Clinical Study Protocol

Protocol Title:	**An Open Label, Multi-Center Phase 2 Study to Evaluate Efficacy and Safety of BGB-290 in the Treatment of Metastatic HER2-Negative Breast Cancer Patients with *BRCA* mutation in China**
Protocol Identifier:	BGB-290-201
Phase:	2
Date of Protocol:	30 October 2018, Amendment 1.0
Sponsor:	BeiGene (Beijing) Co., Ltd No. 30, Science Park Rd. Zhong-Guan-Cun Life Science Park Changping District Beijing, China 102206
Sponsor Medical Monitor:	[redacted]

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FINAL PROTOCOL APPROVAL SHEET

An Open Label, Multi-Center Phase 2 Study to Evaluate Efficacy and Safety of BGB-290 in the Treatment of Metastatic HER2-Negative Breast Cancer Patients with *BRCA* mutation in China

BeiGene Approval:

_____ _____

[redacted] Date

Sponsor Medical Monitor

PROTOCOL AMENDMENT, VERSION 1.0

The primary purpose of this amendment is to revise the dose modification algorithm for anemia. Content in the Notes to File to the original protocol were incorporated. Administrative updates, editorial changes, and/or style and formatting revisions were made to improve clarity and consistency throughout the document. Changes were made throughout the synopsis to match changes made in the protocol body.

This amendment version number is Version 1.0.

Key changes are summarized by section in the table below (where appropriate for clarity, additions may be in **bold** text and deletions may be in ~~strikethrough~~ text):

Section	Key Changes	Rationale for change
All sections	• Revised "BGB-290" to "pamiparib"	To align with other protocols.
Section 1.3: Biology of Germline *BRCA*-mutant Breast Cancer and PARP Inhibitors	• Deleted "OlympiAD study has established the basis for approval of Olaparib in HER2(-) metastatic breast cancer patients." • Deleted "Two additional Phase 3 studies investigating a single-agent PARP inhibitor versus physician's choice of chemotherapy in patients with germline *BRCA1/2*-mutated breast cancer are ongoing for niraparib and talazoparib." • Added a description of the EMBRACA study. • Added "Both the OlympiAD and EMBRACA studies have consistently shown that a PARP inhibitor is a reasonable treatment option for patients with advanced TNBC or HR(+)/HER2(-) breast cancer with a germline *BRCA1/2* mutation, since its use is associated with a PFS benefit, improvement in quality of life, and a favorable toxicity profile. Olaparib was approved in the US for patients with deleterious or suspected deleterious germline *BRCA*-mutant, HER2-negative metastatic breast cancer (Lynparza [olaparib] prescribing information)."	To provide updated information regarding PARP inhibitors.

Section	Key Changes	Rationale for change
Section 1.5 Rationale for Selection of Pamiparib Dose	• Added "The 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: o The AE profile observed from 15 female Chinese patients in the BGB-290-102 study was generally consistent with that from the BGB-290-AU-002 (Australia) study, and AEs could be managed clinically. o No DLTs and drug-related SAEs were observed across the dose range evaluated. o The average steady-state pamiparib plasma exposure (C_{max}, AUC) at 60 mg BID in Chinese patients was approximately 35% higher than for Australian patients (BGB-290-AU-002). In summary, pamiparib is an excellent candidate to determine the effects of PARP inhibition in advanced cancers."	To provide additional dose rationale information based on study results in Chinese patients.
Section 3 Study Design	• Clarified study schema footnotes to "Key assessments during treatment phase: tumor assessments every 8 weeks **± 7 days** in the first year and every 12 weeks **± 7 days** in the second year and above."	To align with other sections of the protocol.
Section 4.1 Inclusion Criteria	• Inclusion Criterion 4d: Revised to "Prior therapy with an anthracycline and/**or** a taxane in neoadjuvant/adjuvant or metastatic setting" • Inclusion Criterion 5: Added "Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion." • Inclusion Criterion 9: Revised to: Absolute neutrophil count ≥ 1,500/mL **or ≥ 1.5 x 10^9/L** Platelet count ≥ 75,000/mL **or ≥ 75 x 10^9/L** Hemoglobin ≥ 9 g/dL **or ≥ 90 g/L** (≥14 days after growth factor support or transfusion)	To clarify prior anthracycline and taxane therapy use. To clarify measurable disease definition. To clarify values/units for adequate hematologic function per Note to File 001. To specify liver enzyme levels for

Section	Key Changes	Rationale for change
	Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × ULN**, if liver function abnormalities are due to liver metastasis, then AST and ALT ≤ 5 × ULN**	patients with liver metastasis.
Section 4.2 Exclusion Criteria	• Exclusion Criterion 3: Revised to: "Chemotherapy, **hormonal therapy,** radiotherapy, biologic therapy, immunotherapy, investigational agent, anticancer Chinese medicine, or anticancer herbal remedies ≤ 14 days (or ≤ 5 half-lives, if applicable, whichever is shorter) prior to Day 1 of Cycle 1" o Revised from "Bisphosphonate and denosumab use is permitted if the patient has already been receiving it at a stable dose for >28 days prior to the first dosing." to "Bisphosphonate and RANK-L inhibitors are allowed for bone metastases if initiated before enrollment and at a stable dose."	To add hormonal therapy to exclusion criteria. To permit the use of any RANK-L inhibitor (not solely denosumab) and to specify requirements for bisphosphonate and RANK-L inhibitor use per Note to File 003.
	• Exclusion Criterion 13: Revised to: "Females of childbearing potential require a negative **urine or** serum pregnancy test ≤ 7 days prior to Day 1 of Cycle 1"	To allow flexibility in the method of pregnancy screening tests.
Section 5.2 Screening	• Added "Rescreening under limited conditions 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."	To specify that rescreening may be permitted under certain circumstances.

Section	Key Changes	Rationale for change
Section 5.6.2 End of Treatment Visit and Appendix 1, Table a Study Visit Schedule, Footnote 3	• Added "If discontinuation is due to unresolved toxicities for more than 28 days (56 days for anemia), the EOT visit should be conducted at the earliest day possible within 7 days after permanent discontinuation is determined." • Regarding tumor assessments or CT/MRI: Revised to "…do not have to be repeated if they were performed ~~within 14 days of the EOT visit or~~ at a prior response evaluation that documented disease progression."	To specify timing for the End of Treatment Visit if discontinuation is due to unresolved toxicities. To simplify when tumor assessments do not need to be repeated.
Section 5.7.1 Safety Follow-up and Appendix 1, Table a Study Visit Schedule, Footnote 4	• Added "If discontinuation is due to unresolved toxicities for more than 28 days, safety follow-up could be scheduled approximately 30 days after the last dose of study drug. 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 7 days after permanent discontinuation is determined."	To specify timing for safety follow-up if discontinuation is due to unresolved toxicities.
Section 6.1.1 Packaging and Labelling)	• Deleted "40-mg, or 60-mg capsules"	Only 20-mg capsules will be supplied for this study.
Section 6.1.3 Dosage and Administration	• Revised 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 pamiparib may cause, patients are encouraged to take pamiparib with food." • Revised from "A dose of BGB-290 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)."	To clarify the time difference between 2 consecutive doses and to specify how to reduce potential gastrointestinal irritation with dosing.

Section	Key Changes	Rationale for change
Section 6.1.4 Dose Hold and Modification	• Revised from "Dosing of BGB-290 can be withheld for up to 28 days consecutively." to "Dosing of pamiparib can be withheld for up to 28 days consecutively for medical events (56 days for anemia)." • Table 3 (Criteria for Modification of Pamiparib Dosing for Related Adverse Events): o Revised the dose modification algorithm for anemia. o Revised the dose modification algorithm for Grade 3 thrombocytopenia o Revised the dose modification algorithm for Grade 3 AST/ALT level increases o Revised the dose modification algorithm for cardiac – prolonged QTc interval o Revised the dose modification algorithm for Grade 3 cardiac events	Revised guidance on dose reduction/modification to increase patient's safety
	• Table 3 (Criteria for Modification of Pamiparib Dosing for Related Adverse Events): o Deleted "(>20 × ULN)" from Other AEs section of table o Revised footnote from "Dosing of BGB-290 can be withheld for up to 28 days consecutively." to "Dosing of pamiparib can be withheld for up to 28 days consecutively for medical events (56 days for anemia)."	Editorial changes.
Section 6.2.2 Prohibited Medications	• Revised from "Bisphosphonate and denosumab use is permitted if the patient has already been receiving it at a stable dose for >28 days prior to the first dosing." to "Bisphosphonate and RANK-L inhibitors are allowed for bone metastases if initiated before enrollment and at a stable dose." • Added "Bisphosphonates are permitted during the study for a non-malignant indication."	To permit the use of any RANK-L inhibitor (not solely denosumab) and to specify requirements for bisphosphonate and RANK-L inhibitor use per Note to File 003.
	• Revised from "Please refer to the drugs/substances listed in Appendix 6 and to http://medicine.iupui.edu/clinpharm/ddis/main table/ for a more complete list of medications that are not permitted." to "Please refer to the drugs/substances listed in Appendix 6 for a more complete list of medications that are not permitted."	Removed outdated reference. Appendix 6 provides complete information.

Section	Key Changes	Rationale for change
Section 7.4.2 Physical Examination, Vital Signs, ECOG Performance Status, and Weight	• Revised to "A complete or limited physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, ~~oral,~~ and ~~temporal or tympanic~~ temperature), weight, height, and ECOG performance status will be performed at time points specified in Appendix 1."	To allow flexibility in the method of obtaining patients' temperature per Note to File 003.
Section 7.5.2 Chemistry and Appendix 2 Clinical Laboratory Assessments	• Revised "blood urea nitrogen" to "blood urea nitrogen or urea". • Revised "phosphate" to "phosphate or phosphorus".	To clarify clinical chemistry assessments.
Section 7.5.4 Pregnancy Testing	• Updated from "During screening, a serum pregnancy test must be obtained within 7 days prior to Day 1 of Cycle 1. For subsequent pregnancy testing, if clinically indicated, urine pregnancy tests are allowed. If a urine pregnancy test is positive, a confirmatory serum pregnancy test is required." to "During screening, for women of childbearing potential including those who have had a tubal ligation, a urine or serum pregnancy test must be performed and documented as negative within 7 days prior to Day 1 of Cycle 1, and urine pregnancy tests will be performed at each visit before dosing. A serum pregnancy test must be performed if the result of a urine pregnancy test is positive or equivocal."	To allow flexibility in the method of pregnancy tests.
Section 7.6 Pharmacokinetics	• Deleted "A 1 mL blood sample will be taken and discarded prior to collecting the blood sample for PK analysis."	Details of blood draw should be provided in the laboratory manual. Text only applies to situation where a catheter is placed

Section	Key Changes	Rationale for change
		(usually for serial blood draw) and does not apply when sparse blood draw is conducted with needles.
Section 7.7 Biomarkers	• Added "[redacted] from this sample will be stored and may be used at later time for [redacted] testing including, but not limited to, [redacted] assays." • Added "The most recent [redacted] is preferred."	To allow for [redacted] in the future. To specify [redacted] requirements.
Section 7.7 Biomarkers and Appendix 1, Table a Study Visit Schedule, Footnote 17	• Revised from "Optional paired biopsy samples will be collected on Cycle 1 Day 1and Cycle 2 Day 1 for the assessment of changes [redacted] in response to BGB-290." to "Optional paired biopsy samples will be collected at baseline (any time before receiving the first dose of study drug on Cycle 1 Day 1) and Cycle 2 Day 1 for the assessment of changes in [redacted] in response to pamiparib."	Widened the collection window for the first [redacted] sample to allow more flexibility for study sites.
Section 9.1.3 Assessment of Causality	• Revised from "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." to "The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE using best clinical judgment. Alternative	Revised for consistency with other pamiparib protocols.

Section	Key Changes	Rationale for change
	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 should consult the Pamiparib Investigator's Brochure in the determination of his/her assessment."	
Section 9.1.4 Follow-Up of Adverse Events	• Revised from "New or updated information will be recorded on the originally completed SAE report/eCRF, with all changes signed and dated by the investigator. The updated SAE report/eCRF should be resent to the sponsor within the time frames outlined in Section 9.5.1." 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 9.5.1."	Revised for consistency with other pamiparib protocols.
Section 9.1.5 Laboratory Test Abnormalities	• Revised from "Abnormal laboratory findings (eg, hematology or chemistry) or other abnormal assessments (eg, ECGs or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE (as defined in Section 9.1.1) or an SAE (as defined in Section 9.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the patient's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs. They should be reported as AEs or SAEs if they induce clinical signs or symptoms, need active intervention, require a dose hold or permanent discontinuation, or are clinically significant in the opinion of the investigator. The investigator will exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant." to "Abnormal laboratory findings (eg, chemistry, hematology, or coagulation) or other abnormal assessments (eg, ECGs, x-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and	Revised for consistency with other pamiparib protocols.

Section	Key Changes	Rationale for change
	significantly worsen during the study. The definition of clinically significant is entrusted to the judgment of the investigator. In general, these are the abnormalities that: • Are associated with clinical signs or symptoms, or • Require active medical intervention, or • Lead to dose interruption or discontinuation, or • Require close observation, more frequent follow-up assessments, or • Further diagnostic investigation"	
Section 9.2 Definition of a Serious Adverse Event	• Moved the following text to the end of the section and edited as shown: **The following are NOT considered SAEs:** o Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline ~~is not considered an SAE.~~ o Hospitalization for social/convenience considerations ~~is not considered an SAE.~~ o Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience~~, is not considered an SAE.~~	Revised for consistency with other pamiparib protocols.
Section 9.3.1 Adverse Event Reporting Period	• Revised from "After the ICF has been signed, but prior to initiation of study drug, only SAEs should be reported. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. After this period, the investigator should report any SAEs that are believed to be related to study drug." to "After the ICF has been signed, but prior to initiation of study drug, only SAEs should be reported to the sponsor.	Revised for consistency with other pamiparib protocols.

