples (to be performed at the precise protocol scheduled time, and to be completed within 30 minutes after completion of vital sign measurements, and within 5 minutes after completion of ECG); and 4) any other scheduled or unscheduled measurements at that time point. For sparse PK sampling, the sequence of collection at a particular time point may be determined by the sites based on feasibility.

1. The window period is within 1 hour before the morning dose and, ±20 min for the samples 2 hours post dose
   Note: About 2 mL blood volume will be taken for each sample
2. Triplicate ECGs will be collected from at least 15 patients who contribute to serial PK, with the option to be collected from more patients from sparse PK group, if applicable. Triplicate ECGs for each patient should be obtained from a calibrated machine provided for the study and the same machine must be used for all ECG assessments. The triplicate ECGs results will also be sent to a central reader so that a concentration-QTc analysis can be attempted12-lead ECGs will be performed on the rest of patients who contribute to sparse PK without triplicate ECGs. Triplicate or 12-lead ECGs will be performed on Cycle 1 Day 1 and Cycle 2 Day 1 prior to pamiparib PK assessments.
3. Serial PK sampling will be collected on approximately 15 patients on Cycle 1 Day 1 and Cycle 2 Day 1 at time points of pre-dose, 0.5, 1, 2, 4, 6, 9, and 12 hours after study drug is taken. A window period of ± 10 min exists within 0.5-1 hour, ± 20 min within 2-4 hours, ±30 min within 6-12 hours. Serial PK sampling will be collected in this study and only in patients from sites that area able to adequately perform PK sampling, handling, and processing procedures as outlined in the laboratory manual
4. Sparse PK sampling will be collected in this study from sites that are able to adequately perform PK sampling, handling, and processing procedures as outlined in the laboratory manual

4.1.3 Follow-up for Toxicities

When treatment is interrupted or permanently discontinued due to an AE or abnormal laboratory value, the patient must be followed at a frequency as medically indicated until resolution or stabilization of the event, whichever comes first. All patients will be followed for AEs and SAEs for at least 30 days following the last dose of pamiparib.

For prolonged hematological toxicities, treatment should be interrupted and blood counts should be monitored weekly until recovery. If the levels have not recovered to NCI-CTCAE ≤ Grade 1 or baseline after 8 weeks, the patient should be referred to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is diagnosed, treatment of pamiparib must be permanently discontinued, and the event should be reported as an SAE regardless of causality.

4.1.4 End of Study

The study termination is defined as the time point when data collection for the patient will stop. The study will continue until the last patient has died, becomes lost to follow up, or withdraws from study, or until sponsor decides to terminate the study.

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

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

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for an EOT visit and Safety Follow-up visit.

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

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Good Clinical Practice (GCP) noncompliance

- Study activity is completed (ie, all patients have completed and all obligations have been fulfilled)]

4.2 Selection of Study Population

4.2.1 Inclusion Criteria

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

1. Patients have voluntarily agreed to participate by giving written informed consent
2. Age 18 years (including 18 years) on the day of signing informed consent
3. Patients meet the following eligibility criteria for the corresponding part of the study:

   1) Phase 1 Portion:

      a) The patients must have a histologically or cytologically confirmed locally advanced or metastatic TNBC, or high-grade, non-mucinous, epithelial ovarian cancer (including fallopian or primary peritoneal cancer) for which no effective standard therapy is available

      b) *BRCA1* and *BRCA2* mutations are not required but enrichment of this patient population is preferred

      c) Patients must agree to retrospective germline *BRCA* testing using blood samples

      d) Archival tumor tissues will be collected, if available

   2) Phase 2 Portion:

      a) Patients who have histologically or cytologically confirmed high-grade (Grade 2 or Grade 3 endometrioid epithelial cancer is acceptable too), non-mucinous, epithelial ovarian cancer (including fallopian, or primary peritoneal cancer), harboring germline *BRCA1/2* mutation and must meet the following criteria:

         i. Patients must have received at least 2 lines of standard chemotherapy, currently with relapsed/progressive disease or have withdrawn due to unacceptable toxicity from most recent standard treatment
         ii. Platinum-sensitive or platinum-resistant patients
         (Patients are defined as platinum sensitive if disease progression by RECIST, version 1.1, had occurred ≥ 6 months after their last platinum treatment, while platinum-resistant is defined if disease progression occurred < 6 months after the

last platinum treatment

iii. If mixed histology, >50% of the primary tumor had to be confirmed to be high-grade (Grade 2 or Grade 3 endometrioid epithelial cancer is acceptable too), non-mucinous, epithelial ovarian cancer

b) All patients will be required to undergo germline *BRCA1/2* mutation testing using blood samples prior to enrolment

c) Archival tumor tissues will be collected, from all patients, if available

4. Patients must have measurable disease as defined per the RECIST, version 1.1

5. Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 (Appendix 3)

6. Life expectancy ≥ 12 weeks

7. Patients must have adequate organ function as indicated by the following laboratory values:

- Absolute neutrophil count (ANC) ≥ 1,500/mm^3 or 1.5 x 10^9/L
- Platelets ≥ 75,000/mm^3 or 75 x 10^9/L
- Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L

(If transfusion is used, at least 14 days should pass before re-test for hematology is performed at the screening visit)

- Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m^2 by Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI EQ; Appendix 6)
- Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN)
- Aspartate aminotransferase and alanine aminotransferase ≤ 3 × ULN

8. Females of childbearing potential and nonsterile males (only for Phase 1), must practice highly effective method of birth control (Appendix 11) for the duration of the study and for at least 6 months after the last study drug administration

4.2.2 Exclusion Criteria

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

1. Patients who have been treated with chemotherapy, biologic therapy, immunotherapy, investigational agent, anti-cancer Chinese medicine, or anti-cancer herbal remedies ≤ 14 days (or ≤5 half-lives, whichever is shorter) prior to starting study drug, or who have not adequately recovered from the side effects of such therapy

2. Patients who have undergone major surgery for any cause ≤ 4 weeks prior to starting study drug. Patients must have adequately recovered from the previous treatment and have a stable clinical condition before entering this study

3. Patients who have undergone radiotherapy for any cause ≤ 14 days prior to starting study drug. Patients must have adequately recovered from the previous treatment and have a stable clinical condition before entering this study

4. Untreated and/or active brain metastases

   - A scan to confirm the absence of brain metastases is not required.
   - Patients with treated brain metastases must be off corticosteroids for ≥ 14 days and have no signs or symptoms of progressive brain metastases

5. Prior therapies targeting PARP

6. Inability to swallow oral medications (capsules and tablets) without chewing, breaking, crushing, opening or otherwise altering the product formulation.

7. Patients with any of the following cardiovascular criteria:

   - Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days prior to Day 1
   - Evidence of symptomatic pulmonary embolism within 28 days prior to Day 1
   - Acute myocardial infarction ≤ 6 months prior to Day 1
   - Heart failure of the New York Heart Association Classification III or IV (see Appendix 12) ≤ 6 months prior to Day 1
   - ≥ Grade 2 ventricular arrhythmia ≤ 6 months prior to Day 1
   - Cerebrovascular accident ≤ 6 months prior to Day 1

8. Patients with other malignant cancer:

   - Except for surgically excised non-melanoma skin cancer, adequately treated carcinoma *in situ* of the cervix, adequately treated low-stage bladder cancer, ductal carcinoma *in situ* treated surgically with curative intent, or a malignancy diagnosed ≥ 5 years ago with no current evidence of disease and no therapy ≥ 5 years prior to Day 1

9. Diagnosis of myelodysplastic syndrome (MDS)

10. Known human immunodeficiency virus (HIV) infection, active viral hepatitis, or active tuberculosis

11. Use ≤ 10 days (or ≤ 5 half-lives, whichever is shorter), prior to Day 1, or anticipated need for food or drugs known to be strong or moderate CYP3A inhibitors or strong CYP3A inducers (Appendix 8)

12. Pregnancy or nursing:

    - Females of childbearing potential require a negative urine or serum pregnancy test ≤ 7 days

before Day 1

13. Significant intercurrent illness that may result in the patient's death prior to death from HGOC, or TNBC (only for Phase 1 portion)
14. Known history of intolerance to the excipient of the pamiparib capsule
15. Previous complete gastric resection, chronic diarrhea, active inflammatory gastrointestinal disease, or any other disease-causing malabsorption syndrome
    - Gastroesophageal reflux disease under treatment with proton pump inhibitors is allowed
16. Active bleeding disorder, including gastrointestinal bleeding, as evidenced by hematemesis, significant hemoptysis, or melena ≤ 6 months before Day 1
17. Any illness that investigator thinks makes the patient unsuitable for entry into the study
18. Unsolved acute effects of prior therapy of ≥ Grade 2
    - Except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)

4.2.3 Other Eligibility Criteria Considerations

To assess any potential impact on 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 pamiparib being used in this study (BGB-290 Investigator's Brochure).

4.2.3.1 Patient Restrictions

The following restrictions may affect patient participation in this study:

- The investigator must be informed as soon as possible about any medications taken from the time of screening until the patient is discharged from the study
- In Phase 1 portion, patients will be required to fast for 2 hours before and 1 hour after pamiparib administration on all days throughout the study, water will be allowed freely. Grapefruit juice is not allowed throughout the study. No other dietary restrictions will apply
- In Phase 2 portion, patients will be instructed to swallow the capsules whole, in rapid succession, with water. Pamiparib can be administered with or without food based on the pamiparib food effect evaluation result

4.2.4 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 AEs 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 AE. Any AE which is present at the time of

discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.4. In the event that a patient is prematurely discontinued from the study at any time due to an AE (as defined in Section 9.1) the procedures stated in Section 9 must be followed.