Section	Key Changes	Rationale for change
	After initiation of treatment, all AEs and SAEs, regardless of relationship to treatment, will be reported until 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment. After a patient is discontinued from the study, investigators are not obligated to actively seek AEs or SAEs from the former patients. However, if the investigator learns of any SAE, including a death, at any time, and considers the SAE related to pamiparib, the investigator will notify the sponsor."	
Section 9.4 Study-Specific Instructions for Recording Adverse Events and Serious Adverse Events	• Changed section heading to **"Study-**Specific Instructions for Recording Adverse Events and Serious Adverse Events" • Deleted old subsections Section 9.4.1 Diagnosis versus Signs and Symptoms, Section 9.4.2 Adverse Events Occurring Secondary to Other Events, Section 9.4.3 Persistent or Recurring Adverse Events, and Section 9.4.6 Myelodysplastic Syndrome and Acute Myeloid Leukemia • Revised newly numbered Section 9.4.1 Disease Progression text from "Disease progression is measured as an efficacy endpoint and not considered to be an AE. However, if there are separate identifiable clinical sequelae that result from disease progression, those sequelae are reportable as AEs. For instance, a patient with pleural effusion presents with shortness of breath. The cause of the shortness of breath is a pleural effusion resulting from disease progression. The AE term should be reported as "pleural effusion" instead of disease progression or metastasis to lungs. If a patient has a seizure that is determined to be associated with a brain metastasis, the term "seizure" should be recorded as the AE instead of disease progression or brain metastasis. If a patient experienced multi-organ failure due to disease progression, the term "multi-organ failure" should be reported as the AE instead of disease progression. Deaths that are assessed by the investigator as solely due to disease progression should be recorded on study completion or early discontinuation eCRF as efficacy data. They should not be reported as an SAE. If deaths are assessed by the investigator as not solely due to disease progression, whether they are assessed as related or not related to the study drug, they should be reported as SAE immediately. If there is any uncertainty regarding whether an AE is due to disease progression, it should be reported as an AE."	Revised for consistency with other pamiparib protocols.

Section	Key Changes	Rationale for change
	to ““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 event term. Instead, the symptoms, signs, or clinical sequelae that result from disease progression should be reported as the event terms. For example, 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 multiorgan failure due to disease progression, the term “multiorgan failure” should be reported as the SAE with death as outcome instead of reporting “fatal disease progression” or “death due to disease progression”.” • Revised newly numbered Section 9.4.2 Death text from “When recording a death as an SAE, the AE that caused or contributed to fatal outcome should be recorded as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “unexplained death”.” to “Death is an outcome and not usually considered an event. If the only information available is death and the cause of death is unknown, then the death is reported as an event, eg, “death”, “death of unknown cause”, or “death unexplained”.”	

<table>
<tr><th>Section</th><th>Key Changes</th><th>Rationale for change</th></tr>
<tr><td>Section 9.5.1 Time Frames and Documentation Methods for Submitting Serious Adverse Events</td><td>

Revised section heading to “Time Frames and Documentation Methods for Submitting Serious Adverse Events”
Revised to “SAEs will be reported promptly (within 24 hours) to the sponsor or designee as described in Table 4 once the investigator determines that the AE meets the protocol definition of an SAE.”
Revised Table 4 title to “Time Frames and Documentation Methods for Submitting Serious Adverse Events” and table from

<table>
<tr><th>Type of SAE</th><th>Initial SAE Report</th><th>Document</th></tr>
<tr><td>All SAEs</td><td>Within 24 hours of first knowledge of the AE</td><td>eCRF/SAE form</td></tr>
</table>
Abbreviations: AE, adverse event; eCRF, electronic case report form; SAE, serious adverse event.

to
<table>
<tr><th>Type of SAE</th><th>Initial SAE Report</th><th>Document</th><th>Follow-up SAE and AE of Special Interest Report</th><th>Reporting Method</th></tr>
<tr><td>All SAEs</td><td>Within 24 hours of first knowledge of the SAE</td><td>SAE report</td><td>As expeditiously as possible</td><td>Email or fax SAE form or Pregnancy form</td></tr>
</table>
Abbreviations: SAE, serious adverse event.
</td><td>Revised for consistency with other pamiparib protocols.</td></tr>
<tr><td>9.5.2 Completion and Transmission of the Serious</td><td>

Revised from “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 9.5.1. The SAE eCRF will always be completed as thoroughly as possible with all available details of the SAE, e-signed by the investigator, and forwarded to the sponsor or designee within

</td><td>Revised for consistency with other pamiparib protocols.</td></tr>
</table>

Section	Key Changes	Rationale for change
Adverse Event Report	the designated time frames. The data alert letter will automatically be submitted to sponsor or designee immediately after investigator signature. 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. In case the EDC is nonoperational, email or facsimile transmission of the paper SAE form is the preferred backup method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone or email is acceptable with a copy of the paper SAE form sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the paper SAE form within the time frames outlined in Section 9.5.1. After the EDC becomes operational again, the investigator will enter the information in the EDC system. The sponsor will provide a list of project contacts for SAE receipt, fax numbers, telephone numbers, and mailing addresses." to "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 9.5.1. The SAE Report will always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated time frames. If the investigator does not have all information regarding an SAE, he/she 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."	

Section 9.5.3 Regulatory Reporting Requirements for Serious Adverse Events	• Revised from "The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.5.2. 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. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other patients are met. 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. This protocol is being filed under an investigational new drug (IND) protocol amendment with the China Food and Drug Administration (CFDA). Once active, a given SAE may qualify as an IND safety report if the SAE is both attributable to the study drug and unexpected. In this case, all investigators filed to the IND (and associated INDs for the same compound) will receive an expedited investigator safety report, identical in content to the IND safety report submitted to the CFDA. Expedited investigator safety reports are prepared according to the sponsor's policy and are forwarded to investigators as necessary. The purpose of the report is to fulfill specific regulatory and GCP requirements regarding the product under investigation. When a study center receives an initial or follow-up report or other safety information (eg, revised IB) from the sponsor, the responsible person according to local requirements is required to promptly notify his/her IRB or IEC." to "The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.5.2. 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 suspected unexpected serious adverse reactions (as defined in Section 9.6) will be submitted to all applicable regulatory authorities and investigators for pamiparib studies. When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated	Revised for consistency with other pamiparib protocols.

Section	Key Changes	Rationale for change
	responsible person is required to promptly notify his/her IRB or IEC. The investigator should place copies of Safety Reports from the sponsor in the Investigator Site File.	
Section 9.6 Suspected Unexpected Serious Adverse Reactions and Expedited Reporting	• Added new section titled "Suspected Unexpected Serious Adverse Reactions and Expedited Reporting" with the following text "A suspected unexpected serious adverse reaction is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information in the Investigator's Brochure) and assessed as related to pamiparib either by the investigator or the sponsor. The sponsor will promptly assess the expectedness for all SAEs against the list of expected serious adverse reactions in the Reference Safety Information and expeditiously submit suspected unexpected serious adverse reactions to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation."	Added for consistency with other pamiparib protocols.
Section 9.7 Pregnancy Reporting	• Deleted "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."	Deleted for consistency with other pamiparib protocols.
Section 9 Safety Monitoring and Reporting	• Deleted old subsections Section 9.7 Post-study Adverse Event and Section 9.8 Expedited Reporting to Health Authorities, Ethics Committees and Investigators	Deleted for consistency with other pamiparib protocols.
Appendix 1, Table a Study Visit Schedule (continued)	• Hematology, Footnote 9: Added "Weekly hematology test should be done for the first 3 cycles during the study. For all Grade 2 or higher anemia, hematology tests should be done weekly thereafter until adequate recovery. At the investigator's discretion, weekly tests may take place at an alternate fixed hospital near the patient's home. The investigator's permission and choice of hospital should be documented in the patient chart and the medical monitor needs to be notified. Hematology results from this fixed hospital are acceptable." • Pregnancy test, Footnote 13: Updated from "Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to Cycle 1 Day 1. Urine pregnancy tests will	To specify hematology testing requirements. To allow flexibility in the method of pregnancy tests.

Section	Key Changes	Rationale for change
	be performed as clinically indicated during treatment. A serum pregnancy test must be performed if the urine pregnancy test is positive." to "For women of childbearing potential including those who have had a tubal ligation, a 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 before dosing. A serum pregnancy test must be performed if the result of a urine pregnancy test is positive or equivocal." • [redacted]	To clarify the timing of the sample collection on Cycle 1 Day 1.
Appendix 1, Table b Pharmacokinetic Sampling	• Deleted columns that did not have assessments marked. • Deleted footnote designator "1" from ECG and vital signs rows in table. • General notes: Reorganized from "Thus, the sequence at a particular time point is: 1) scheduled 12-lead ECGs; 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." to "Thus, the sequence at a particular time point is: 1) vital sign measurements; 2) scheduled 12-lead ECGs; 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." • General notes: Added "For sparse PK sampling, the sequence of collection at a particular timepoint may be determined by the sites based on feasibility."	To clarify timing of PK assessments and to reorder the sequence of other assessments in relation to PK blood draws.

Section	Key Changes	Rationale for change
Appendix 2 Clinical Laboratory Assessments	• Deleted from the footnote "and a random urine sample for total protein and creatinine to determine a protein to creatinine ratio".	To clarify urinalysis assessment.
Appendix 4 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation	• Revised from "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" to "The online calculator for CKD-EPI can be found here: https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators"	Updated website link

SYNOPSIS

Name of Sponsor/Company:	BeiGene (Beijing) Co., Ltd
Name of Finished Product:	Pamiparib (BGB-290) Capsule
Name of Active Ingredient:	Pamiparib (BGB-290)
Title of Study:	An Open Label, Multi-Center Phase 2 Study to Evaluate Efficacy and Safety of BGB-290 in the Treatment of Metastatic HER2-Negative Breast Cancer Patients with *BRCA* mutation in China
Protocol No:	BGB-290-201
Number of Patients:	Approximately 75 patients will be enrolled.
Study Centers:	Approximately 25 study centers
Study Phase:	2
Treatment Duration:	Patients will receive treatment continuously during the study until occurrence of disease progression as assessed by the investigator, unacceptable toxicity, death, withdrawal of consent, lost to follow-up, or study termination by sponsor.

Objectives:

Primary:

- To evaluate the efficacy of pamiparib (also known as BGB-290) in patients with advanced triple negative breast cancer (TNBC) or hormone receptor-positive (HR[+])/human epidermal growth factor receptor 2-negative (HER2[-]) breast cancer harboring germline breast cancer susceptibility gene 1/2 (*BRCA1/2)* mutation, as measured by:
    - Objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, by independent radiology review (IRR)

Secondary:

- To further evaluate the efficacy of pamiparib in patients with TNBC or HR(+)/HER2(-) breast cancer harboring germline *BRCA1/2* mutation, as measured by:
    - ORR by investigator assessment
    - Progression-free survival (PFS) and duration of response (DOR) by independent radiology review and investigator assessment
    - Disease control rate (DCR), best overall response (BOR) and clinical benefit rate (CBR) assessment by independent radiology review and investigator

assessment

- Overall survival (OS)

- To evaluate the safety and tolerability of pamiparib, as measured by:
  - Incidence, timing, and severity of treatment-emergent adverse events (TEAEs), graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03 (Common Toxicity Criteria Version 4.03) or higher

Exploratory:

[redacted]

Study Design:

This is a Phase 2, open-label, multi-center study of pamiparib administered orally (PO) twice daily (BID) in adult Chinese patients with advanced HER2(-) breast cancer harboring germline *BRCA* mutation, which have progressed despite standard therapy, or for which no standard therapy exists. In this study, the efficacy, safety, tolerability and PK profile of pamiparib will be further evaluated. All eligible patients will be enrolled into one of the below cohorts:

1. Approximately 55 previously treated patients with locally advanced or metastatic TNBC with confirmed either deleterious or suspected deleterious germline *BRCA1/2* mutation
2. Approximately 20 previously treated patients with locally advanced or metastatic HR(+)/HER2(-) breast cancer with confirmed either deleterious or suspected deleterious germline *BRCA1/2* mutation

In this study, all patients, including those with known germline *BRCA1/2* mutation status, need to undergo germline *BRCA* mutation testing prior to pamiparib dosing. 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 the first dosing.

Archival tumor tissues will be collected for all patients, if available.

All patients will receive pamiparib BID continuously from Day 1 of Cycle 1 and in subsequent 28-day cycles. Patients will receive treatment continuously during the study until occurrence of disease progression as assessed by the investigator, unacceptable toxicity, death, withdrawal of consent, lost to follow-up, or study termination by sponsor. Once the treatment phase has been completed, an end of treatment (EOT) visit will be conducted at the earliest day possible within 7 days of the last dose of pamiparib, and a safety follow-up will be conducted for approximately 30 days after the last dose of pamiparib. All patients will be followed for

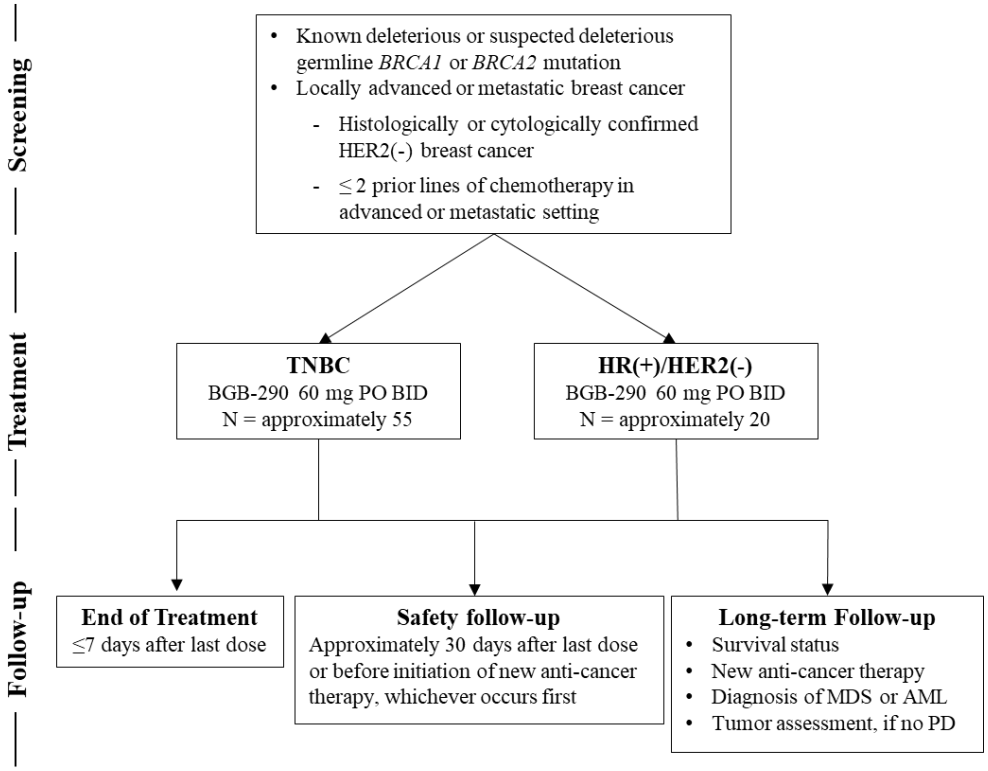
adverse events (AEs), serious adverse events (SAEs) and concomitant medications (including any new anticancer treatment) for 30 days following the last dose of pamiparib.

All patients will be followed for safety, tolerability, and efficacy from the first dosing day to the 30 days after the last dose.

Safety evaluations will be conducted at the clinical site as indicated in Appendix 1. Clinical laboratory evaluations should be conducted before dosing on visit days at the clinical sites. A 12-lead electrocardiogram (ECG) will be performed as clinically indicated during treatment and at EOT visit.

Tumor response will be assessed separately by IRR and Investigator's review based on RECIST, version 1.1 (Appendix 5). Tumor response will be evaluated once every 8 weeks ± 7 days in the first year and then once every 12 weeks ± 7 days starting in the second year.

Study Schema



Abbreviations: BC, breast cancer; BID, twice daily; HER2(-), human epidermal growth factor receptor 2 negative; HR(+), hormone receptor-positive; PD, progression disease; PO, oral; TNBC, triple negative breast cancer
Note: Key assessments during treatment phase: tumor assessments every 8 weeks ± 7 days in the first year and once every 12 weeks ± 7 days in the second year and above. Hematology every 2 weeks in Cycle 1 and Cycle 2, then keep once every 4 weeks in subsequent cycles. Adverse events at each visit. Chemistry every 4 weeks until disease progression. Pamiparib is to be administered continuously.

Key Eligibility Criteria:

The population under study is adult patients (≥18 years of age) with histologically or cytologically confirmed locally advanced or metastatic HER2(-) breast cancer (TNBC or HR[+]/HER2[-] breast cancer) harboring germline *BRCA1/2* mutation. All patients are required to have received ≤2 prior lines of chemotherapy in the advanced or metastatic setting. Prior therapy with an anthracycline and/or a taxane in either neoadjuvant/adjuvant or metastatic setting are required. Prior platinum therapy is allowed as long as no breast cancer progression occurred on treatment, or if given in neoadjuvant/adjuvant setting, at least 6 months from last platinum to relapse. For HR(+)/HER2(-) breast cancer, patients must have received and progressed on at least one endocrine therapy either in adjuvant or metastatic setting, or have disease that the treating physician believes to be inappropriate for endocrine therapy. All patients will be required to undergo germline *BRCA1/2* mutation testing prior to Day 1 of Cycle 1. Patients with diagnosis of myelodysplastic syndrome (MDS) are excluded.

Test product, dose, and mode of administration:	Pamiparib: 60 mg will be administered PO BID

Dose Modifications:

Dosing of pamiparib can be withheld for up to 28 days consecutively for medical events (56 days for anemia). A maximum of 2 dose reductions is allowed before the patient will be permanently withdrawn from study drug. If drug is planned to be held > 28 days, the medical monitor should be contacted prior to permanent patient discontinuation from the study drug.

Concomitant Therapy and Clinical Practice:

All treatments and supportive care, including antiemetic therapy, hematopoietic growth factors, and/or red blood cell/platelet transfusions, 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, including all prescription and over-the-counter drugs, herbal supplements, and intravenous (IV) medications and fluids, taken by or administered to the patient within 28 days before the first dosing and 30 days after the last day of pamiparib will be recorded.

Patients are not allowed to receive other anticancer therapy, including surgery, radiation therapy (except for palliative radiation therapy to non-targeted lesion), immunotherapy, investigational agents, cytotoxic, biologic or hormone therapy, anticancer Chinese medicine, or anticancer herbal remedies. Bisphosphonate and RANK-L inhibitors are allowed for bone metastases if initiated before enrollment and at a stable dose. Bisphosphonates are permitted during the study for a non-malignant indication.

[redacted]

Criteria for Evaluation:

Efficacy:

Tumor imaging studies will be reviewed for the purposes of eligibility determination and on-study tumor monitoring. Disease assessment during the screening may be completed within 28 days prior to the first dose of pamiparib. Afterward, disease assessments will be performed every 8 weeks (±7 days) in the first year and then every 12 weeks (±7 days) in the second year and subsequent years. Any measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Patients who do not have disease progression at the time of pamiparib permanent discontinuation but meet other discontinuation criteria (eg, discontinued for AE and no new anticancer therapy) will continue to have tumor assessments per protocol. ORR will be assessed by IRR and by the investigator. PFS and DOR will be assessed by IRR and investigator using RECIST, version 1.1. The same imaging method(s) used at screening must be used throughout the study. A documented standard-of-care tumor assessment may be used as the screening assessment if it meets protocol requirements. Survival status of patients will be monitored through all phases of the study.

Safety:

Safety will be monitored throughout the study. Safety assessments include AE monitoring and reporting, physical examinations, vital sign measurements, ECGs, and clinical laboratory tests.

Statistical Methods:

Analysis Sets

The Safety Analysis Set includes all patients who receive at least one dose of pamiparib.

The Efficacy Analysis Set includes all patients in the Safety Analysis Set who have measurable disease at baseline per RECIST, version 1.1, and have at least one evaluable post baseline tumor assessment by IRR unless discontinued treatment due to clinical progression or death prior to tumor assessment. This is the primary analysis set for all the tumor response endpoints (ORR, BOR, DOR, etc).

The Intent-to-Treat (ITT) Analysis Set is defined as all enrolled patients who receive any amount of study drug. This is the primary analysis set for OS.

The PK Evaluable Analysis Set includes all patients for whom valid pamiparib PK parameters can be estimated.

Statistical and Analytical Methods

Efficacy and safety of pamiparib will be evaluated in two cohorts (TNBC and HR[+]/HER2[-] breast cancer) separately.

Efficacy Analyses

Primary Efficacy Analyses

TNBC cohort

Hypothesis testing of ORR by IRR will be performed in the patients with evaluable tumor assessment pre- and post-baseline. The primary analysis will be carried out using IRR data in the Efficacy Analysis Set. Efficacy endpoints based on investigator assessed tumor response will be presented as the sensitivity analysis.

ORR of pamiparib per IRR is assumed as 46% in patients with TNBC. The historical rate in a

similar population is estimated as 25%. The null and alternative hypotheses are set as follows:

H_0: ORR=25%

H_a: ORR >25%

A binomial exact test will be performed for hypothesis testing in the Efficacy Analysis Set. 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 ITT analysis set.

HR(+)/HER2(-) breast cancer Cohort

ORR and its two-sided binomial exact 95% confidence interval (CI) will be calculated similarly as described above in the TNBC cohort. However, no statistical comparison to a specified historical rate is planned.

Secondary Efficacy Analyses

TNBC and HR(+)/HER2(-) breast cancer cohort

As in the primary efficacy analyses, secondary efficacy analyses will be performed by cohort. Tumor response assessed by IRR and investigator will be summarized.

BOR is defined as the best response recorded from the start of pamiparib until data cut or start of new anti-neoplastic treatment. The proportion of each response category (complete response [CR], partial response [PR], stable disease [SD], disease progression and not evaluable [NE]) will be presented in the Efficacy Analysis Set and ITT Analysis Set.

DCR and CBR and their 95% CIs will be summarized by cohort in the Efficacy Analysis Set and ITT Analysis Set.

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)

Other time to event variables (PFS and OS) will be similarly analysed in the Efficacy Analysis Set 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.

Exploratory Efficacy Analyses

[redacted]

Safety

Verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (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. All AEs will be included in the listings and only TEAEs will be included in the summary tables. SAEs, deaths, TEAEs with Grade 3 or above, related TEAEs and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

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.

Pharmacokinetic Analysis

Pamiparib concentrations after single-dose and at steady-state will be summarized by the sampling timepoint. Descriptive statistics will include means, medians, and standard deviations, as appropriate.

Population PK analysis may be carried out to include plasma concentrations from this study. Additional PK parameters such as apparent clearance (CL/F) of the drug from plasma and area under the plasma concentration-time curve from 0 to 12 hours postdose (AUC_{0-12}) may be derived from the population PK analysis if supported by data.

Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data.

Sample Size

A total of approximately 75 patients will be enrolled into one of the below cohorts.

1) Approximately 55 evaluable patients will be enrolled into the TNBC cohort. In TNBC cohort, it is assumed that ORR is 46% in patients with pamiparib. There is an 90% power of demonstrating a statistical difference versus a historical response rate of 25% using a binomial exact test at an alpha of 0.025 in 55 evaluable patients. The 2-sided exact 95% CI is (32.0%, 59.5%) when the observed ORR is 46%. Additional patients may be enrolled to meet the required number of evaluable patients.
2) [redacted]

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}12h}$	area under the plasma concentration-time curve from zero to 12 hours post-dose
BID	twice daily
BGB-290	study drug code
BOR	best overall response
BRCA1/2	breast cancer susceptibility gene 1/2
CBR	clinical benefit rate
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum observed plasma concentration
CR	complete response
CT	computed tomography
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
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
EOT	end of treatment
FDA	Food and Drug Administration
GCP	good clinical practice
HER2(-)	human epidermal growth factor receptor 2-negative
HGOC	High-grade non-mucinous ovarian cancer
HR(+)	hormone receptor-positive
Hgb	hemoglobin
IC_{50}	half inhibitory concentration

Abbreviation	Definition
ICF	informed consent form
IEC	independent ethics committee
IRB	institutional review board
IRR	independent radiology review
ITT	Intent-to-Treat
MDS/AML	myelodysplastic syndrome/acute myeloid leukemia
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NE	not evaluable
ORR	objective response rate
OS	overall survival
pamiparib	BGB-290
PAR	poly(ADP-ribose)
PARP	poly(ADP-ribose) polymerase
PBMCs	peripheral blood mononuclear cells
PET	positron emission tomography
PFS	Progression-free survival
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PT	preferred term
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SOC	system organ class
TEAE	Treatment-emergent adverse event
T_{max}	time of maximum plasma concentration
TNBC	triple negative breast cancer
ULN	upper limit of normal
US	United States

1. INTRODUCTION

1.1 Metastatic Breast Cancer

Breast cancer is the most common cancer among women worldwide, with approximately 1.7 million new cases and 520,000 deaths according to GLOBOCAN 2012. In China, breast cancer accounts for 17% (approximately 280,000) of all new cancer cases and approximately 65,000 cancer deaths in 2013, ranking as the top female malignancy and the 5th leading cause of cancer-related death (Chen et al 2017).

Triple negative breast cancer (TNBC) is characterized by the absence of estrogen receptor, progesterone receptor, and HER2, and represents 15% to 20% of all breast cancers (Metzger-Filho et al 2012). In addition, HR(+) and HER2(-) tumors constitute approximately 65% to 70% of all breast cancers (Hart et al 2015). Recurrences of TNBC typically occur during the first 3 years after diagnosis with a high rate of visceral metastases, particularly to the lungs and brain, and, less frequently, metastases to bone. (Haffty et al 2006). Once breast cancer becomes metastatic, it is generally considered incurable. The median survival for metastatic TNBC ranges from 6 months to 13.3 months. (Dent et al 2007; Kassam et al 2009). The aim of systemic therapies for metastatic breast cancer is to optimize survival and quality of life, and to minimize the side effects of treatment.

Women with TNBC do not benefit from endocrine therapy or trastuzumab. The only established therapeutic strategies for metastatic TNBC are cytotoxic chemotherapy, with no targeted therapies approved so far (Cardoso et al 2017; NCCN Guidelines 2017). Currently, there is no standard recommendation of chemotherapy for metastatic TNBC. Preferred single agents recommended by National Comprehensive Cancer Network guideline include anthracyclines, taxanes, anti-metabolites and other microtubule inhibitor, with objective response rates (ORRs) ranging from ~11% to 23% (Rugo et al 2009; O'Shaughnessy et al 2010; Brufsky et al 2012; Curigliano et al 2013). Thus, further development of effective targeted treatment represents an important unmet medical need.