If a patient is prematurely discontinued from participation in the study for any reason, the investigator must make every effort to perform end of treatment (EOT) visit at the earliest day possible within 5 days of the last dose of pamiparib: physical examination, vital signs,12-lead ECG, hematology, biochemistry, and AE assessment. If the discontinuation is due to unresolved toxicities for more than 21 days (56 days for anemia), EOT visit should be conducted at the earliest day as possible within 5 days after permanent discontinuation is determined.

In the Phase 1 portion, in addition to the post-study assessments, if a DLT occurs, the investigator will obtain, when possible, a 4 mL blood sample for analysis of plasma pamiparib concentration.

Patients who discontinue or are withdrawn for any reason other than DLT during Cycle 1 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 RP2D is not met.

4.2.4.1 Reasons for Permanent Discontinuation of Pamiparib

The reason for discontinuation of pamiparib will be recorded in the electronic case report form (eCRF). These reasons include:

- PD
- AE
- Pregnancy
- Protocol violation
- Patient withdrew consent for study treatment
    - Patients may voluntarily withdraw consent from study treatment at any time
    - Patients should continue to participate in the follow-up phase, if a patient withdraws consent from the treatment phase only
- Investigator's discretion
- Start of other anti-cancer therapy

4.2.4.2 End of Treatment Visit

The end of treatment (EOT) visit should occur within 5 days after pamiparib has been permanently discontinued. Required assessments are listed in Table 5 for Phase 1 and Table 7 for Phase 2. The visit at which tumor assessments showed PD may be used as the EOT visit as long as all required assessments were performed. Tumor assessments do not have to be repeated if they were performed at a prior response evaluation that documented PD. For the other required

assessments, if they were performed within 4 days of the EOT visit, they do not need to be repeated on EOT visit. ECG does not have to be repeated if it was performed within 14 days of the EOT visit.

5 STUDY TREATMENTS

5.1 Description of Pamiparib

Patients will receive pamiparib as 10 mg [redacted] capsules, or 40 mg [redacted] capsules, depending on the dose level for Phase 1.

Patients will receive pamiparib as 20 mg rich [redacted] capsules for Phase 2.

5.2 Dosage and Administration

Phase 1 Portion

The pamiparib will be taken once on Day 1 of Cycle 1 (morning only), followed by a 1-day treatment-free period (Day 2). Regular daily administration of pamiparib will commence on the morning of Day 3 of Cycle 1, as a 21-day period of repeated drug administration (Days 3 to 23). During subsequent cycles, the patients will take pamiparib BID from Day 1 to Day 21 (with no treatment-free or rest period).

Patients will be required to fast for at least 2 hours before and 1 hour after each administration of pamiparib throughout the study.

Phase 2 Portion

The patients will take pamiparib at 60 mg BID daily from Day 1 of Cycle 1 (with no treatment-free or rest period). Pamiparib capsules will be administered PO BID, once in the morning and once in the evening. The time difference between two consecutive doses will be approximately 12 hours with a window of ± 4 hours. Patients will be instructed to swallow the capsules whole, in rapid succession, with water. Pamiparib can be administered with or without food. However, to reduce gastrointestinal irritation that parmiparib may cause, patients are encouraged to take parmiparib with food.

A dose of pamiparib should be skipped if it is not taken within the upper range of the scheduled time, ie, within 16 hours. An extra dose of pamiparib should not be taken to make up for a missed dose. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

On days with PK assessments, the morning dose of pamiparib should be administered in the clinic in accordance with the schedule for the PK samples.

The toxicity-related treatment delay must be agreed upon by the investigator and the sponsor Medical Monitor.

5.2.1 Treatment interruption and treatment discontinuation

All dose modifications should be based on the worst preceding toxicity. Generally, all dose interruptions or treatment discontinuation will be based on investigational drug-related AEs. For

reasons other than drug-related AEs, eg, safety concerns due to the poor health condition, if deemed necessary by the investigators, dose modifications could be applied after discussion with medical monitor.

Each patient is only allowed up to 2 dose reductions. In addition, a patient must discontinue treatment with pamiparib if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity.

Table 9. Criteria for interruption and re-initiation of Pamiparib due to treatment associated adverse event

Toxicity		Recommended Dose Modification[a]
Hematologic		
Anemia (hemoglobin, Hgb)		
Hgb < 9.0 g/dL		• **First occurrence of Hgb < 9.0 g/dL:** Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, and then ↓ pamiparib by 1 dose level to 40 mg BID
Grade 2 (8 ≤ Hgb <10 g/dL)	9 ≤ Hgb < 10 g/dL	• Continue dosing at current dose level and treat with appropriate supportive care as medically indicated
	8 ≤ Hgb < 9 g/ dL	• **Subsequent occurrence following dose reduction for anemia:** ➢ Continue pamiparib without interruption with appropriate supportive care based on clinical assessment OR ➢ Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then restart at reduced dose level OR ➢ Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then ↓ pamiparib by 1 additional dose level to 20 mg BID
Grade 3 (Hgb < 8 g/dL)		• **Subsequent occurrence following dose reduction for anemia:** ➢ Continue pamiparib without interruption with appropriate supportive care based on clinical assessment OR ➢ Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then restart at reduced dose level OR ➢ Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then ↓ pamiparib by 1 additional dose level to 20 mg BID

Toxicity	Recommended Dose Modification[a]
Grade 4 (life-threatening consequences; urgent intervention indicated)	• **Second occurrence following dose reduction for anemia:** ➢ Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then ↓ pamiparib by 1 additional dose level to 20 mg BID • **Third occurrence following 2 dose reductions for anemia:** ➢ Discontinue pamiparib if anemia is not caused by any other confounding event, eg GI hemorrhage. ➢ Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then restart at reduced dose level.
Note: 1) Weekly hematology test should be done for the first 3 cycles during the study. For all Grade 2 or higher anemia, hematology test should be done weekly thereafter until adequate recovery. 2) For any patients showing Hgb dropping > 2 g/dL especially within a short time without alternative explanation such as gastrointestinal bleeding, ↓ pamiparib by 1 dose level should be considered 3) Dose increase can be considered in certain cases, depending on approval from the medical monitor, provided Hgb has been maintained above 9 g/dL for at least 3 months	
Neutropenia (absolute neutrophil count, 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
Thrombocytopenia (platelet count, 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

Toxicity	Recommended Dose Modification[a]
Renal	
Estimated glomerular filtration rate (CKD-EPI EQ; Appendix 6)	
If ≥60 mL/min/1.73 m^2 at baseline: <30 to 15 mL/min/1.73 m^2 or If <60 mL/min/1.73 m^2 at baseline: ≥50% reduction from baseline	Hold pamiparib until resolved to ≥60 mL/min/1.73 m^2 • If resolved ≤7 days, then maintain dose levels • If resolved >7 days, then ↓ pamiparib by 1 dose level
Regardless of baseline: <15 mL/min/1.73 m^2	Permanently discontinue pamiparib
Hepatic	
Bilirubin	
Grade 2 (>1.5 - 3.0 × ULN) *Only applies to patients with normal bilirubin at baseline*	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 - 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
Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)	
Grade 3 (>5 and ≤20 × ULN)	Hold pamiparib until AST and/or ALT resolved to ≤5 × ULN or baseline • If ≤5 × ULN within 14 days, then ↓ pamiparib by 1 dose level • If second episode, permanently discontinue pamiparib • If persistent for >14 days, permanently discontinue pamiparib
Grade 4 (>20 × ULN)	Permanently discontinue pamiparib

Toxicity	Recommended Dose Modification[a]
Pancreatic	
Pancreatitis	
Grade 3 or 4	Permanently discontinue pamiparib
Cardiac	
Cardiac - Prolonged QTc interval	
QTcF >500 msec A change in QTc interval >60 msec from baseline or pre-dose value of whichever is the highest	• Obtain triplicate ECGs (2 to 3 minutes apart) ~1 hour after initial ECG • If mean QTcF >500 msec, or a change in QTc interval >60 msec from baseline, 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 msec, or a change in QTc interval >60 msec from baseline confirmed by cardiologist, permanently discontinue pamiparib
Cardiac - General	
Grade 3	Hold pamiparib until resolved to Grade ≤1 or baseline and ↓ pamiparib by 1 dose level
Grade 4	Permanently discontinue pamiparib
Other AEs	
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 (>20 × ULN)	Permanently discontinue pamiparib

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CKD-EPI EQ: Chronic Kidney Disease Epidemiology Collaboration Equation; ECG, electrocardiogram; Hgb, hemoglobin; PLT, platelet (count); QTc, QT interval corrected for heart rate; QTcF, QT interval corrected for heart rate using Fridericia's formula; ULN, upper limit of normal.

For Phase 2 portion, the dose level of pamiparib is 60 mg BID (level 1), 40mg BID (level -1) and 20mg BID (level -2). Reescalation using intermediate doses may be possible providing tolerability is good, please contact sponsor medical monitor for discussion.