1.2 Poly (ADP-ribose) Polymerase Inhibitors

Poly (ADP-ribose) polymerase (PARP) proteins are involved in DNA replication, transcriptional regulation, and DNA damage repair. DNA-bound PARP1/2 catalyzes the synthesis of poly (ADP ribose) (PAR) onto a range of DNA-associated proteins that mediate DNA repair. PARP1 also undergoes auto-PARylation, a molecular change that ultimately leads to its release from DNA. Inhibition of PARP converts common single-strand DNA breaks (SSBs) into double-strand breaks during DNA replication. Small-molecule inhibitors of PARP1/2 represent a class of anticancer agents that exert their cytotoxic effects by interfering with DNA repair mechanisms. Since the discovery of

synthetic lethality of PARP inhibitors in *BRCA*-deficient cells and, more broadly, cells with homologous recombination deficiency, accumulation of unrepaired SSBs resulting from catalytic PARP inhibition has been considered central to the mechanism of action of PARP inhibitors. More recently, it has been demonstrated that PARP inhibitors also trap PARP1- and PARP2-DNA complexes at DNA damage sites and that PARP trapping can be more cytotoxic than unrepaired SSBs (Pommier et al 2016; O'Connor 2015; Lord and Ashworth 2017).

In clinical studies, PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, have demonstrated sustained antitumor responses as single agents in patients with *BRCA1*- or *BRCA2*-mutated tumors, while achieving a favorable safety profile. Olaparib has been approved in the United States (US) as single agent for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a CR or PR to platinum-based chemotherapy, as well as for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. In 2016, rucaparib was approved for monotherapy for the treatment of patients with advanced ovarian cancer with deleterious *BRCA* mutation (germline and/or somatic) who have been treated with two or more chemotherapies. Niraparib was approved in 2017 for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy (Lynparza [olaparib] prescribing information; Rubraca [rucaparib] prescribing information, Zejula [niraparib] prescribing information).

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

1.3 Biology of Germline *BRCA*-mutant Breast Cancer and PARP Inhibitors

Breast cancer is a clinically and biologically heterogenous disease characterized by diverse genomic signatures and protein expression patterns. Up to 10% of TNBC and 5% HR(+) breast cancers can be linked to germline mutations in *BRCA1* and/or *BRCA2* genes (Lang et al 2017; Sun et al 2017; 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 recombination or homology-directed repair (Yoshida and Miki 2004; O'Sullivan et al 2014). *BRCA1/2* mutations also sensitize cells to inhibition of PARP activity because it leads to chromosomal instability, cell-cycle

arrest, and subsequent apoptosis (Sonnenblick et al 2015). Approximately 70% of *BRCA1*-mutant and 20% of *BRCA2*-mutant breast tumors present as TNBC (Mavaddat et al 2017).

Clinical studies support the use of platinum compounds for *BRCA1/2*-mutated breast cancers in the neoadjuvant and advanced setting, including 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 ORR 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 ORR in the subgroup of patients with germline *BRCA1/2*-mutated breast cancer.

PARP inhibitors have been tested clinically in metastatic breast cancer patients with *BRCA1/2.* In a single-arm, open-label study, olaparib (400 mg or 100 mg oral [PO] twice daily [BID]) was administered to women with *BRCA1*- and/or *BRCA2*-mutant, advanced breast cancer (of which >50% 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 AEs were fatigue, nausea, and vomiting.

OlympiAD was a randomized, open-label, Phase 3 trial in which olaparib monotherapy was compared to physician's choice chemotherapy (capecitabine, eribulin, or vinorelbine in 21-day cycles) in 302 patients with a germline *BRCA* mutation and HER2(-) metastatic breast cancer who had received no more than two previous chemotherapy regimens for metastatic disease (Robson et al 2017). In this trial, 205 patients were assigned to the olaparib group, and 97 patients were assigned to the physician's choice group. The randomized, phase 3 OlympiAD trial showed that, among patients with HER2(-) metastatic breast cancer and a germline *BRCA* mutation, median PFS was significantly longer with oral olaparib monotherapy than with standard chemotherapy (7.0 months versus 4.2 months; hazard ratio for disease progression or death, 0.58; 95% confidence interval [CI], 0.43 to 0.80). The risk of disease progression or death was 42% lower and the median PFS was 2.8 months longer with olaparib than with standard therapy. The response rate in the olaparib group was approximately double the rate in the standard-therapy group (59.9% versus 28.8%). Although no significant difference in OS was observed between olaparib treatment and standard therapy, this trial was not powered to assess differences in OS between treatment groups. Analysis of OS is also likely to be confounded by subsequent treatment, and more patients in the standard-therapy group than in the olaparib group received treatment with PARP inhibitors, platinum-based therapy, and cytotoxic chemotherapy after they had disease progression while receiving the assigned treatment (Robson et al 2017).

ABRAZO (NCT02034916) is a 2-cohort, 2-stage Phase 2 study of talazoparib (1 mg/d) following platinum-based therapy (Cohort 1) or ≥ 3 platinum-free cytotoxic-based regimens (Cohort 2) in patients with locally advanced or metastatic breast cancer and germline *BRCA1/2* mutation (Turner et al 2017). The final results were reported at the 2017 ASCO meeting. In this study, 84 patients were enrolled (Cohort 1, n = 49; Cohort 2, n = 35). ORR by independent radiology facility was 21% in Cohort 1 and 37% in Cohort 2, ORR by IRF for *BRCA1/BRCA2* was 24%/34%, and ORR by independent radiology facility for TNBC/HR(+) was 26%/29%, respectively. Most common AEs were anemia (52%), fatigue (45%), nausea (42%), diarrhea (33%), thrombocytopenia (33%), and neutropenia (27%). AEs of ≥ Grade 3 were anemia (35%), thrombocytopenia (19%), and neutropenia (15%). This study showed talazoparib was exhibiting promising antitumor activity in cohort 1 and cohort 2.

EMBRACA (NCT01945775) is a randomized, open-label, Phase 3 study comparing the efficacy and safety of talazoparib (1 mg once daily) with single-agent chemotherapy of physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine) in patients with advanced breast cancer and a germline *BRCA1/2* mutation. Patients were randomized in a 2:1 ratio; 287 were assigned to receive talazoparib and 144 were assigned to receive standard therapy. Median PFS was significantly longer in the talazoparib group than in the standard chemotherapy group (8.6 months versus 5.6 months; hazard ratio for disease progression or death, 0.54; 95% CI, 0.41 to 0.71; $p < 0.001$). The ORR was higher in the talazoparib group than in the standard-therapy group (62.6% versus 27.2%; odds ratio, 5.0; 95% CI, 2.9 to 8.8; $p < 0.001$). The interim median hazard ratio for death was 0.76 (95% CI, 0.55 to 1.06; $p = 0.11$ [57% of projected events]). Common AEs included anemia, fatigue, and nausea in the talazoparib group and nausea, fatigue, and neutropenia in the standard-therapy group. Hematologic Grade 3 to 4 AEs (primarily anemia) occurred in 55% of the patients who received talazoparib and in 38% of the patients who received standard therapy; nonhematologic Grade 3 AEs occurred in 32% and 38% of the patients, respectively (Litton et al 2018).

Both the OlympiAD and EMBRACA studies have consistently shown that a PARP inhibitor is a reasonable treatment option for patients with advanced TNBC or HR(+)/HER2(-) breast cancer with a germline *BRCA1/2* mutation, since its use is associated with a PFS benefit, improvement in quality of life, and a favorable toxicity profile. Olaparib was approved in the US for patients with deleterious or suspected deleterious germline *BRCA*-mutant, HER2-negative metastatic breast cancer (Lynparza [olaparib] prescribing information).

1.4 PARP Inhibitor Pamiparib

1.4.1 Nonclinical Data for 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, as well as in vivo models, harboring *BRCA* gene mutations or with homologous recombination deficiency.

1.4.1.1 Nonclinical Safety Data

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-à-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. [redacted]

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 [redacted]. No effects on blood pressure, heart rate, or 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 (Pamiparib Investigator's Brochure).

1.4.2 Nonclinical Activity Data

Pamiparib potently inhibits enzyme activity of PARP1 and PARP2, [redacted] Most PARP inhibitors are able to trap PARP enzymes at damaged DNA sites, and these trapped PARP-DNA complexes appear to be more cytotoxic than unrepaired DNA breaks caused by PARP inactivation (Section 1.2). The PARP-trapping activity of pamiparib was measured by a fluorescence polarization binding assay, similar to the method described in the literature (Murai et al 2012).

[redacted]

[redacted]			
[redacted]			
[redacted]			
[redacted]			

[redacted]

[redacted]

Pamiparib as a single agent has demonstrated excellent in vitro activity against tumor cell lines with defects of the homologous repair pathway. In vivo, pamiparib showed strong anti-tumor activity against a *BRCA1*-mutant mouse xenograft model (MDA-MB-436 breast cancer) and was 16-fold more potent than olaparib. In a PK/pharmacodynamic study, oral administration of pamiparib resulted in time- and dose-dependent inhibition of PARylation in MDA-MB-436 breast cancer xenografts in mice. Inhibition of PARylation in the tumor tissues correlated well with tumor drug concentrations of pamiparib.

Please refer to the IB for additional information (Pamiparib Investigator's Brochure).

1.4.3 Clinical Data for BGB-290

Pamiparib is currently being studied in two Phase 1/2 studies: BGB-290-AU-002 in Australia, n=68 (as of 1 June 2017) and BGB-290-102 in China, n=15 (as of 25 September 2017) (Lickliter et al 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, as are preliminary safety and PK data for pamiparib in China patients (BGB-290-102).

1.4.3.1 Pharmacokinetics Data for BGB-290-AU-002

In the first-in-human Phase 1 study, interim PK data of pamiparib showed that pamiparib is rapidly absorbed and eliminated after oral administration. The maximum serum concentration (C_{max}) and the drug exposure (the area under the concentration-time curve [AUC]) increased in a nearly dose-proportional manner from 2.5 mg 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.

[redacted]

1.4.3.2 Pharmacokinetics for BGB-290-102 in China

In this Phase 1a 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), these differences represent a very preliminary result and need to be interpreted with caution. [redacted]

Although all 3 demographic factors were inter-related and showed statistical significance in the forward-addition step, they were not retained in the backward elimination process of the covariate analysis. The apparent difference in plasma exposure observed between BGB-290-AU-002 and BGB-290-102 could ultimately be due to the difference in patient body weight, as the median weight from 15 female patients in BGB-290-102 (China) was 61 kg, and the median body weight from 60 male and female patients in BGB-290-AU-002 (Australia) was 71.5 kg.

1.4.3.3 Exploratory Biomarker Data

[redacted]

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

BGB-290-AU-002 is a first-in-human study evaluating pamiparib to characterize the safety, the maximum tolerated dose, 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 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 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 AEs (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 maximum tolerated dose 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.

1.4.3.5 Clinical Safety and Preliminary Efficacy for BGB-290-102 in China

The Phase 1 portion of Study BGB-290-102 evaluates the safety, tolerability, PK, and preliminary efficacy of pamiparib in Chinese patients with advanced high-grade non-mucinous ovarian cancer (HGOC), 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). 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 5 TNBC patients showed progressive disease for all 5 (*BRCA1/2* mutation: n=1). Median duration of treatment for 9 HGOC patients was 133 days (range: 8–260). 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 6 with stable disease (on treatment: n=3; *BRCA1/2* mutation: n=4).

1.5 Rationale for Selection of Pamiparib Dose

Based upon the overall safety, efficacy, and PK profile of pamiparib, the dose of pamiparib 60 mg PO BID was selected using available clinical data from Studies BGB-290-AU-002 and BGB-290-102 (Sections 1.4.3.4 and 1.4.3.5, respectively). 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 the IB [Pamiparib 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

The recommended dose for further investigation in Chinese patients was also determined to be 60 mg PO BID.

The 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:

- The AE profile observed from 15 female Chinese patients in the BGB-290-102 study was generally consistent with that from the 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.
- The average steady-state pamiparib plasma exposure (C_{max}, AUC) at 60 mg BID in Chinese patients was approximately 35% higher than for Australian patients (BGB-290-AU-002).

In summary, pamiparib is an excellent candidate to determine the effects of PARP inhibition in advanced cancers.

1.6 Study Rationale

This is a Phase 2 study to evaluate the anti-tumor activity of pamiparib, its safety and PK profile in advanced or metastatic HER2(-) breast cancer patients with confirmed either deleterious or suspected deleterious germline *BRCA1/2* mutations susceptible to treatment with a PARP inhibitor. Preliminary biomarkers for efficacy and resistance will also be explored.

Pamiparib 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 recommended Phase 2 dose (10 mg versus 60 mg BID). PK modeling predicts that the recommended Phase 2 dose of pamiparib can achieve brain concentrations required for anti-tumor activity. [redacted].

Breast cancer is now the most common cancer among Chinese women, and 15-20% of them are TNBC. The prognosis of TNBC is poor, and effective treatment choices are limited. The 3rd ESO-ESMO International Consensus Guideline for advanced breast cancer recommends that genetic counseling and possibly *BRCA* testing should be discussed with TNBC patients, if the results can impact on treatment decisions and/or clinical trial entry. In China, there is currently no PARP inhibitor approved for the treatment of breast cancer.

Data from the OlympiAD study support the use of PARP inhibitors as monotherapy in HER2(-) breast cancer patients with deleterious *BRCA* mutation.

In summary, pamiparib is an attractive drug candidate to determine the effects of PARP inhibition in this unmet medical need of HER2(-) breast cancer patients with *BRCA* mutation.

1.7 Benefit-Risk Assessment

Pamiparib has been studied in nonclinical toxicity and Phase 1 clinical studies, and pamiparib toxicities are largely consistent with the safety profile shared by other PARP inhibitors.

MDS and AML have been reported in a small number (<1%) of patients treated with PARP inhibitors, especially in patients harboring a germline *BRCA* mutant (Ricks et al 2015). Typically, patients who develop MDS and AML while on therapy with a PARP inhibitor have a history of extensive previous chemotherapy and some have a history of previous cancer or bone marrow abnormalities. To date, there have been no reports of MDS or AML in patients treated with pamiparib. Patients in this study will be monitored monthly for hematological toxicities, and events of MDS and AML will be reported as SAEs irrespective of time elapsed since end of study treatment.

In this study, patients with advanced HER2(-) breast cancer harboring germline *BRCA1/2* mutation will be recruited. Given that PARP inhibitors have shown clinical benefit in this patient populations (Refer to Section 1.3), the risk of toxicities of the PARP inhibitor pamiparib appears acceptable.

1.8 Study Conduct

This study will be conducted in compliance with the protocol approved by the institutional review board (IRB) or Independent Ethics Committee (IEC), and in accordance with good clinical practice (GCP) standards.

2. STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the efficacy of pamiparib in patients with advanced triple negative breast cancer or HR(+)/HER2(-) breast cancer harboring germline *BRCA1/2* mutation, as measured by:
    - Objective response rate according to Response Evaluation Criteria in Solid Tumors, version 1.1, by independent radiology review

2.2 Secondary Objectives

- To further evaluate the efficacy of pamiparib in patients with TNBC or HR(+)/HER2(-) breast cancer harboring germline *BRCA1/2* mutation, as measured by:
    - Objective response rate by investigator assessment
    - Progression-free survival and duration of response by independent radiology review and investigator assessment
    - Disease control rate, best overall response and clinical benefit rate assessment by independent radiology review and investigator assessment
    - Overall survival
- To evaluate the safety and tolerability of pamiparib, as measured by:
    - Incidence, timing, and severity of treatment-emergent adverse events, graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events, version 4.03 (Common Toxicity Criteria Version 4.03) or higher

2.3 Exploratory Objectives

[redacted]

3. STUDY DESIGN

This is a Phase 2, open-label, multi-center study of pamiparib administered PO BID in adult Chinese patients with advanced HER2(-) breast cancer harboring germline *BRCA* mutation, which have progressed despite standard therapy, or for which no standard therapy exists. In this study, the efficacy, safety, tolerability and PK profile of pamiparib will be further evaluated. All eligible patients will be enrolled into one of the below cohorts:

1. Approximately 55 previously treated patients with locally advanced or metastatic TNBC with confirmed either deleterious or suspected deleterious germline *BRCA1/2* mutation
2. Approximately 20 previously treated patients with locally advanced or metastatic HR(+)/HER2(-) breast cancer with confirmed either deleterious or suspected deleterious germline *BRCA1/2* mutation

Patients will be screened for eligibility up to 28 days prior to the first dose of pamiparib and will take pamiparib at 60 mg BID continuously for all cycles (28-day cycles) starting on Day 1 of Cycle 1. Patients will be instructed to swallow the capsules whole, in rapid succession, with water. Pamiparib can be administered with or without food.

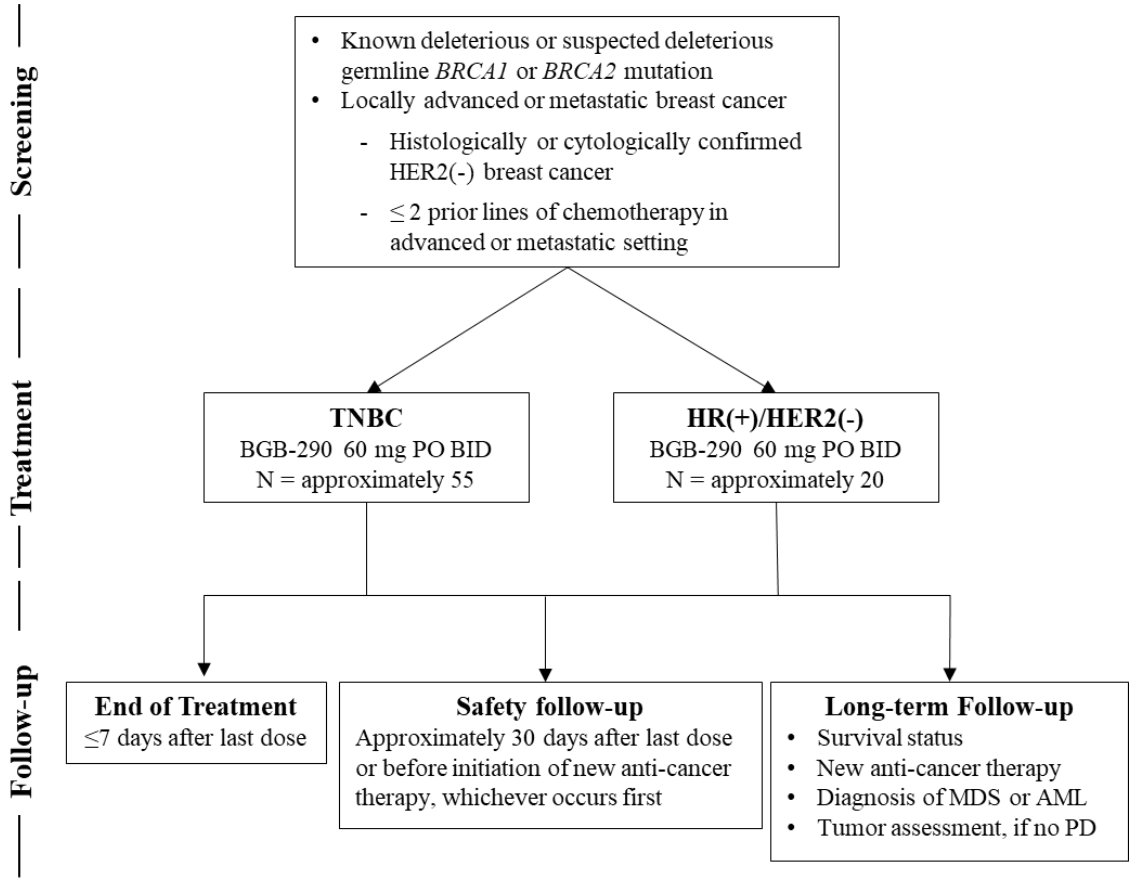
Tumor response will be assessed by IRR and investigators based on RECIST, version 1.1.

Patients will be monitored for safety, tolerability, and efficacy throughout the study. Tumor assessments will be performed every 8 weeks ± 7 days in the first year, and then every 12 weeks ± 7 days thereafter, or as clinically indicated.

Patients will continue treatment until occurrence of disease progression as assessed by the investigator, unacceptable toxicities, death, withdrawal of consent, lost to follow-up, or study termination by sponsor.

Study procedures and assessments are detailed in Appendix 1. The study schema is provided in Figure 2.

Figure 2. Study Schema



Abbreviations: BC, breast cancer; BID, twice daily; HER2(-), human epidermal growth factor receptor 2 negative; HR(+), hormone receptor-positive; PD, progression disease; PO, oral; TNBC, triple negative breast cancer.

Note: Key assessments during treatment phase: tumor assessments every 8 weeks ± 7 days in the first year and every 12 weeks ± 7 days in the second year and above. Hematology assessments every 2 weeks in Cycles 1 and 2, then every 4 weeks in subsequent cycles. Adverse events at each visit. Chemistry assessments every 4 weeks throughout the study. Pamiparib is to be administered continuously.

4. STUDY POPULATION

4.1 Inclusion Criteria

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

1. Signed informed consent form (ICF)
2. Age ≥ 18 years on day of signed ICF
3. Confirmed deleterious or suspected deleterious germline *BRCA1* or *BRCA2* mutation
   - Germline *BRCA1/2* mutation testing in central laboratory prior to Day 1 of Cycle 1
4. Locally advanced or metastatic breast cancer despite standard therapy and the following:
   a. Histologically or cytologically confirmed HER2(-) breast cancer (TNBC or estrogen receptor-positive and/or PR+)
   b. ≤ 2 prior lines of chemotherapy in advanced or metastatic setting
   c. Prior platinum therapy allowed as long as no disease progression while on treatment, or if given in neoadjuvant/adjuvant setting with ≥ 6 months from last platinum to relapse
   d. Prior therapy with an anthracycline and/or a taxane in neoadjuvant/adjuvant or metastatic setting
   e. Archival tumor tissues will be collected from all patients, if available
   f. For HR(+)/HER2(-) breast cancer only: patients must have received and progressed on at least one endocrine therapy either in adjuvant or metastatic setting, or have disease that the treating physician believes to be inappropriate for endocrine therapy
5. Measurable disease as defined per RECIST, version 1.1
   - Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 (Appendix 3)
7. Ability to swallow whole capsules
8. Ability to comply with study requirements independently

9. Adequate hematologic and organ function as defined by the following laboratory values (obtained ≤ 14 days before Day 1 of Cycle 1):
    - Absolute neutrophil count ≥ 1,500/mL or ≥ 1.5 x 10^9/L
    - Platelet count ≥ 75,000/mL or ≥ 75 x 10^9/L
    - Hemoglobin ≥ 9 g/dL or ≥ 90 g/L (≥14 days after growth factor support or transfusion)
    - Estimated glomerular filtration rate ≥30mL/min/1.73m^2 by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI EQ; Appendix 4)
    - Total serum bilirubin ≤ 1.5 × upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × ULN, if liver function abnormalities are due to liver metastasis, then AST and ALT ≤ 5 × ULN
10. For females of childbearing potential and nonsterile males, must practice highly effective methods of birth control (Appendix 8) for the duration of the study and for at least 6 months after last study drug

4.2 Exclusion Criteria

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

1. Unresolved acute effects of prior therapy of ≥ Grade 2
    - Except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
2. Prior treatment with a PARP inhibitor
    - Subtherapeutic exposure to a PARP inhibitor for ≤ 28 days is permissible provided it was not the most recent prior therapy
3. Chemotherapy, hormonal therapy, radiotherapy, biologic therapy, immunotherapy, investigational agent, anticancer Chinese medicine, or anticancer herbal remedies ≤ 14 days (or ≤ 5 half-lives, if applicable, whichever is shorter) prior to Day 1 of Cycle 1
    - Bisphosphonate and RANK-L inhibitors are allowed for bone metastases if initiated before enrollment and at a stable dose
4. Major surgical procedure, open biopsy, or significant traumatic injury ≤ 14 days prior to Day 1 of Cycle 1, or anticipation of need for major surgical procedure during the course of the study
    - Placement of vascular access device is not considered major surgery

5. Diagnosis of MDS
6. Other diagnosis of malignancy
   - Except for surgically excised nonmelanoma skin cancer, adequately treated carcinoma in situ of the cervix, localized prostate cancer treated with curative intent, 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 of Cycle 1
7. Untreated and/or active brain metastases
   a. A scan to confirm the absence of brain metastases is not required
   b. Patients with treated brain metastases must be off corticosteroids for ≥ 2 weeks and have no signs or symptoms of progressive brain metastases
8. Active infection requiring systemic treatment, active viral hepatitis, or active tuberculosis
9. Any of the following cardiovascular criteria:
   a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days prior to Day 1 of Cycle 1
   b. Symptomatic pulmonary embolism ≤ 28 days prior to Day 1 of Cycle 1
   c. Any history of acute myocardial infarction ≤ 6 months prior to Day 1 of Cycle 1
   d. Any history of heart failure meeting New York Heart Association Classification III or IV (see Appendix 9) ≤ 6 months prior to Day 1 of Cycle 1
   e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months prior to Day 1 of Cycle 1
   f. Any history of cerebral vascular accident ≤ 6 months prior to Day 1 of Cycle 1
10. 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.
11. Active bleeding disorder, including gastrointestinal bleeding, as evidenced by hematemesis, significant hemoptysis, or melena ≤ 6 months prior to Day 1 of Cycle 1
12. Use ≤ 10 days (or ≤ 5 half-lives, whichever is shorter), prior to Day 1 of Cycle 1, or anticipated need for food or drugs known to be strong or moderate [redacted]s (Appendix 6)

13. Pregnancy or nursing
    a. Females of childbearing potential require a negative urine or serum pregnancy test ≤ 7 days prior to Day 1 of Cycle 1
14. Significant intercurrent illness that may result in the patient's death before death from breast cancer
15. Known history of intolerance to the excipients of the pamiparib capsule

5. STUDY PHASES FROM SCREENING TO END OF STUDY

5.1 Pre-screening

In this study, all patients including those with known germline *BRCA1/2* mutation must undergo blood sampling for examination or confirmation of germline *BRCA1/2* mutation prior to Day 1 of Cycle 1.

Patients with unknown mutation status must undergo germline *BRCA1/2* testing in pre-screening phase prior to screening. The mutation testing will be performed in the qualified central laboratory. 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 ICF from the patient
- Prepare blood sample and ship to the qualified central laboratory for mutation analysis as specified in the laboratory manual

5.2 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 a of Appendix 1. The PK sampling time points are presented in Table b of Appendix 1.

Rescreening under limited conditions 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.

5.3 Enrollment

After a patient is screened and the investigator determines the patient is eligible for enrollment, study site personnel will complete an eligibility form and email it to the medical monitor or designee to approve the enrollment in writing. Study site personnel should ensure that a medical monitor approved eligibility form is in the patient's file before proceeding with study procedures. Each patient enrolled in this study will receive a unique patient number which will be assigned when the patient is enrolled in the study. Patients will be assigned in chronological order starting with the lowest number. Once a

patient number has been assigned to a patient, it cannot be reassigned to any other patient.

5.4 Treatment

Day 1 of Cycle 1 is the first day of pamiparib administration.

Study procedures of each clinic visit are outlined in Appendix 1.