In the event of a DLT (see Table 4), treatment will be stopped and supportive therapy administered as required. If the toxicity resolves or subsides to Grade 0, Grade 1 or Grade 2 (Grade 2 is only applicable to neutropenia) within 14 days and interruption or delay of treatment for no more than 21 days of the onset of the DLT and the patient is showing clinical benefit in the investigator's opinion, resumption of treatment after resolution of a DLT will be at the next lower dose level tested

(or 50% lower if the DLT occurs with the first dose level). If the toxicity does not resolve to Grade 0, Grade 1 or Grade 2 (Grade 2 is only applicable to neutropenia) within 14 days of onset, the patient must be withdrawn from the study. Any exception to this must be agreed upon by the investigator and the medical monitor.

For management and follow-up of toxicity also refer to Section 4.1.3.

5.3 Treatment Assignment

Each patient enrolled in this study will receive a unique patient number which will be assigned when the patient is enrolled in the study. Patient will be assigned in chronological order starting with the lowest number. Once a patient number have been assigned to a patient, it cannot be reassigned to any other patient.

If a patient is replaced in Phase 1 portion, the replacement patient will be assigned the next available patient number.

5.4 Packaging and Labelling

Pamiparib capsules will be provided in a child-resistant high-density polyethylene bottle with an induction seal and bottle label. The label will include at a minimum, drug name, dose strength, contents, sponsor, protocol number, lot number, directions for use, storage conditions, caution statements, retest or expiry date, and space to enter the patient number and name of investigator.

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

5.5 Handling and Storage

The pamiparib 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 pamiparib product must be dispensed or administered according to procedures described herein. Only patient enrolled in the study may receive pamiparib, in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or administer pamiparib. Pamiparib 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. Pamiparib must be kept at 15-30^{o}C and protected from light.

5.6 Product Accountability

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 drug accountability records throughout the course of the study.

This person(s) will document the amount of pamiparib received from the sponsor, the amount supplied and/or administered to and returned by patients, if applicable.

After completion of the study, all unused pamiparib 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.

5.7 Assessment of Treatment Compliance

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

5.8 Treatment of Pamiparib Overdose

Overdose is defined as: the patient has taken (accidentally or intentionally) a dose exceeding 120 mg BID or higher. Patients with a suspected overdose should be managed with appropriate supportive therapy as determined by the investigator in consultation with the medical monitor. Any adverse effects occurring as a result of an overdose should be reported to the medical monitor as well as being included in standard AE reporting.

5.9 Occupational Safety

Pamiparib is 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.

6 CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

6.1 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 local standards of medical care. All concomitant medications taken during the study will be recorded on the eCRF including all prescription, over-the-counter (OTC) drugs, herbal supplements, and intravenous (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 eCRF.

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, indication, and start and stop dates of use of the prior and concomitant medication.

6.2 Prohibited Medications

Patients are not allowed to receive other anti-cancer therapy, including surgery, radiation therapy, immunotherapy, investigational agents, cytotoxic, biologic or hormone therapy, anti-cancer Chinese medicine or anti-cancer herbal remedies. Hormone replacement therapy is allowed. Bisphosphonate and denosumab use is permitted if the patient has already been receiving it at a stable dose for >28 days prior to Day 1.

The primary metabolic pathway for pamiparib involves the CYP3A isoform. Co-administration of strong/moderate inhibitors of CYP3A or strong CYP3A inducers with pamiparib is not permitted (FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers). Please refer to the drugs/substances listed in Appendix 8 and to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a more complete list of medications that are not permitted.

Grapefruit juice is not allowed at any time during the study. No other dietary restrictions will apply.

6.2.1 Medications to be used with Caution

Based on preliminary in vitro screening assays, pamiparib is not a strong inhibitor of other human CYP isoenzymes tested. It is a moderate inhibitor of CYP2C9 (IC50 = 6.48 μM). Investigators should be aware that pamiparib has the potential to interfere with the appropriate metabolism of medications that rely on CYP2C9. Investigators should follow the prescribing information recommendations for use with CYP2C9 inhibitors. Examples of these medications include, but are not limited to medications presented in Appendix 9 and these should be used cautiously with the monitoring of drug concentrations where appropriate.

In addition to CYP3A, pamiparib can also be metabolized by CYP2C8 in human liver microsomes, but to a lesser extent. The compounds/substances presented in Appendix 10 are associated with possible interactions with pamiparib through the CYP2C8 metabolic pathway and should also be used cautiously.

7 STUDY ASSESSMENTS

7.1 Pre-screening

In Phase 2, all patients including those with known germline *BRCA1/2* mutation should undergo blood sampling for examination or confirmation of germline *BRCA1/2* mutation prior to screening. The mutation test will be performed in the qualified central laboratory.

Patients with unknown mutation status must undergo germline *BRCA1/2* testing in pre-screening phase prior to screening. Patients with known germline *BRCA1/2* mutation can proceed to the screening phase once they have signed the pre-screening informed consent and submitted their blood samples for confirmatory germline *BRCA1/2* mutation testing, but patients need to have germline *BRCA1/2* mutation confirmed before being eligible for the study.

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

- Obtain written pre-screening informed consent form (ICF) from the patient or the patient's legal representative
- Prepare blood sample and ship to the qualified central lab for mutation analysis as specified in the laboratory manual

7.2 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 Table 5 for the Phase 1 portion, and Table 7 for the Phase 2 portion. The PK sampling time points are presented in Table 6 for the Phase 1 portion, and Table 8 for the Phase 2 portion.

Rescreening under limited condition may be allowed after consultation with BeiGene, and it is allowed only once. Repeating screening assessments within the original screening window is allowed if the patient did not previously meet certain eligibility criteria.

7.2.1 Demographic and Baseline Assessments

7.2.1.1 Demographics

Demographic data will include date of birth, race, height (in cm), body weight (in kg), and body mass index (in kg/m^2). For height and weight measurements, the patient will be allowed to wear indoor daytime clothing with no shoes. These data will be captured in the eCRF and database.

7.2.1.2 Medical History/ Prior medications

Clinically significant medical history findings (eg, previous diagnoses, diseases, or surgeries) which started prior to signing the ICF, and are considered relevant for the patient's study eligibility, will be collected and captured, including baseline severity, if ongoing, in the eCRF. Clinically significant is defined as any events, diagnoses, or laboratory values requiring treatment, follow-up or the presence

of signs or symptoms that require medical intervention. Concurrent medical signs and symptoms must be documented to establish baseline severities.

The details regarding prior therapies administered for the disease under investigation which include: start/stop dates, reason for stopping, best response, and date of best response, will be collected.

7.2.1.3 Other Baseline Characteristics

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 4.1.4. Except for disease assessment, screening assessments will be completed within 21 days prior to the first dose of the pamiparib. Disease assessments may be completed up to 28 days prior to pamiparib administration. In the Phase 1 portion, baseline blood samples should be collected from all patients at screening for retrospective germline *BRCA* mutation testing. In the Phase 2 portion, a blood sample at baseline for germline *BRCA* mutation testing will not be collected because all patients will have undergone this collection during the pre-screening phase. Screening assessments completed within 96 hours of administration can be used as Day 1 assessments as indicated in Table 5 for Phase 1, and Table 7 for Phase 2.

All the baseline data will be captured in the source documents and in the eCRF. Any results falling outside the normal range will be repeated at the discretion of the investigator.

7.3 Assessments During Treatment

Safety, PK, and efficacy assessments will be performed throughout the study. The list of events and the time when they will be performed are presented in Table 5 for Phase 1 and Table 7 for Phase 2.

7.3.1 Laboratory Evaluation

Laboratory assessments should be performed at a local certified laboratory on Day 1 before pamiparib administration. Laboratory assessments need not be repeated on Day 1 if these assessments were completed for screening within 96 hours of the first administration. Required assessments are listed in Appendix 2.

Clinical chemistry, hematology, and urinalysis will be performed at the time points specified in Table 5 for Phase 1, and Table 7 for Phase 2.

7.3.2 Physical Examination and Vital Signs

A complete physical examination, vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, temperature), and weight will be performed at the time points specified in Table 5 for Phase1 and Table 7 for Phase 2.

Full physical examination includes: 1) examination of 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; and 11) neurological status. Only at baseline and EOT visit is the

full physical examination required. In other visits (or as clinically indicated), limited symptom-directed physical examinations will be performed.

ECOG performance status will be evaluated at screening, on Day 1 of Cycle 1 and additional Cycles, and at mandatory EOT Visit.

Vital signs will include body temperature, pulse 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 should 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.

7.3.3 Electrocardiogram

7.3.3.1 For Phase 1 Portion

Three 12-lead ECGs will be performed at screening, at least 5 minutes apart and after at least a 10-minute rest. Patients should be in the semi-recumbent or supine position. To minimize postural variability, it is important that patients are resting and in a supine position for 5 minutes prior to each ECG collection. Blood draws and other procedures should be avoided during the period immediately before ECG measurement, and activity should be controlled as much as possible to minimize variability because of the effects of physiologic stress.

Electrocardiograms will be obtained at the time points specified in Table 6. If prolongation of QT or QT interval corrected for heart rate (QTc) is noted during the first 15 days, 12-lead ECGs will be performed weekly during Week 3 to Week 6, and then once every 3 weeks, on Day 1 of every cycle from Cycle 3 onwards, for the remaining duration of treatment.

Significant QTcF 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. Where two or more ECG tracings are carried out, confirm that the PK blood sample has been collected within the specified time window; the time points for PK blood collection shall not be deferred due to repeated ECG tracings. 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 3 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.

- The medical monitor will be consulted prior to administering higher doses.

7.3.3.2 For Phase 2 Portion

A single 12-lead ECG with assessment of PR interval, QRS duration, and QTc interval will be obtained as outlined in Table 6. Additional ECGs will be performed if clinically indicated. To minimize postural variability, follow procedures as outlined in the Phase 1 portion. Screening ECG must be performed within 14 days of first dose. For the scheduled ECG assessment at the EOT visit, ECG does not have to be repeated if it was performed within 14 days of the EOT visit.

During the PK sample collection (Table 8), ECGs will be performed in triplicate on Day 1 of Cycles 1 and 2 prior to pamiparib PK assessments. ECGs for each patient should be obtained from a calibrated machine provided for the study and the same machine must be used for all ECG assessments on Day 1. Triplicate ECGs results will be sent to a central reader.

7.3.4 Computed Tomography

A CT scan of the chest, 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 as target or non-target lesions using RECIST, version 1.1. The CT scan will be used for disease assessment by the investigator at each study center.

Unless contraindicated, intravenous contrast product must be used to maximize visualization of all lesions. Five-millimeter contiguous scans at baseline and subsequent scanning once every 6 weeks ± 7 days (as calculated by the date of the first administration of pamiparib) for the first 18 weeks, thereafter once every 9 weeks± 7 days for the remaining period in the first year, and then once every 12 weeks ±7 days starting with the second year until progression, with mandatory imaging coverage from thoracic inlet to symphysis pubis should be performed. For patients with a first response as CR or PR, a response confirmation will need to be performed during the following 4-6 weeks, then patient will keep original tumor assessments schedule per protocol. Patients who are at increased risk of allergic reaction to iodinated contrast media should not have enhanced CT, but should instead be provided MRI with gadolinium enhancement according 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.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

If clinically indicated, bone ECT scans (Technetium-99m [TC-99m]) or sodium fluoride PET (NaF-PET) should be performed at screening for patients with ovarian cancer, fallopian cancer, and primary peritoneal cancer. If bone metastases are present at screening and cannot be seen on CT or MRI scans, or if clinically indicated, ECT or NaF-PET bone scans should be repeated when CR is identified in target disease, or when progression in bone is suspected.

The same imaging technique should be used in a patient throughout the study.

Patients with treatment terminated prior to documentation of PD shall be subjected to CT/MRI radiographic assessment according to the previous visit assessment scheme, until 1) commencement of new treatment, 2) disease progression, 3) death or 4) termination of the study. (eg, once every 6 weeks ± 7 days in the first year, then every 12 weeks ±7 days afterwards).

Lesions that are expected to require palliative radiotherapy while in the study should not be included as target lesions, but should be listed as non-target lesions.

For Phase 2 section, all CT/MRI etc, imaging materials will be required to be sent for IRR.

7.3.5 Tumor Antigens

For Phase 1, blood tumor antigen such as CA-125 will be tested in a certified local laboratory during screening (within 14 days prior to administration), every 6 weeks ± 7 days in the first year after the initiation of the study, then approximately every 12 weeks ± 7 days thereafter as specified Table 5. For Phase 2, CA-125 will be tested in a certified local laboratory during screening (within 14 days prior to administration), once every 6 weeks ± 7 days for the first 18 weeks, thereafter once every 9 weeks ± 7 days for the remaining period in the first year, and then once every 12 weeks ± 7 days starting with the second year as specified in Table 7.

7.4 Safety Assessment

Vital signs, weight, physical examinations, ECOG performance status, ECGs and laboratory safety tests (eg, prothrombin time/activated partial thromboplastin time, urinalysis, complete blood count, serum chemistries) will be obtained and assessed at designated intervals throughout the study (see Table 5 for Phase 1, and Table 7 for Phase 2).

For the Phase 2 portion, unscheduled visits may occur any time as necessary as per investigator decision, or patient's request for reasons such as assessment or follow-up of AEs. Study activities of an unscheduled visit should be performed based on the reason for the unscheduled visit and are outlined in Table 7. If PD is suspected, imaging studies should be performed and [redacted].

AEs will be graded and recorded throughout the study according to NCI-CTCAE, version 4.03. 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.

7.4.1 Safety Evaluation

The continuous safety evaluation will be performed by the sponsor, the coordinating investigator, and investigators. For Phase 1 portion, a SMC will be established for the determination of dose levels to be administered during dose escalation and dose regimens in this study. Details of the safety monitoring process will be specified in a dedicated SMC charter.

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

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. At the conclusion of the dose escalation phase, the SMC will determine the RP2D(s) to be further investigated.

The SMC will carry out analysis of cohort safety data after all patients in a dosing cohort have completed the first treatment cycle. All available safety data will also be provided for patients who prematurely discontinue the treatment. 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 DLT. The SMC may weigh collective evidence and may determine a DLT for reasons in addition to those explicitly stated in the protocol.

Adequate time for review of results will be given to SMC members (approximately 1 to 2 business days). Enrollment in subsequent dose levels 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
- Explore any other dose levels; ie, an intermediate, not pre-defined, previously evaluated or not previously evaluated dose level
- 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 4.1.1.2). The SMC will make the dose escalation decisions.

7.5 Efficacy Assessment

7.5.1 Phase 1 Portion

Efficacy is not a primary objective of the dose escalation phase, but the following efficacy endpoints will be assessed by the investigator based on the RECIST, version 1.1:

- ORR is defined as the proportion of patients who had confirmed CR or PR
- DOR is defined as the time from the fist determination of a confirmed overall response until the first documentation of progression or death, whichever comes first
- DCR is defined as a BOR of CR, PR and SD
- CBR is defined as BOR of CR, PR and SD lasting ≥ 24 weeks
- PFS is defined as time from first dose of study medication to the first documented disease progression or death due to any cause, whichever occurs first

Tumor assessment will be performed and recorded at screening and thereafter every 6 weeks ± 7 days after the first dose of pamiparib in the first year and approximately every 12 weeks ± 7 days thereafter until progression according to the RECIST, version 1.1 guidelines as shown in Appendix 5. For patients with ovarian cancer, tumor response may also be assessed by investigators using CA-125 criteria (Appendix 7).

7.5.2 Phase 2 Portion

Survival status of patients will be monitored throughout the study as outlined in Table 7. The date and cause of death will be recorded.

Tumor imaging studies will be reviewed for the purposes of eligibility determination and on-study tumor monitoring. Following the screening tumor assessment, tumor assessments will occur at the schedule of once every 6 weeks ± 7 days after the first dose of pamiparib for the first 18 weeks, thereafter once every 9 weeks ± 7 days for the remaining period in the first year, and then once every 12 weeks ± 7 days starting with the second year. For patients with a first response as CR or PR, a response confirmation will need to be performed during following 4-6 weeks, then patients will keep original tumor assessments schedule per protocol. Any measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. The same imaging method(s) used at screening must be used throughout the study. Patients who did not have PD at the time of pamiparib discontinuation and meet criteria otherwise (eg, discontinued for AE and no new anti-cancer therapy) will continue to have tumor assessments per protocol as outlined in Table 7. ORR, PFS, OS and DOR will be assessed by the investigator using RECIST, version 1.1 (Appendix 5). ORR, PFS, and DOR will also be assessed by IRR. CA-125 will also be assessed at the schedule of once every 6 weeks ± 7 days after the first dose of pamiparib for the first 18 weeks, thereafter once every 9 weeks ± 7 days for the remaining period in the first year, and then once every 12 weeks ± 7 days starting with the second year.

7.6 Follow-up Assessments

Approximately 30 days after the last administration of pamiparib, all patients should return for a safety follow-up evaluation. Assessments to be performed are presented in Table 5 for Phase 1, and Table 7 for Phase 2.

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.

Patients with treatment terminated prior to documentation of PD shall be subjected to CT/MRI/CA-125 disease assessment according to the previous visit assessment scheme, until 1) commencement of new treatment, 2) disease progression, 3) death or 4) termination of the study. Following completion of the treatment and safety follow-up periods, all patients will be followed for survival status in the survival follow-up period specified by the protocol (only for Phase 2). Patients will have their survival status assessed approximately every 3 months by either a telephone or in-person contact until study completion or termination by the sponsor. No other data (eg, subsequent therapies, performance status, etc.) beyond survival will be collected during these calls/visits.

7.7 Pharmacokinetic Assessment

Blood samples (2 mL for determination of pamiparib concentration) for PK analysis will be collected according to the laboratory manual. Plasma will be separated and immediately frozen. Samples must remain frozen in a freezer set at or below -70°C and in a box with dry ice during shipping.

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

7.7.1 Blood Samples collection and handling

Time points of PK sampling are specified in Table 6 for Phase 1 and Table 8 for Phase 2. PK sampling will be conducted according to 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. The time of the last dose administration of pamiparib prior to PK sampling should also be recorded in the database.

For detailed collection and handling opinion of PK blood sample and sample for *BRCA1/2* mutation test, please refer to laboratory manual. If there is any inconsistency in blood sample collection and handling between protocol and lab manual, lab manual will take priority.