On days with PK assessments, pamiparib should be administered in the clinic in accordance with the schedule for the PK samples. Assessments should be obtained before study treatment unless stated otherwise in Appendix 1 and should be performed in order of least invasive to most invasive assessment. All safety-related assessments have to be reviewed and dose modifications, if necessary, be made by the investigator or sub-investigator before study treatment.

5.5 Unscheduled Visit

Unscheduled visits may occur any time as necessary as per investigator's 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 Appendix 1. If disease progression is suspected, imaging studies should be performed and blood for biomarkers should be obtained, as appropriate.

5.6 Permanent Discontinuation of Study Drug

5.6.1 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:

- Disease progression
- AE(s)
- Pregnancy
- Protocol violation
- Patient withdrew consent for study treatment
    - Patients may voluntarily withdraw consent from study treatment at any time
    - Patients should be requested to participate in the follow-up phase, if a patient withdraws consent from the treatment phase only
- Investigator's discretion
- Start of other anticancer therapy

Patients may discontinue pamiparib for other reasons but these will result in premature discontinuation from study (Section 5.8) and, consequently, result in lack of an EOT visit.

5.6.2 End of Treatment Visit

The EOT visit should occur within 7 days after pamiparib has been permanently discontinued. Required assessments are listed in Appendix 1. If discontinuation is due to unresolved toxicities for more than 28 days (56 days for anemia), the EOT visit should be conducted at the earliest day possible within 7 days after permanent discontinuation is determined. The visit at which tumor assessments showed disease progression 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 disease progression. 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.

5.7 Follow-Up Phase

5.7.1 Safety Follow-up

All patients who discontinue study drug and have not initiated new anticancer therapy will be followed for AEs and SAEs as outlined in Section 9.3.1. A safety follow-up will occur with the safety assessments outlined in Appendix 1, until approximately 30 days after the last day of pamiparib or before initiation of new anticancer therapy, whichever occurs first. If new anticancer therapy is inadvertently initiated before this safety follow-up (eg, without the knowledge of the study center team), a safety follow-up should be scheduled as soon as possible. If discontinuation is due to unresolved toxicities for more than 28 days, safety follow-up could be scheduled approximately 30 days after the last dose of study drug. 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 7 days after permanent discontinuation is determined.

For patients who do not want to or cannot return to the clinic for the safety follow-up, the patient should be contacted by telephone for a review of AEs. If these attempts to contact are unsuccessful, the additional attempts detailed in Section 5.7.3 should be made.

When treatment is interrupted or permanently discontinued due to an AE or abnormal laboratory value the patient will be followed at a frequency as medically indicated until resolution or stabilization of the event, whichever comes first.

Patients who are discontinued from the study due to an unacceptable drug-related AE will be followed until the resolution of the AE to ≤ Grade 1 or stabilization.

If MDS/AML is diagnosed, treatment of pamiparib must be permanently discontinued.

5.7.2 Long-term Follow-up

Patients will be followed for survival, further anticancer therapy, and diagnosis of MDS or AML via telephone contact or other means (eg, clinic visit) approximately every 12 weeks (Appendix 1).

Patients who were permanently discontinued from study drug for reasons other than disease progression and meet criteria otherwise (eg, discontinued for AE and no new anticancer therapy) will be followed with tumor assessments per protocol as outlined in Appendix 1 until disease progression or any other reason listed in Section 5.8, whichever occurs first. For efficacy assessments as per protocol, refer to Section 7.3 and Appendix 1. If the patient refuses to return for these tumor assessments or is unable to do so, every effort should be made to contact the patient by telephone to determine the patient's disease status and survival.

5.7.3 Lost to Follow-up

Should attempts of telephone contact be unsuccessful, the following additional attempts should be made to obtain protocol-required follow-up information. The patient should be contacted by mail in a manner that provides proof of receipt by the patient. If unsuccessful, other contacts should be explored, such as referring physicians or relatives. Attempts of contact should be documented in the patient's source documents. If a patient cannot be contacted despite all attempts, the patient will be considered lost to follow-up, and death information should be obtained through a public record search if local agencies permit.

5.8 End of Study

Premature discontinuation from the study (without EOT and any follow-up visits) will occur under the following circumstances:

- Patient withdrew consent for study participation
    - Patients may voluntarily withdraw consent from the study at any time
- Investigator's discretion
- Lost to follow-up
    - Lost to follow-up should be recorded as such in the eCRF
    - The investigator should show due diligence by documenting in the source documents steps taken to contact the patient (Section 5.7.3)
- Death

- Study termination by sponsor
- Other, as per the discretion of the sponsor or health authority

6. STUDY TREATMENTS

6.1 Study Drug

6.1.1 Packaging and Labelling

Pamiparib capsules will be provided in 20-mg capsules and in a child-resistant high-density polyethylene (HDPE) 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.

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

6.1.2 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 patients 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. [redacted].

6.1.3 Dosage and Administration

The patients will take pamiparib at 60 mg BID 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 pamiparib may cause, patients are encouraged to take pamiparib 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.

6.1.4 Dose Hold and Modification

AEs should be assessed as best as possible regarding their relatedness to pamiparib. Regardless of discontinuation of pamiparib, patients should continue on study with follow-up as outlined in Sections 5.6 and 5.7.

Investigators should make every effort to maintain dose intensity in patients. Dosing of pamiparib can be withheld for up to 28 days consecutively for medical events (56 days for anemia). If drug is planned to be held > 28 days, the medical monitor should be contacted prior to permanent patient discontinuation from the study drug.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery, study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any biopsy procedure. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Criteria for treatment modifications and suggested guidelines for the management of some toxicities related to pamiparib are summarized below. These general guidelines may be modified at the discretion of the investigator based on discussions with the sponsor medical monitor and the best clinical judgment at that time; any decisions should be documented. Any toxicities related to pamiparib should be managed according to standard medical practice.

A maximum of 2 dose reductions is allowed before the patient must be permanently withdrawn from study drug. Dose levels for pamiparib are summarized in Table 2. Pamiparib will be dose modified as outlined in Table 3.

Table 2. Dose Levels for Pamiparib

Dose Level	Pamiparib
1	60 mg PO BID
-1	40 mg PO BID
-2	20 mg PO BID

Table 3. Criteria for Modification of Pamiparib Dosing for Related Adverse Events

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 (Hgb <10 - 8 g/dL)	Hgb <10 - 9 g/dL	• Continue dosing at current dose level and treat with appropriate supportive care as medically indicated
	Hgb <9 - 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
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 gastrointestinal 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 tests 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

Toxicity	Recommended Dose Modification[a]
Thrombocytopenia (platelet count, PLT)	
Grade 3 (PLT <50 - 25 × 10^9/L)	Hold pamiparib until resolved to Grade ≤1 or baseline and ↓ pamiparib by 1 dose level
Grade 4 (PLT <25 × 10^9/L)	Hold pamiparib until resolved to Grade ≤1 or baseline and ↓ pamiparib by 1 dose level
Renal	
Estimated glomerular filtration rate (CKD-EPI EQ; Appendix 4)	
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

Toxicity	Recommended Dose Modification[a]
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 not resolved within 7 days to ≤ 5 × ULN*, then pamiparib should be decreased by 1 dose level • If second episode, permanently discontinue pamiparib *if other etiologies have been reasonably excluded and not solely based on abnormality/increase of AST/ALT laboratory results
Grade 4 (>20 × ULN)	Permanently discontinue pamiparib
Pancreatic	
Pancreatitis	
Grade 3 or 4	Permanently discontinue pamiparib
Cardiac	
Cardiac - Prolonged QTc interval	
QTcF >500 msec or Change in QTc interval >60 msec from the highest value at baseline or predose	• Obtain triplicate ECGs (2 to 3 minutes apart) ~1 hour after initial ECG • If mean QTcF >500 ms or mean change in QTc interval > 60 msec, hold pamiparib until evaluation of ECGs by cardiologist o Cardiology evaluation as soon as practical but within 7 days of initial abnormal ECG • If mean QTcF >500 ms or mean change in QTc interval > 60 msec 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 In the event of acute coronary syndrome, congestive heart failure and myocardial infarction, treatment should be permanently discontinued
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

Toxicity	Recommended Dose Modification[a]
Grade 4	Permanently discontinue pamiparib

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CKD-EPI: 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.

[a] Dosing of pamiparib can be withheld for up to 28 days consecutively for medical events (56 days for anemia).

6.1.5 Compliance and Accountability

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient.

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

6.1.6 Disposal and Destruction

After completion of the study, all unused pamiparib will be inventoried and packaged for return shipment by the hospital unit pharmacist or other designated study center personnel. The inventoried supplies can be destroyed on site or at the depot according to institutional policies after receiving written sponsor approval.

6.2 Concomitant Medications and Non-drug Therapies

6.2.1 Permitted Medications and Supportive Care

All treatments and supportive care, including antiemetic therapy, hematopoietic growth factors, and/or red blood cell/platelet transfusions, 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, including all prescription and over-the-counter drugs, herbal supplements, and IV medications and fluids, taken by or administered to the patient within 28 days before Day 1 of Cycle 1 and 30 days after the last day of pamiparib will be recorded.

6.2.2 Prohibited Medications

Patients are not allowed to receive other anticancer therapy, including surgery, radiation therapy (except for palliative radiation therapy to non-targeted lesion), immunotherapy, investigational agents, cytotoxic, biologic or hormone therapy, anticancer Chinese medicine or anticancer herbal remedies. Bisphosphonate and RANK-L inhibitors are allowed for bone metastases if initiated before enrollment and at a stable dose. Bisphosphonates are permitted during the study for a non-malignant indication.

[redacted].

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

6.2.3 Medications to be used with Caution

Based on preliminary in vitro screening assays, pamiparib is not a strong inhibitor of other human [redacted] tested. It is a moderate inhibitor of [redacted] Investigators should be aware that pamiparib has the potential to interfere with the appropriate metabolism of medications that rely on [redacted]. Investigators should follow the prescribing information recommendations for use with [redacted]. Examples of these medications include, but are not limited to, medications presented in Appendix 6 and these should be used cautiously with the monitoring of drug concentrations where appropriate.

[redacted], pamiparib can also be metabolized by [redacted], but to a lesser extent. The compounds/substances presented in Appendix 7 are associated with possible interactions with pamiparib through the [redacted] and should also be used cautiously.

7. STUDY ASSESSMENTS

7.1 Study Flow and Visit Schedule

The study-specific assessments and procedures with allowed time windows are outlined in Appendix 1. Assessments of efficacy will occur as outlined in Section 7.3. Assessments of safety will be based on AE monitoring and reporting (including attribution of AEs and SAEs), physical examinations, vital signs, ECGs, and clinical laboratory tests as outlined in Section 7.4.

7.2 Patient Demographic and Other Baseline Assessments Characteristics

7.2.1 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.

7.2.2 Medical History and Prior Medications

Clinically significant medical history findings (eg, previous diagnoses, diseases, or surgeries) which started prior to signing the ICF, 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.

For breast cancer history, the date of initial diagnosis and current disease status, staging, sites of disease, prior anticancer therapies and dates administered, responses, and duration of response to these treatments will also be recorded.

7.2.3 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. Screening assessments will be completed within 28 days prior to the first dose of the pamiparib. Screening assessments completed within 4 days of administration can be used as Cycle 1 Day 1 assessments as indicated in Appendix 1.

All the baseline data will be captured in the source documents and in the eCRF.

7.3 Efficacy

7.3.1 Tumor Assessments

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 every 8 weeks ± 7 days after the first dose of pamiparib in the first year, then every 12 weeks ± 7 days afterwards. 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 disease progression at the time of pamiparib discontinuation and meet criteria (eg, discontinued for AE and no new anticancer therapy) will continue to have tumor assessments per protocol as outlined in Appendix 1, until 1) commencement of new treatment, 2) disease progression, 3) death, or 4) termination of the study. ORR, PFS, OS and DOR will be assessed by IRR and investigator using RECIST, version 1.1 (Appendix 5).

7.3.1.1 Screening Tumor Assessment

The baseline tumor assessment should include the following:

- Diagnostic-quality, computed tomography (CT) scans of the chest, abdomen, and pelvis
  (Day -28 to -1)
  - To be suitable for RECIST, version 1.1, assessments, CT scans should have a maximum thickness of 5 mm and no gaps.
  - CT is the preferred imaging method for tumor assessments of the chest, abdomen, and pelvis.
  - If a positron-emission tomography (PET)/CT scan is performed, the CT portion should meet the CT scan requirements described above.
  - In patients for whom the preferred CT scans are contraindicated because of, for example, a CT IV contrast allergy, a CT of the chest without contrast and magnetic resonance imaging (MRI) of the abdomen and pelvis with contrast are recommended.
  - MRI scans may be performed in lieu of CT scans. At screening, tumor assessments should include a diagnostic quality, contrast enhanced MRI scan of the chest, abdomen, and pelvis. To be suitable for RECIST Version 1.1 assessments, MRI scans should ideally have a maximum thickness of 5 mm and minimal gaps.
- For all patients, a bone scan (Technetium-99m [TC-99m] or NaF-PET) at screening is required (Day -28 to -1)
- CT scan of the neck, if clinically indicated (Day -28 to -1)
  - Only to be performed at screening if the patient has known or suspected metastases in this area
  - MRI scan of the neck may be substituted for CT scan of the neck.
- MRI scan of the brain, if clinically indicated (Day -28 to -1)

- Only to be performed at screening if the patient has symptoms that could be due to brain metastases
- MRI is the preferred imaging method for tumor assessments of the brain.
- In patients for whom MRI of the brain is not available or who are claustrophobic, a CT scan of the brain with IV contrast may be performed.

7.3.1.2 On-study Tumor Assessments

All target and nontarget lesions must be assessed with the same imaging method used at baseline.