Phase 1 Portion:

For patients participating in Phase 1 of the study, a total of 22 blood samples will be collected for determination of pamiparib concentration. These samples will be collected at the time points presented in Table 6. Details concerning handling of the PK plasma samples, including labeling and shipping instructions will be provided in the study manual.

Cycle 1 Days 1, 2 and 3 Blood Samples

Ten blood samples (2 mL each) will be collected on Days 1, 2 and 3 at the following time points: pre-dose (within 1 hour before pamiparib administration) and 0.5, 1, 2, 4, 6, 9, 12, 24 and 48 hours post-dose (the 48-hour PK sample will be collected on Day 3 before morning dose).

Cycle 1 Day 10 Blood Samples

Eight blood samples (2 mL each) will be collected on Cycle 1 Day 10 at the following time points: pre-dose (within 1 hour before pamiparib administration) and 0.5, 1, 2, 4, 6, 9 and 12 hours post-dose.

Cycle 2 Day 1 and Cycle 3 Day 1 Blood Samples

Two blood samples (2 mL each) will be collected on Cycle 2 Day 1 and Cycle 3 Day 1 pre-dose (within 1 hour before pamiparib administration) and 2 hours post-dose.

Other Blood Samples

Blood samples (2 mL) should be obtained, when possible, for analysis of plasma pamiparib in the event of a DLT. the investigator must record the time the blood samples obtained and the time of the previous administration in the eCRF.

Should a drug-drug interaction (DDI) between pamiparib and a concomitant medication be suspected, further blood samples for PK analyses may be taken to characterize the extent of the interaction.

Phase 2 Portion:

Sparse PK samples will be collected for all patients at sites with the capacity to collect PK samples for determination of pamiparib and possibly its major metabolite(s). Serial PK samples will be collected in approximately 15 patients at selected sites with the capacity to collect serial PK samples on Cycle 1 Day 1 and Cycle 2 Day 1 at the following time points: pre-dose, 0.5, 1, 2, 4, 6, 9 and 12 hours post dose. These samples will be collected at the time points presented in Table 8. The triplicate ECGs will also be collected from at least 15 patients from those who could contribute to PK collection in this Phase 2 trial, with the option to collect from more patients. The triplicate ECGs results will also be sent to a central reader so that a concentration-QTc analysis can be attempted.

Cycle 1 Day 1 and Cycle 2 Day 1 Blood Samples

Four blood samples (2 mL each) will be collected on Cycle 1 Day 1 and Cycle 2 Day 1 at the following time points: pre-dose (within 1 hour before pamiparib administration) and 2 hours post-dose for sparse PK sample collection.

Except for sparse PK sample collection, on Cycle 1 Day 1 and Cycle 2 Day 1, sixteen additional blood samples (2 mL each) will be collected at the following time points: 0.5, 1, 4, 6, 9 and 12 hours

post-dose for serial PK sample collection (only 15 patients will participate in serial PK test in selected sites, which have the capability to conduct intensive PK sample collection).

If DDI between pamiparib and concomitant drug is suspected, additional blood samples can be collected for PK analysis to characterize the extent of interaction.

7.8 [redacted]

[redacted]

7.9 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.

8 QUALITY CONTROL AND QUALITY ASSURANCE

According to the GCP guidelines, 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 12-lead 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
- Certified independent radiology review (Phase 2 Section)
- Certified ECT result central reading (for patients who contribute to PK sample collection in Phase 2 portion)

In addition, the sponsor and/or the contract research organization clinical quality assurance department may conduct periodic audits of the study processes, including, but not limited to the study center, central laboratories, vendors, clinical database, and the final clinical study report. 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.

8.1 Monitoring

In accordance with applicable regulations, GCP, and sponsor procedures, the sponsor and/or contract research organization monitors will contact the study center prior to the patient enrollment to review the protocol and data collection procedures with the study center personnel. In addition, the medical monitor will periodically contact the study center, including conducting on-site visits. The extent, nature and frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrollment rate.

During these contacts, the medical 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 in order to verify that:

- 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 medical monitor to discuss findings and any relevant issues.

At study closure, monitors will also conduct all activities described in Section 12.1.

8.2 Data Management/Coding

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

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 as soon as possible 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 pamiparib, 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 user, by means of their unique user ID. 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 user ID 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.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.1 or higher, and graded using the current version of NCI-CTCAE. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA, version 18.1 or higher.

8.3 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 any relevant issues found.

9 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.

9.1 Adverse Events

9.1.1 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.

9.1.2 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 NCI-CTCAE, version 4.03.

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
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated

- Grade 5: Death related to AE

NOTE: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities as described in Section 9.2.

9.1.3 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, and 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.

Investigators must also systematically assess the causal relationship of AEs to study drug (including any other non-study drugs, radiation therapy, etc.) using the following definitions:

- Definitely related: There is clear evidence to suggest a causal relationship to the study drug, and there is reasonable temporal relationship; the occurrence of AE is definitely attributed to the pharmacological effect of study treatment.
- Probably related: There is a reasonable temporal relationship to suggest a causal relationship to the study drug; the occurrence of AE could not be explained by the patient’s medical history, concurrent medical condition, or other the patient’s signs or symptoms.
- Possibly related: There is some evidence to suggest a causal relationship to the study drug (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 (such as the patient’s clinical condition, other concomitant AEs).
- Unlikely related: There is little evidence to suggest there is a causal relationship to the study drug. There is another reasonable explanation for the AE such as disease or other drugs.
- Unrelated: An AE will be considered “not related” to the use of study drug if any of the following criteria are met:

- An unreasonable temporal relationship between administration of the drug and the onset on the AE (eg, the AE occurred either before, or too long after administration of the drug for it to be considered drug-related);
- A causal relationship between study drug and the AE is biologically implausible (eg, death as a passenger in an automobile accident);
- A clearly more likely alternative explanation for the AE is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related AE).

The causality for cases assessed with 5-point scale will be mapped to 2-point scale during aggregate safety data analysis according to the BeiGene latest mapping rule.

9.1.4 Follow-Up of Adverse Events

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

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

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, 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 should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in Section 9.6.1.

9.1.5 Laboratory Test Abnormalities

Abnormal laboratory findings (e.g., chemistry, hematology, coagulation [only for Phase 1 portion]) or other abnormal assessments (ECGs, X-rays, vital signs) that are judged by the investigator as clinically significant will be recorded as adverse events or serious adverse events. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator; in general, these are the abnormalities that are associated with clinical signs or symptoms, require active medical intervention, or lead to dose interruption or

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

9.2 Definition of a Serious Adverse Event

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

- Results in death
- Is life-threatening

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

- Requires hospitalization or prolongation of existing hospitalization

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

- Results in disability/incapacity

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

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

The following are NOT considered SAEs:

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

9.3 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] in the IB) 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 IB.

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

9.4.1 Adverse Event Reporting Period

After main informed consent has been signed at screening but prior to study treatment, only SAEs should be reported.

After initiation of study treatment, all AEs and SAEs, regardless of relationship to study treatment, will be reported until 30 days after last study treatment or initiation of new anti-cancer therapy, whichever occurs first. After this period, the investigator should report any SAEs including death that are believed to be related to prior study treatment.

9.4.2 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?

9.5 Study Specific AEs/SAEs Reporting Instructions

9.5.1 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 adverse event term. Instead, the symptoms, signs or clinical sequelae that result from disease progression should be reported as the adverse events.

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".

9.5.2 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, e.g. "death", "death of unknow cause", or "death unexplained".

9.6 Prompt Reporting of Serious Adverse Events

9.6.1 Timeframes for Submitting Serious Adverse Events

SAEs will be reported promptly (within 24 hours) to the sponsor or designee as described in Table 10 once the investigator determines that the AE meets the protocol definition of an SAE.

Table 10. 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

9.6.2 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 9.6.1. The SAE Report will always be completed as thoroughly as possible with all available details of the SAE, signed by the investigator, 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 9.1.3.

The sponsor will provide contact information for SAE receipt.

9.6.3 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 9.6.2. 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 IRB/IEC.

All SUSARs (as defined in Section 9.3), will be submitted to applicable regulatory authorities and investigators.

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

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

9.7 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 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.

9.8 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 IB

10 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

10.1 Sample Size Considerations

Approximately 14-18 evaluable patients will be enrolled in Phase 1 portion of the trial. In the Phase 2 portion of the trial, approximately 100 evaluable patients will be enrolled.

In recurrent HGOC patients, it is assumed that ORR is 52% with pamiparib in previously treated platinum-sensitive patients with *BRCA* mutation. A total of 80 evaluable patients will give 98% power to demonstrate a statistical difference versus a historical response rate of 30% using a binomial exact test at an alpha of 0.025. The 2-sided exact 95% CI is (40.5%, 63.3%) when the observed ORR is 52%. Approximately 20 patients will be enrolled to the platinum-resistant HGOC patients.

Hence, approximately 118 patients will be enrolled to obtain 14-18 evaluable patients in Phase 1 and 100 evaluable patients in Phase 2.

10.2 General Considerations for Data Analysis

Data will be listed and summarized using SAS®, version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina) according to sponsor agreed reporting standards, where applicable. Complete details will be documented in the statistical 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 evaluable observations, number of missing, mean, standard deviation, coefficient of variation (CV%) as appropriate, 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 median times, 25th and 75th percentiles and associated 95% CIs will also be provided for specific time to event variables

All data will be presented by phase, then by dose. The analysis methods described in this section are directed to Phase 2 portion of the trial. However, they will be applied to the Phase 1 portion of data analyses whenever appropriate.

Further description of the statistical methods and analyses will be provided in the statistical analysis plan.

10.2.1 Analysis Populations

The Safety Population (SP) includes all patients who received at least one dose of pamiparib.

The Efficacy Evaluable Population (EEP) includes all patients in the SP who had measurable disease at baseline per RECIST, version 1.1 and had at least one post baseline tumor assessment unless discontinued treatment due to clinical progression or death prior to tumor assessment.

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

The PK Population includes all patients for whom valid pamiparib PK parameters can be estimated.

The Evaluable for CA-125 Response Population is defined as the subset of subjects in the SP with baseline CA-125 ≥ 2 x ULN (Rustin et al 2004). This will be the primary analysis set for the analysis of CA-125 response rate.

10.2.2 Interim Analysis

No formal interim analysis is planned. A brief data summary will be performed once the Phase 1 dose escalation portion of the trial is completed.

10.2.3 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 discontinuation will be summarized according to the categories in the eCRF. The end of study status (alive, death, 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.

10.2.4 Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the SP using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, time since metastatic disease diagnosis; categorical variables include age group, race, disease stage, ECOG-PS, and prior line of therapy in the metastatic setting.

10.2.5 Prior and Concomitant Therapy

Concomitant medications will be assigned an 11-digit code using the World Health Organization 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 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 clinical study report of this protocol.

10.3 Efficacy Analyses

10.3.1 Primary Efficacy Analyses

Phase 2

Hypothesis testing of ORR will only be performed in the patients with high grade platinum-sensitive ovarian cancer (PSOC). The primary analysis will be carried out using IRR data in EEP. Efficacy endpoints based on investigator assessed tumor response will be presented as the sensitivity analysis. ORR of pamiparib per IRR is assumed as 52% in patients with recurrent PSOC. The historical rate in a similar population is estimated as 30%. The null and alternative hypotheses are set as follows:

H_0: ORR=30%

H_a: ORR >30%

A binomial exact test will be performed for hypothesis testing in recurrent PSOC EEP. If the obtained one-sided p-value is ≤ 0.025, it will be concluded that pamiparib monotherapy statistically significantly increases ORR compared with historical control. A two-sided binomial exact 95% CI of ORR will be constructed to assess the precision of the rate estimate.

The primary efficacy analysis will be conducted when mature response rate data have been observed, estimated as no more than 12 months after the last patient received the first dose of study drug.

Sensitivity analysis of ORR will be carried out in the SP.

ORR in evaluable recurrent high-grade platinum-resistant ovarian cancer (PROC), as well as in all evaluable recurrent HGOC will be summarized descriptively.

10.3.2 Secondary Efficacy Analyses

Phase 2

Kaplan-Meier method will be used to estimate the key secondary endpoint, DOR, and corresponding quartiles (including the median) in the responders. A two-sided 95% CIs of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method.

The DOR censoring rule will follow FDA *Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (2007).

Other time to event variables (PFS and OS) will be similarly analyzed in the SP using the Kaplan-Meier method as described above. The Kaplan-Meier estimates of PFS and OS will be plotted over time. The PFS time point estimates, defined as the percentages of patients in the analysis population who remain alive and progression-free at the specified time point (ie, 3 or 6 months), will be estimated using the Kaplan-Meier method along with the corresponding 95% CI constructed using Greenwood's formula. The OS time point estimates will be calculated similarly.

BOR is defined as the best response recorded from the start of pamiparib until data cut off or start of new anti-neoplastic treatment. BOR and their 95% CIs will be summarized in the EEP. Sensitivity analysis of BOR will be carried out in the SP. The proportion of each response category (CR, PR, SD, PD and NE) will be presented in the EEP and SP.

Data will be summarized by platinum status and overall. Data assessed by IRR and investigator will be summarized.

DCR and CBR and their 95% CIs will be summarized in the EEP and SP.

The analysis of CA-125 response rate will be conducted on the evaluable for CA-125 analysis set and will be same as the analysis of objective response rate. The analysis of change in CA-125 (the maximum percent change from baseline) will be conducted in the SP. Summary statistics, 2-sided 95% confidence intervals, and graphical summaries will be generated for the percent change from baseline in CA-125.

10.3.3 Exploratory Efficacy Analyses

[redacted]

[redacted]

10.4 Safety Analyses

Pamiparib exposure will be summarized, including duration, dosage, and dose intensity.

Safety will be assessed by monitoring and recording of all AEs. Laboratory values (hematology, clinical chemistry, and urinalysis), vital signs, physical examination, and ECGs findings will also be used in determining the safety. Descriptive statistics will be used to analyze all safety data in the SP.

10.4.1 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 dose level at which 0/6 or 1/6 patients experiences DLT, provided that ≥33% of patients experienced DLT at the next higher dose level in Cycle 1.

10.4.2 Adverse Event

Verbatim description of AEs will be mapped to the MedDRA terms and graded according to the NCI CTCAE, version 4.03. A TEAE is defined as an AE that had an onset date on or after the first dose of study drug up to 30 days following study drug discontinuation or was worsening in severity from baseline (pretreatment). All AEs will be included in the listings and only TEAEs will be included in the summary tables. SAEs, deaths, TEAEs Grade 3 or above, related TEAEs and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

DLT events will be summarized by dose level in Phase 1 dose escalation portion.

A patient will be counted only once by the highest grade according to NCI CTCAE, version 4.03 within a system organ class (SOC) and preferred term (PT), even if the patient experienced more than 1 TEAE within a specific SOC and PT.

Clinical laboratory data with values outside of the normal ranges will be identified. Select laboratory data will be summarized by grade. Vital signs and physical examination will also be summarized by visit.

10.4.3 Laboratory Assessments

Hematology, clinical chemistry, and urinalysis values will be listed for each patient and flagged as high or low relative to the normal range, where applicable. Pre-dose values will be used to assess laboratory shifts occurring at post-dose. A comparison of pre-study and post-study values may be performed to identify any parameters that have not returned to pre-study levels.

10.4.4 Extent of Exposure

Extent of exposure to pamiparib will be calculated for each patient. Duration of treatment, total dosages taken and dose intensity will be summarized. Dose interruption, reduction and discontinuation will be summarized by frequency.

10.5 Pharmacokinetic Analyses

PK parameters will be derived using standard non-compartmental methods with WinNonlin Professional, version 5.2 or higher (Pharsight Corp., Mountain View, California) or SAS®, version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina). Nominal sampling times will be used for interim PK parameter calculations, while actual sampling times will be used in the final PK parameter calculations.

Where possible, the following PK parameters will be determined for pamiparib and possibly its major metabolite(s) on Cycle 1 Days 1, 2, 3:

$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from zero extrapolated to infinity calculated using the linear up/log down trapezoidal method
$AUC_{0\text{-}12h}$	Area under the plasma concentration-time curve from zero to 12 hours post dose
AUC_{last}	Area under the plasma concentration-time curve from zero to last time point of administration
C_{max} and $C_{max,ss}$	Maximum observed plasma concentration
T_{max} and $T_{max,ss}$	Time of maximum observed plasma concentration
$t_{1/2}$	Elimination half-life

CL/F	Apparent clearance
V_z/F	Apparent volume of distribution during the terminal phase
RAUC	AUC accumulation ratio
RC_{max} C_{max}	accumulation ratio (Phase IA: C_{max} Cycle 1 Day 10/C_{max} Cycle 1 Day 1)

For patients in Phase 2, T_{max}, C_{max}, C_{min}, and $AUC_{0\text{-}12h}$ (PK intensive patients only).

Additional PK parameters may be calculated if deemed appropriate.

Plasma pamiparib concentration-time data will be summarized and displayed in both tabular and graphical form. Concentration-time data will be analyzed with standard non-compartmental and/or compartmental PK methods. The PK parameters for a single dose profile ($AUC_{0\text{-}12h}$, $AUC_{0\text{-}inf}$, AUC_{last}, C_{max}, T_{max}, $t_{1/2}$, CL/F, and V_z/F) and after steady-state ($AUC_{last,ss}$, $C_{max,ss}$, $T_{max,ss}$), will be calculated, if there are sufficient data. Individual patient parameter values, as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, and the standard deviation and geometric mean of log-transformed parameters) by treatment group will be reported. Individual patient parameter values will be plotted against dose.

Dose proportionality of $AUC_{0\text{-}inf}$, AUC_{ss}, C_{max}, and $C_{max,ss}$ for pamiparib may be assessed using the power model as described below and evaluated visually in graphical form.

A linear regression model with the logarithm of the PK parameter (AUC, C_{max}, and AUC_{last}) as the dependent variable and the logarithm of the dose as the independent variable ($\log[PK]=\alpha+\beta*\log[Dose]$) will be fitted. The model parameters (slope [β] and intercept [α]) will be estimated using least square regression. A minimum of 3 values per dose must be available for a given PK parameter to estimate dose proportionality with the power model. Point estimates and corresponding 2-sided 95% CIs for the slope parameter and the intercept parameter will be provided.