- Diagnostic-quality, CT scans of the chest, abdomen, and pelvis (every 8 weeks ±7 days, as calculated by the date of the first administration of pamiparib) in the first year, and then every 12 weeks ±7 days thereafter until progression
  - CT scan with IV contrast is preferred but the imaging method at screening determines the imaging method of subsequent tumor assessments and must be used.
- Imaging of all other known sites of disease (every 8 weeks ±7 days, as calculated by the date of the first administration of pamiparib) in the first year and every 12 weeks ±7 days thereafter until progression
- If bone metastases are present at screening and cannot be seen on CT or MRI scans, or if clinically indicated, TC-99m or NaF-PET bone scans should be repeated when CR is identified in target disease, or when progression in bone is suspected.

In addition to the protocol-specified tumor assessments, CT scans or other imaging studies may be performed at the investigator's discretion at any time as clinically indicated. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

After first documentation of response (CR or PR), confirmation of response should be obtained no sooner than 4 weeks following the initial evaluation and be better to occur at the next regularly scheduled assessment (4 weeks later, if possible).

7.3.2 Survival Assessments

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. Patients will have their survival status assessed approximately every 12 weeks 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.

Survival status of patients will be monitored throughout the study as outlined in Appendix 1. The date and cause of death will be recorded.

7.4 Safety

7.4.1 Adverse Events

Safety assessments should be performed at the study center visits indicated in Appendix 1.

All AEs and SAEs, regardless of their relationship to study treatment, will be collected in the fashion and for the time periods outlined in Section 9. The accepted regulatory definition of AEs and important additional requirements for SAE reporting are outlined in Section 9.

7.4.2 Physical Examination, Vital Signs, ECOG Performance Status, and Weight

A complete or limited physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, and temperature), weight, height, and ECOG performance status will be performed at time points specified in Appendix 1.

A complete physical examination should include an evaluation of head, eyes, ears, nose and throat, neck, heart, chest (including lungs), abdomen, extremities, skin, lymph nodes, cardiovascular status, and neurological status. A limited physical examination should be directed at the evaluation of symptoms or specific safety issues. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as AEs if appropriate.

ECOG performance status will be determined as outlined in Appendix 3.

7.4.3 Electrocardiogram

Single 12-lead ECGs with assessment of PR interval, QRS duration, and QT interval corrected for heart rate (QTc) will be obtained at screening and EOT visit. Additional ECGs will be performed if clinically indicated. To minimize postural variability, it is important that patients are resting and in a supine position for ≥5 minutes prior to each ECG measurement. 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. Screening ECG must be performed within 14 days prior to Day 1 of Cycle 1. 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.

7.5 Laboratory Assessments

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

Laboratory assessments should be performed at a local certified laboratory on Day 1 of Cycle 1 before pamiparib administration. Screening blood tests must be performed within 14 days of Day 1 of Cycle 1. Laboratory assessments need not be repeated on Day 1 Cycle 1 if these assessments were completed for screening within 4 days 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 Appendix 1.

7.5.1 Hematology

Hematology includes hemoglobin, lymphocyte count, neutrophil count, platelet count, and white blood cell count.

7.5.2 Chemistry

Chemistry includes ALT, alkaline phosphatase, AST, albumin, blood urea nitrogen or urea, creatinine, chloride, glucose, lactate dehydrogenase, phosphate or phosphorus, potassium, total bilirubin, total protein, and sodium.

7.5.3 Urinalysis

Urinalysis includes glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, and white blood cells.

7.5.4 Pregnancy Testing

The Clinical Trials Facilitation Group recommendations related to contraception and pregnancy testing in clinical studies include for women with childbearing potential the use of highly effective forms of birth control (Appendix 8). During screening, for women of childbearing potential including those who have had a tubal ligation, a urine or serum pregnancy test must be performed and documented as negative within 7 days prior to Day 1 of Cycle 1, and urine pregnancy tests will be performed at each visit before dosing. A serum pregnancy test must be performed if the result of a urine pregnancy test is positive or equivocal.

7.6 Pharmacokinetics

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 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.

Time points of PK sampling are specified in Table b of Appendix 1. PK sampling will be conducted according to the laboratory manual. The actual time that each sample was collected at 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 details on collection and handling of PK blood samples, please refer to laboratory manual. If there is any inconsistency in blood sample collection and handling between protocol and laboratory manual, laboratory manual will take priority.

Four blood samples (2 mL each) will be collected on Cycle 1 Day 1 and Cycle 2 Day 1 (± 3 days) at the following time points: pre-dose (within 1 hour before pamiparib administration) and 2 hours post-dose for sparse PK sample collection.

7.7 Biomarkers

A blood sample for all patients will be collected for germline *BRCA* mutation test. The blood sample should be collected prior to screening and will be processed according to the laboratory manual and sent to central laboratory for testing. DNA from this sample will be stored and may be used at later time for biomarker testing including, but not limited to, bridging to candidate companion diagnostic assays.

Archival tumor tissues will be collected, if available. Either a formalin-fixed, paraffin embedded block with tumor tissue (preferred) or approximate 10 unstained slides are acceptable for the baseline archived tumor tissue. The most recent tumor block is preferred.

Instructions for the processing, storage, and shipping of samples will be provided in the study laboratory manual.

7.8 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. DATA HANDLING AND QUALITY ASSURANCE

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

8.1 Data Collection

Data will be entered into the eCRFs in an electronic data capture (EDC) system that is compliant with all regulatory requirements.

Data collection on the eCRF must follow the instructions described in the eCRF completion guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee must sign the completed casebooks to attest to its accuracy, authenticity, and completeness.

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

8.2 Data Management/Coding

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

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

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

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

AEs will be coded using the MedDRA®, version 20.0 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary

(WHODRUG). Concomitant diseases/medical history will be coded using the MedDRA, version 20.0 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 findings and any relevant issues.

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 preexisting 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 the 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 assess the 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 or higher.

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 (eg, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]); whereas, seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 9.5.

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 using best clinical judgment. 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 should consult the Pamiparib Investigator's Brochure in the determination of his/her assessment. There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always provides an assessment of causality for every SAE before 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 based on 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 that there is reasonable temporal relationship; the positive of de-challenge result (when necessary the positive of re-challenge result); the occurrence of AE that could be attributed to the pharmacological effect of study drug.
- Probably related: This causality assessment will be applied for AE that is regarded by the investigator as highly positive related to the study drug that: there is reasonable temporal relationship; the occurrence of AE could not be explained by the subject's medical history, concurrent medical condition, or other the subject's signs or symptoms; the positive of de-challenge result; the positive of re-challenge result.
- Possibly related: There is some evidence to suggest a causal relationship (eg, the

AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the subject's clinical condition, other concomitant AEs).

- Unlikely related: There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the AE.
- Unrelated: An AE will be considered "not related" to the use of study drug if any of the following tests are met:
    - An unreasonable temporal relationship between administration of study drug and the onset on the AE (eg, the AE occurred either before, or too long after administration of study 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. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

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

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in Section 9.5.1.

9.1.5 Laboratory Test Abnormalities

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

- Are associated with clinical signs or symptoms, or
- Require active medical intervention, or
- Lead to dose interruption or discontinuation, or
- Require close observation, more frequent follow-up assessments, or
- Further diagnostic investigation

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. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the AE is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

- Results in disability/incapacity

Note: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea,

influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgment (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 preexisting condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

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

9.3.1 Adverse Event Reporting Period

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

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

After a patient is discontinued from the study, investigators are not obligated to actively seek AEs or SAEs from the former patients. However, if the investigator learns of any SAE, including a death, at any time, and considers the SAE related to pamiparib, the investigator will notify the sponsor.

9.3.2 Eliciting Adverse Events

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

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

9.4 Study-Specific Instructions for Recording Adverse Events and Serious Adverse Events

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

For example, 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 multiorgan failure due to disease progression, the term "multiorgan failure" should be reported as the SAE with death as outcome instead of reporting "fatal disease progression" or "death due to disease progression".

9.4.2 Death

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

9.5 Prompt Reporting of Serious Adverse Events

9.5.1 Time Frames and Documentation Methods for Submitting Serious Adverse Events

SAEs will be reported promptly (within 24 hours) to the sponsor or designee as described in Table 4 once the investigator determines that the AE meets the protocol definition of an SAE.

Table 4. Time Frames and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

Type of SAE	Initial SAE Report	Document	Follow-up SAE and AE of Special Interest Report	Reporting Method
All SAEs	Within 24 hours of first knowledge of the SAE	SAE report	As expeditiously as possible	Email or fax SAE form or Pregnancy form

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

9.5.2 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 9.5.1. The SAE Report will always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding an SAE, he/she 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.

9.5.3 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 9.5.2. 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 suspected unexpected serious adverse reactions (as defined in Section 9.6) will be submitted to all applicable regulatory authorities and investigators for pamiparib studies.

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

9.6 Suspected Unexpected Serious Adverse Reactions and Expedited Reporting

A suspected unexpected serious adverse reaction is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information in the Investigator's Brochure) and assessed as related to pamiparib either by the investigator or the sponsor. The sponsor will promptly assess the expectedness for all SAEs against the list of expected serious adverse reactions in the Reference Safety Information and expeditiously submit suspected unexpected serious adverse reactions to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

9.7 Pregnancy Reporting

If a female patient or the partner of a male patient becomes pregnant while receiving study drug 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.

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

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

10. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

10.1 Sample Size Considerations

A total of approximately 75 patients will be enrolled into one of the below cohorts.

- Approximately 55 evaluable patients will be enrolled into the TNBC cohort. In TNBC cohort, it is assumed that ORR is 46% in patients with pamiparib. There is an 90% power of demonstrating a statistical difference versus a historical response rate of 25% using a binomial exact test at an alpha of 0.025 in 55 evaluable patients. The 2-sided exact 95% CI is (32.0%, 59.5%) when the observed ORR is 46%. Additional patients may be enrolled to meet the required number of evaluable patients.
- [redacted]

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 as appropriate, median, minimum, and maximum.
- Categorical variables: frequencies and percentages.
- Time to event variables: number of non-missing observations, 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 cohorts. The analysis methods described in this section are directed to both cohorts in general

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

10.2.1 Analysis Sets

The Safety Analysis Set includes all patients who receive at least one dose of pamiparib.

The Efficacy Analysis Set includes all patients in the Safety Analysis Set who have measurable disease at baseline per RECIST, version 1.1, and have at least one evaluable post baseline tumor assessment by IRR unless discontinued treatment due to clinical progression or death prior to tumor assessment. This is the primary analysis set for all the

tumor response endpoints (ORR, BOR, DOR, etc).

The ITT Analysis Set is defined as all enrolled patients who receive any amount of study drug. This is the primary analysis set for OS.

The PK Evaluable Analysis Set includes all patients for whom valid pamiparib PK parameters can be estimated.

10.2.2 Interim Analysis

No formal interim analysis is planned.

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 Safety Analysis Set 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

TNBC cohort

Hypothesis testing of ORR by IRR will be performed in the patients with evaluable tumor assessment pre- and post-baseline. The primary analysis will be carried out using IRR data in the Efficacy Analysis Set. Efficacy endpoints based on Investigator assessed tumor response will be presented as the sensitivity analysis.

ORR of pamiparib per IRR is assumed as 46% in patients with TNBC. The historical rate in a similar population is estimated as 25%. The null and alternative hypotheses are set as follows:

H_0: ORR= 25%

H_a: ORR > 25%

A binomial exact test will be performed for hypothesis testing in the Efficacy Analysis Set. 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 ITT analysis set.

HR(+)/HER2(-) breast cancer cohort

ORR and its two-sided binomial exact 95% CI will be calculated similarly as described above in the TNBC cohort. However, no statistical comparison to a specified historical rate is planned.

10.3.2 Secondary Efficacy Analyses

TNBC and HR(+)/HER2(-) breast cancer cohort

As in the primary efficacy analyses, secondary efficacy analyses will be performed by cohort. Tumor response assessed by IRR and investigator will be summarized.

BOR is defined as the best response recorded from the start of pamiparib until data cut or start of new anti-neoplastic treatment. The proportion of each response category (CR, PR, SD, disease progression and NE) will be presented in the Efficacy Analysis Set and ITT Analysis Set.

DCR and CBR and their 95% CIs will be summarized by cohort in the Efficacy Analysis Set and ITT Analysis Set.

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 analysed in the Efficacy Analysis Set 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.

10.3.3 Exploratory Efficacy Analyses

[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 ECG findings will also be used in determining the safety. Descriptive statistics will be used to analyze all safety data in the Safety Analysis Set.

10.4.1 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. 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.

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

10.4.2 Laboratory Assessments

Clinical laboratory (eg, hematology and chemistry) values to be evaluated will be specified in the statistical analysis plan and collected in the EDC system. Analyzed laboratory values that are abnormal will be flagged and identified as outside (above or below) the normal range.

Laboratory parameters that are graded in NCI-CTCAE, version 4.03, or higher will be summarized by NCI-CTCAE grade. Shift tables will be provided as appropriate

10.4.3 Physical Examinations

Physical examination results collected in association with an AE will be listed and summarized.

10.4.4 Vital Signs

Specific vital signs, eg, blood pressure and temperature, will be summarized and listed. The change from baseline will also be presented.

10.4.5 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 by cohort. Dose interruption, reduction and discontinuation will be summarized by frequency.

10.5 Pharmacokinetic Analyses

Pamiparib concentrations after single-dose and at steady-state will be summarized by the sampling timepoint. Descriptive statistics will include means, medians, and standard deviations, as appropriate.

Population PK analysis may be carried out to include plasma concentrations from this study. Additional PK parameters such as CL/F of the drug from plasma and AUC_{0-12} may be derived from the population PK analysis if supported by data.

Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data.

10.6 Biomarker Analyses

All patients will have blood samples collected for germline *BRCA1/2* mutation test.