10.6 Biomarker Analyses

[redacted]

11 ETHICS

11.1 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 before the study is initiated at a study center in China.

11.2 Ethical Conduct of the Study and Ethics Approval

This study will be conducted in accordance with GCP and all applicable regulatory requirements, including, where applicable, current version of the Declaration of Helsinki.

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the study center's ICF, and any other information that will be presented to potential patients (eg, advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IEC/IRB. The investigator agrees to allow the IEC/IRB direct access to all relevant documents. The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. The sponsor will provide the investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study. Before pamiparib and CRFs can be shipped to the study center, the sponsor must receive copies of the IEC/IRB approved study, the approved ICF, and any other information that the IEC/IRB has approved for presentation to potential patients.

If the protocol, the ICF, or any other information that the IEC/IRB has approved for presentation to potential patients is amended during the study, the investigator is responsible for ensuring the IEC/IRB reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended ICF including obtaining IEC/IRB approval of the amended form before new patients consent to take part in the study using this version of the form. Copies of the approved amended ICF/other information must be forwarded to the sponsor promptly.

11.3 Informed Consent

Informed consent will be obtained before the patient can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

11.4 Investigator Reporting Requirements

As indicated in Section 9.6, 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.

12 STUDY ADMINISTRATION

12.1 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
- Resolution of data queries
- Accountability, reconciliation, and disposal for unused pamiparib
- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of PK and pharmacodynamic samples to assay laboratories

In addition, the sponsor reserves the right to temporarily 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, disposal will be made for all unused pamiparib 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.

12.2 Records Retention

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true

and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

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

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

12.3 Provision of Study Results and Information to Investigators

When the clinical study report is completed, the sponsor will provide the major findings of the study to the investigator.

The sponsor will not routinely inform the investigator or patient of the test results, because the information generated from this study will be preliminary in nature, and the significance and scientific validity of the results will be undetermined at such an early stage of research.

12.4 Information Disclosure and Inventions

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

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

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

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) will be kept by the investigator and other study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study.

These restrictions do not apply to:

- Information which becomes publicly available through no fault of the investigator or study

center personnel

- Information which is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information which is necessary to disclose in order to provide appropriate medical care to a patient
- Study results which may be published as described Section 12.4.1
- If a written contract for the conduct of the study which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

12.4.1 Publication Policy

The sponsor recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals, and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts and presentations based on the data from this trial will be described in the Clinical Study Agreement.

13 REFERENCES

Arun B, Bayraktar S. Liu DD, et al. Response to neoadjuvant systemic therapy for breast cancer in BRCA mutation carriers and non-carriers: a single-institution experience. J Clin Oncol. 2011: 29(28):3739-3746.

Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005; 434: 913-917.

Center for Drug Evaluation and Research: NDA/BLA Multi-disciplinary Review and Evaluation NDA 209115 Rubraca (rucaparib). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209115Orig1s000AdminCorres.pdf

Coleman RL, Sill MW, Bell-McGuinn K, et al. A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation - An NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol. 2015;137(3):386.

Common Toxicity Criteria Version 4.03. Cancer Therapy Evaluation Program. 14 June 2010.

Fan Y, Xu BH, Yuan P, et al. Docetaxel-cisplatin might be superior to docetaxel-capecitabine in the first-line treatment of metastatic triple-negative breast cancer. Ann Oncol. 2013 May;24(5):1219-25.

Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434(7035):917.

FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007). https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf

FDA Summary Review for Regulatory Action: Olaparib. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000SumR.pdf

Gronwald J, Byrski T, Huzarski R, et al. Neoadjuvant therapy with cisplatin in BRCA-1 positive breast cancer patients. J Clin Oncol. 2009; 27:15s (suppl abst 502).

Hu XC, Zhang J, Xu BH, et al. Cisplatin plus gemcitabine versus paclitaxel plus gemcitabine as first-line therapy for metastatic triple-negative breast cancer (CBCSG006): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol. 2015 Apr;16(4):436-46.

Investigator's Brochure, BGB-290. Edition 2.2, document number BGB-290-022016:2.2, Feb 2016.

Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366(15):1382.

Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol. 2014 Jul;15(8):852-61.

Ledermann JA, Harter P, Gourley C, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Oncol 2016;17(11):1579.

Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017; Mar 17;355(6330):1152-1158.

Mirza MR, Monk BJ, Herrstedt J, et al. ENGOT-OV16/NOVA Investigators. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016;375(22):2154.

Murai J, Huang SY, Das BB, et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. Cancer Res. 2012; 72(21): 5588-99.

O'Connor MJ. Targeting the DNA Damage Response in Cancer. Mol Cell. 2015; Nov 19;60(4):547-60.

Oken MM, Creech RH, Tormey DC, et al. Toxicity in response of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.

O'Shaughnessy J, Osborne C, Pippen J, et al. Efficacy of BSI-201, a poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, in combination with gemcitabine/carboplatin (G/C) in patients with triple-negative breast cancer (TNBC): Results of a randomized phase II trial. J Clin Oncol. 2009 27:18s, (suppl; abstr 3).

O'Sullivan CC. Beyond breast and ovarian cancers: PARP inhibitors for BRCA mutation-associated and BRCA-like solid tumors. Frontiers in Oncology. 2014 Feb 28;4:42.

Pommier Y, O'Connor MJ, de Bono J. Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. Sci Transl Med. 2016; Oct 26;8(362): ps17.

Response Evaluation Criteria in Solid Tumors (RECIST): V 1.1 and Supporting Papers. European Journal of Cancer. 2009;45(2):225-310.

Ricks TK, Chiu HJ, Ison G, et al. Successes and Challenges of PARP Inhibitors in Cancer Therapy. Front Oncol. 2015; Oct 14;5: 222.

Rustin GJ, Quinn M, Thigpen T, et al. Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup. J Natl Cancer Inst. 2004,96:487-488.

Shi T, Wang P, Xie C, et al. BRCA1 and BRCA2 mutations in ovarian cancer patients from China: ethnic-related mutations in BRCA1 associated with an increased risk of ovarian cancer. Int J Cancer. 2017;140(9):2051-9.

Telli M, Optimizing chemotherapy in triple-negative breast cancer: the role of platinum. 2014 ASCO education book. Asco.org/edbook.

Tutt A, Ellis P, Kilburn L, et al. The TNT trial: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer. AACR; Cancer Res. 2015;75(9 Suppl): Abstract nr S3-01.

Tutt A, Robson M, Garber JE, et al. Phase II trial of the oral PARP inhibitor olaparib in BRCA-deficient advanced breast cancer. J Clin Oncol 2009 27:18s, (suppl; abstr CRA501).

Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet. 2010;376(9737):235.

Weil MK, Chen A. PARP Inhibitor Treatment in Ovarian and Breast Cancer. Curr Probl Cancer. 2011 Jan–Feb; 35(1): 7–50.

Welsch PL, Schubert EL, King MC. Inherited breast cancer: an emerging picture. Clin Genet. 1998;54(6):447-58.

Wu X, Wu L, Kong B et al. The First Nationwide Multicenter Prevalence Study of Germline BRCA1 and BRCA2 Mutations in Chinese Ovarian Cancer Patients. Int J Gynecol Cancer. 2017;27(8):1650-7.

Yoshida K, Miki Y. Role of BRCA DNA 1 and BRCA2 as regulators of DNA repair, transcription, and cell cycle in response to damage. Cancer Sci. 2004;95(11):866-71.

14 APPENDICES

APPENDIX 1: SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: An Open Label, Multi-Center Phase I/II Study to Evaluate Efficacy and Safety of BGB-290 in Chinese Subjects with Advanced Ovarian Cancer, Fallopian Cancer, and Primary Peritoneal Cancer or Advanced Triple Negative Breast Cancer

Protocol Identifier: BGB-290-102

This protocol is a confidential communication of BeiGene, Ltd. 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 good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd.

Instructions for 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 or its designee.

I have read the entire protocol and agree to carry out the study according to this protocol.

Investigator's Signature: _____

Investigator's Printed Name: _____

Date (dd mmm yyyy): _____

Name of the center in which the study will be conducted: _____

APPENDIX 2: CLINICAL LABORATORY ASSESSMENTS

Clinical Chemistry	**Hematology**	**Coagulation (only for Phase 1)**	**Urinalysis**
Alanine aminotransferase	Hemoglobin (Hgb)	International normalized ratio	Blood
Alkaline phosphatase	Platelet count	Partial thromboplastin time	Glucose
Aspartate aminotransferase	White blood cell count	Prothrombin time	Ketones
Albumin	Lymphocyte count		pH
Bilirubin (total)	Neutrophil count		Protein[1]
Blood urea nitrogen or urea			Red blood cell
Calcium			Specific gravity
Chloride			White blood cell
Creatinine			
Glucose			
Lactate dehydrogenase			
Magnesium			
Phosphate			
Potassium			
Sodium			
Total protein			

pH: negative of the logarithm to base 10 of the activity of the (solvated) hydronium ion

1. On routine urinalysis, if urine protein is ≥ 2+ by dipstick, then obtain a 24-hour urine sample for the analysis of total protein.

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
As published by (Oken et al 1982). Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

APPENDIX 4: BLOOD REQUIREMENTS

Time point	Assessment	Total blood volume (mL)
Phase 1		
Screening	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	Blood collection for BRCA mutation testing	8
	CA-125[6]	4
	Total	22.5
Cycle 1		
Day 1	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	Pharmacokinetics[1,2]	16[2]
	Total	26.5
Day 2 to Day 23	Clinical chemistry	10
	Hematology	5
	Coagulation	6
	Pharmacokinetics[1,2]	20[2]
	Total	41
Cycle 2		
Day 1 to Day 21	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	Pharmacokinetics[1,2]	4[2]
	Total	14.5
Cycle 3		
Day 1 to Day 21	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	Pharmacokinetics[1,2]	4[2]
	CA-125[6]	4
	Total	18.5
Subsequent cycles		
Day 1	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	Total	10.5

EOT	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	Total	10.5
Other blood samples[3 4,5]		

1 Unscheduled blood samples for pharmacokinetic analysis may also be collected whenever any notable safety is seen, to evaluate if the observation is exposure related.
2 Cannulation for blood sampling for pharmacokinetics will be performed. Blood will be collected via the intravenous cannula pre-dose and at the time points specified in Table 6 for Phase 1 Portion, Table 8 for Phase 2 Portion.
3 Blood samples (4 mL) should be obtained, when possible, for analysis of plasma pamiparib in the event of a DLT.
4 Should a drug-drug interaction between pamiparib and a concomitant medication be suspected, further blood samples for PK analyses may be taken to characterize the extent of the interaction.
5 Additional blood PK samples will be taken to determine the plasma concentration of BGB-290 if there is an intra-patient dose escalation. The Investigator must record the time points for PK sampling and the time of dose administration before PK sampling in eCRFs.
6 For patients with ovarian cancer, fallopian tube cancer or primary peritoneal carcinoma, plasma CA-125 should be monitored every 6 week ± 7 days in the first year and every 12 weeks ± 7 days thereafter in the local laboratory in Phase 1 study.

APPENDIX 5: THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES

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

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 (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

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

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

Cystic lesions:

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

Lesions with prior local treatment:

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

Target Lesions

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

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or

coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

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

Non-target Lesions

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

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

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

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

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

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

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

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

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

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

RESPONSE CRITERIA

Evaluation of Target Lesions

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

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

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

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

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response 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. (Note: the appearance of one or more new lesions is also considered progression).

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

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

New Lesions

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

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

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

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

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

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the trial until the end of the trial 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. The patient's best overall response will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, it also depends on the nature of the trial, the protocol requirements, and result measurements. 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 patient is known.

Best overall response determination in trials where confirmation of complete or partial response is not required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD in Cycle 1, PR in Cycle 2, and PD in the last cycle has a best overall response of PR). When SD is believed to be best overall 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 overall response, the patient's best overall response depends on the subsequent assessments. For example, a patient who has SD in Cycle 1, PD in Cycle 2 and does not meet minimum duration for SD, will have a best overall response of PD. The same patient lost to follow-up after SD in Cycle 1 would be considered inevaluable.

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

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Any	Any	Yes	PD
CR= complete response	PR= partial response	SD= stable disease	PD= progressive disease NE=not evaluated

CR, complete response; NE, not evaluated; PR, partial response; SD, stable disease; and PD, progressive disease.

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 patients 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 clearly explained in determination of response. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy.

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

In some circumstances it may be difficult to distinguish local lesion from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that biopsy be conducted before the local lesion is assigned a status of complete response. FDG-PET may be used to confirm a response to a CR in a manner similar to a biopsy in cases where a local 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 case. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy (including 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

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 been confirmed in such trials. However, in all other circumstances, ie, in randomized trials (Phase 2 or 3) or trials where stable disease or progressive disease 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 to 8 weeks).

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

The duration of stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease. Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment cycle, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

APPENDIX 6: CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In adults, the most widely-used equations for estimating glomerular filtration rate (eGFR) 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 Scr reported in mg/dL. This equation is recommended when eGFR values above 60 mL/min/1.73 m^2 are desired.

GFR = 141 × min (Scr /κ, 1)α × max(Scr /κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [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 Scr /κ or 1, and

max indicates the maximum of Scr /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/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/Pages/gfr-calculators.aspx

APPENDIX 7: EVALUATION OF RESPONSE ACCORDING TO CA-125

The text below was obtained from the following reference: Gordon John Sampson Rustin, etc. 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 Gynecol Cancer*. 2011;21: 419-423.

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 by using the next scheduled CA-125 data (at least 28 days). Patients 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 patient, the same assay method must be used, and the assay must be tested in a quality control scheme.
- Patients 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 antimouse 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 patients 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 patients who have a CA-125 response and whose CA-125 level falls to within the reference range can be classified as CA-125 complete responder see Table 5 for Phase 1, and Table 7 for Phase 2 where CA-125 is stated as normalized or normal, means within the reference range. Patients who have a fall of CA-125 to within the reference range but whose initial CA-125 was less than twice the upper limit of the reference range cannot therefore be classified as a CA-125 complete responder.

Table 11. CA-125 response measurement

CA-125 level	CA-125 measurement
Baseline CA-125 more than twice upper limit of normal, later reduced by 50% to normal and maintaining for at least 28 days	Complete response (CR)
Baseline CA-125 more than twice upper limit of normal, later reduced by 50% but not to normal	Partial response (PR)
CA-125 change out of range of PR and PD	Non-PR, non-PD
CA-125 increased at baseline returning to normal after treatment, later twice or higher upper limit of normal (two consecutive measurement at interval of at least one week)	Progressive disease (date of first evaluation of progression)
CA-125 increased at baseline not returning to normal after treatment, later twice or higher the lowest value (two consecutive measurement at interval of at least one week)	Progressive disease (date of first evaluation of progression)
CA-125 within reference range at baseline, later twice or higher upper limit of normal (two consecutive measurement at interval of at least one week)	Progressive disease (date of first evaluation of progression)

Reporting of response according to GCIG criteria that integrate CA-125 response with RECIST1.1 is shown in Table 12 and Table 13.

Table 12. Evaluation of best overall response in patients without initial measurable disease and who are evaluable by CA-125

CA-125	Nontarget Lesions*	New Lesions	Overall Serological Response	Best Response for This Category Also Requires
Response and Normalized	CR	No	CR	Confirmed and maintained for at least 28 days
Response	Non-PD	No	PR	
Normalized but no response	Non-CR/Non-PD	No	SD	
Non-PR/non-PD	Non-PD	No	SD	
PD	Any	Yes or No	PD	
Any	PD†	Yes or No	PD	
Any	Any	Yes	PD	

CR, Complete response; PD, progressive disease; PR, partial response; SD, stable disease.

*Nontarget lesions include ascites and peritoneal thickening, which are not measurable according to RECIST, version 1.1.

†Unequivocal progression in nontarget lesions may be accepted as disease progression.

Table 13. Best overall response in patients with measurable disease and who are also evaluable by CA-125

Target Lesion*	Nontarget Lesions†	New Lesions	CA-125	Overall Best Response	Best Response for This Category Also Requires
CR	CR	No	Normal	CR	Best RECIST 1.1 response for CR and PR also required it to be confirmed and maintained for at least 28 days if response is primary endpoint
CR	Non-CR Non-PD	No	Not PD	PR	
CR	CR	No	PR but not normal	PR	
CR	NE	No	PR	PR	
PR	Non-PD or NAE	No	Not PD	PR	
NAE	Non-PD	No	PR	PR	
PD or New >28 days from CA-125 PR‡			PR	PR	
SD§	Non-PD	No	PR	PR	
SD§	Non-PD or NAE	No	Not PR and not PD	SD	
PD or New<28 days from CA-125 PR‡			PR	PD	
PD	Any	Yes or No	Any	PD	
Any	PD	Yes or No	Any	PD	
Any	Any	Yes	Any	PD	
Any	Any	Yes or No	PD	PD	

NE, Not evaluated; NAE, not all evaluated.
*Target lesions include up to 5 measurable lesions (2 per organ) as defined by RECIST 1.1.
†Nontarget lesions include ascites and peritoneal thickening which are not measurable according to RECIST 1.1.
‡Patients who have a CA-125 response that occurs more than 28 days from PD according to RECIST 1.1 are considered a PR, according to best response, but PD if the RECIST 1.1 PD is within 28 days (including) of CA-125 response.
§The protocol should specify the minimum time interval between 2 measurements for classification as stable disease.

APPENDIX 8: 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 (anti-cancer): 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

APPENDIX 9: 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.
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 10: MEDICATIONS TO BE USED WITH CAUTION

Strong CYP2C8 Inhibitors

Gemfibrozil

APPENDIX 11: FEMALES OF CHILDBEARING POTENTIAL AND CONTRACEPTION

Contraception guidelines

The Clinical Trials Facilitation Group (CTFG) 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, implantable
- An intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment). Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

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

Definition of childbearing potential

Childbearing potential is defined as being physiologically capable of becoming pregnant. No childbearing potential is defined as one or both of the following criteria:

- Surgically sterile (bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Post-menopausal, defined as
    - ≥ 55 years of age with no spontaneous menses for ≥12 months OR
    - < 55 years of age with no spontaneous menses for ≥12 months AND with a post-menopausal follicle-stimulating (FSH) concentration >30 IU/mL

APPENDIX 12: 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, e.g. walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

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Approval	[redacted] China Development 21-Sep-2018 15:26:18 GMT+0000
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