The baseline tumor biomarker analysis includes but is not limited to somatic mutation analysis.

Predictive biomarkers of efficacy include but not limited to *BRCA1/2* mutation.

[redacted]

11. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

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 or file the protocol to appropriate regulatory agency before the study is initiated at a study center in China.

11.2 Investigator Responsibilities

11.2.1 Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" International Conference of Harmonisation (ICH) guidelines, and that the basic principles of "GCP" as outlined in 21 Code of Federal Regulations (CFR) 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, and 21 CFR, Part 56, are adhered to.

Investigators and all sub-investigators must provide documentation of their financial interest or arrangements with BeiGene, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify BeiGene or its authorized representative of any change reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date that the last patient has completed the protocol-defined activities.

11.2.2 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, the 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 ICF) are reviewed and approved by the appropriate IEC/IRB.

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 the study drug(s) can be shipped to the study center, the sponsor or its authorized representative must receive copies of the IEC/IRB approval, 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 patient consent to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the sponsor promptly.

11.2.3 Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB/IEC-approved ICF for documenting written informed consent. Each ICF will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining 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.

11.2.4 Investigator Reporting Requirements

As indicated in Section 9.5, 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.

11.2.5 Confidentiality

Information on maintaining patient confidentiality in accordance to individual local and national patient privacy regulations must be provided to each patient as part of the informed consent process, either as part of the ICF or as a separate signed document (for example, in the US, a study center specific HIPAA consent may be used). The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient initials, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from BeiGene, including but not limited to the IB, this protocol, eCRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of BeiGene during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except

employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from BeiGene. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

11.2.6 Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the principal investigator or sub-investigator within a reasonable time period after data collection. This also applies to records for those patients those patients who discontinue the study early. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The eCRFs exist within an EDC system with controlled access managed by BeiGene or its authorized representative for this study. Study staff will be appropriately trained in the use of eCRFs and applications of electronic signatures before the study start and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the eCRFs is true by providing an electronic signature within the EDC system. After final database lock, the investigator will receive a copy of the patient data on CD-ROMs for archiving the data at the study center.

11.2.7 Drug Accountability

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

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

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

11.2.8 Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from BeiGene or its representatives, to IRBs/IECs, or to regulatory authority or health authority inspectors.

11.2.9 Protocol Adherence

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

11.3 Sponsor Responsibilities

11.3.1 Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study patients, may be initiated only by BeiGene. All protocol modifications must be submitted to regulatory authorities and the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. As applicable by local requirements, written documentation of regulatory authorities, IRB/IEC, and required study center approval must be obtained by the sponsor before changes can be implemented.

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

11.3.2 Use of Information and Publication

A clinical study report will be prepared and provided to the regulatory agency(ies) of participating countries. The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

The 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 study will be described in the clinical study agreement.

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

11.4 Study and Study Center Closure

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

- Return of all study data to the sponsor

- Resolve and close all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of PK 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 noncompliance. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

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

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

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

11.5 Records Retention and Study Files

11.5.1 Study Files and Retention of Records

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

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

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

pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

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

If the investigator cannot guarantee this archiving requirement at the study center for any or all of the documents, special arrangements must be made between the investigator and BeiGene to store these in sealed containers outside of the study center so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the study center.

Biological samples at the conclusion of this study may be retained in storage by the sponsor as outlined in the study manual.

11.5.2 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 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.

11.6 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) is the sole property of the sponsor.

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

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

These restrictions do not apply to:

- Information 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 that may be published as described in Section 11.3.2

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

11.7 Joint Investigator/Sponsor Responsibilities

11.7.1 Access to Information for Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator

agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

11.7.2 Access to Information for Auditing or Inspections

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

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13. APPENDICES

Appendix 1 Schedule of Assessments

Table a. Study Visit Schedule

Assessments[7]	Pre-screening[1]	Screen-ing[1]	Cycle 1 (28 days)		Cycle 2 (28 days)		Cycle 3 and subsequent Cycles (28 days for one cycle)	Unscheduled Visit[2]	EOT Visit[3]	Safety Follow-up[4]	Long-term Follow-up[5]
Day of Cycle		**D -28 to -1**	**D1**	**D15**	**D1**	**D15**	**D1**	**Varies**	**≤7 days after last dose**	**~30 days after last dose**	**Every 12 weeks**
Allowed time window				**±3 days**	**±3 days**		**±3 days**				
Informed consent	X	X									
Baseline demographics		X									
Medical history/treatment history[6]		X									
Concomitant medications[8]		X	X		X		X	X	X	X	X
Complete physical examination		X							X		
Limited physical examination			X		X		X	X			
Vital signs and weight		X	X	X	X	X	X	X	X		
Height		X									
ECOG performance status		X	X		X		X	X	X		

Assessments[7]	**Pre-screening**[1]	**Screen-ing**[1]	**Cycle 1 (28 days)**		**Cycle 2 (28 days)**		**Cycle 3 and subsequent Cycles (28 days for one cycle)**	**Unscheduled Visit**[2]	**EOT Visit**[3]	**Safety Follow-up**[4]	**Long-term Follow-up**[5]
Day of Cycle		**D -28 to -1**	**D1**	**D15**	**D1**	**D15**	**D1**	**Varies**	**≤7 days after last dose**	**~30 days after last dose**	**Every 12 weeks**
Allowed time window				**±3 days**	**±3 days**		**±3 days**				
Hematology[9]		-14 to -1 X	X	X	X	X	X	X	X		
Clinical chemistry		-14 to -1 X	X		X		X	X	X		
Urinalysis[10]		-14 to -1 X	X					X	X		
12-lead ECG[11]		-14 to -1 X						X	X		
Disease assessment[12]		X	EVERY 8 WEEKS ± 7 DAYS in first year EVERY 12 WEEKS ± 7 DAYS in second year and later								X
Adverse events (including serious)		X	X		X		X	X	X	X	X
Pregnancy test[13]		-7 to -1 X			X		X	X	X	X	
Blood sample collection for *BRCA1/2* mutation testing[14]	X										
PK blood sampling[15]			X		X						

Assessments[7]	**Pre-screening**[1]	**Screen-ing**[1]	**Cycle 1 (28 days)**		**Cycle 2 (28 days)**		**Cycle 3 and subsequent Cycles (28 days for one cycle)**	**Unscheduled Visit**[2]	**EOT Visit**[3]	**Safety Follow-up**[4]	**Long-term Follow-up**[5]
Day of Cycle		**D -28 to -1**	**D1**	**D15**	**D1**	**D15**	**D1**	**Varies**	**≤7 days after last dose**	**~30 days after last dose**	**Every 12 weeks**
Allowed time window				**±3 days**	**±3 days**		**±3 days**				
Tumor Tissues[16]		X									
Optional paired biopsies[17]			X		X						
Investigational product administration[18]			CONTINUOUS					X			
Bone Scan[19]		X						X			X
[redacted]											
Survival follow-up											X

Abbreviations: CT, computed tomography; D, Day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; MRI, magnetic resonance imaging; PK, pharmacokinetic; X, to be performed.

1. Screening assessments will be completed within 28 days prior to the first dose of pamiparib. Pre-screening for germline *BRCA* mutation test (blood sample) can be completed prior to 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 disease progression is suspected, imaging studies should be performed and blood for biomarkers should be obtained as appropriate.
3. EOT visit should be conducted at the earliest day within 7 days of the last dose of pamiparib, if possible. If discontinuation is due to unresolved toxicities for more than 28 days (56 days for anemia), the EOT visit should be conducted at the earliest day possible within 7 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. ECG do not have to be repeated if it was performed within 14 days of the EOT visit, 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.

4. A safety follow-up will occur with the outlined safety assessments, until approximately 30 days after the last day of pamiparib. If new anticancer therapy is initiated before this safety follow-up, a safety follow-up should be scheduled as soon as possible ideally before other anticancer treatment starts. If discontinuation is due to unresolved toxicities for more than 28 days, safety follow-up could be scheduled approximately 30 days after the last dose of study drug. 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 7 days after permanent discontinuation is determined. 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.
5. Patients will be followed for survival, further anticancer therapy, and diagnosis of myelodysplastic syndrome or acute myeloid leukemia via phone contact or other means (eg, clinic visit) approximately every 12 weeks.
   Patients who were permanently discontinued from study drug for reasons other than disease progression and meet criteria otherwise (eg, discontinued for AE and no new anticancer therapy) will be followed with tumor assessments per protocol until disease progression or any other reason listed in Section 5.8, whichever occurs first. For efficacy assessments as per protocol, refer to Section 7.3. If the patient refuses to return for these tumor assessments or is unable to do so, every effort should be made to contact the patient by telephone to determine the patient's disease status and survival.
6. Date of and response to last platinum treatment must be documented (unless no platinum treatment has been received).
7. All assessments, unless stated otherwise, must be performed before investigational product administration in each cycle.
8. All concomitant medications taken by or administered to the patient within 28 days before the first dosing and 30 days after the last dose of study drug will be recorded. Concomitant medications include subsequent anticancer therapy information acquired during the long-term follow-up phase.
9. Weekly hematology test should be done for the first 3 cycles during the study. For all Grade 2 or higher anemia, hematology tests should be done weekly thereafter until adequate recovery. At the investigator's discretion, weekly tests may take place at an alternate fixed hospital near the patient's home. The investigator's permission and choice of hospital should be documented in the patient chart and the medical monitor needs to be notified. Hematology results from this fixed hospital are acceptable.
10. 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 Cycle 1 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.
11. 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 b.
12. Disease assessment during the screening may be completed up to 28 days prior to pamiparib administration. Afterwards, disease assessments will be performed once every 8 weeks ± 7 days after the first dose of pamiparib in the first year, then every 12 weeks ±7 days afterwards. A CT scan or MRI scan of the chest, abdomen, and pelvis will be performed. Patients with treatment terminated prior to documentation of disease progression shall be subject to CT/MRI radiographic assessments according to the previous visit assessment scheme, until 1) commencement of new treatment, 2) disease progression, 3) death or 4) termination of the study.
13. For women of childbearing potential including those who have had a tubal ligation, a 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 before dosing. A serum pregnancy test must be performed if the result of a urine pregnancy test is positive or equivocal.
14. Pre-screening for germline *BRCA1/2* mutation will be performed prior to study eligibility screening (pre-screening phase). Blood sample will be taken for each patient. 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.

15. The PK blood samples will be collected at the time points specified in Table b.
16. Archival tumor tissues will be collected, if available.
17. Optional paired biopsy samples will be collected at baseline (any time before receiving the first dose of study drug on Cycle 1 Day 1) and on Cycle 2 Day 1 for the assessment of changes in tumor microenvironment and other markers (PARP inhibition) in response to pamiparib. A separate informed consent must be obtained for paired biopsy. Specific instructions for tissue collection and shipment are provided in the laboratory manual.
18. BID dosing of pamiparib starts from Cycle 1 Day 1.
19. Bone scan (Technetium-99m [TC-99m]) at baseline is required. 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, TC-99m bone scans should be repeated when a complete response is identified in target lesion or when progression in bone is suspected.
20. [redacted]

Table b. Pharmacokinetic Sampling

Procedure	**Cycle 1**		**Cycle 2**	
Days	**Day 1**		**Day 1±3**	
Hours	**Pre-dose**	**2**	**Pre-dose**	**2**
ECGs	X	X	X	X
Vital signs	X	X	X	X
Sparse PK sampling[2]	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 is: 1) vital sign measurements; 2) scheduled 12-lead ECGs; 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.
For sparse PK sampling, the sequence of collection at a particular timepoint 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 sample will be taken for each sample.
2. 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.

Appendix 2 Clinical Laboratory Assessments

Clinical Chemistry	Hematology	Urinalysis
ALT	Hemoglobin (Hgb)	24-hour protein[1]
Alkaline phosphatase	Lymphocyte count	Glucose
AST	Neutrophil count	Ketones
Albumin	Platelet count	Occult blood
Blood urea nitrogen or urea	White blood cell count	pH
Creatinine		Protein[1]
Chloride		Red blood cells
Glucose		Specific gravity
Lactate dehydrogenase		White blood cells
Phosphate or phosphorus		
Potassium		
Total bilirubin		
Total protein		
Sodium		

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; 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, obtain a 24-hour urine sample for 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 MD, Group Chair.

Appendix 4 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation

In adults, the most widely-used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation1 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/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators

Appendix 5 The Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines, Version 1.1

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

DEFINITIONS

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

Measurable Disease

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

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

Nonmeasurable Disease

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

Bone lesions:

- Bone scan, positron-emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic 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 that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and should not be recorded or followed.

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

Nontarget Lesions

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

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

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

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

Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

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

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

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

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

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

RESPONSE CRITERIA

Evaluation of Target Lesions

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

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

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

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

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

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

Lesions that split or coalesce on treatment: When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of Nontarget Lesions

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

CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).

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

PD: Unequivocal progression (see comments below) of existing nontarget lesions.

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

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

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be

unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

Evaluation of Best Overall Response

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

confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

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

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

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

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 addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

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

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

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

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

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (Phase 2 or 3) or trials where stable disease or PD are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement

for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

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

Duration of Overall Response

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

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

Duration of Stable Disease

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

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between 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 periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

Appendix 6 Prohibited Medications

Data compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664 htm from the Indiana University School of Medicine's "Clinically Relevant" Table http://medicine.iupui.edu/flockhart/table htm; from the University of Washington's Drug Interaction Database www.druginteractioninfo.org

Appendix 7 Medications to be used with Caution

Appendix 8 Contraception Guidelines and Definitions of "Women of Childbearing Potential", "No Childbearing Potential"

Contraception Guidelines

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

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
    - Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized male partner
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment)

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

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

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

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

As defined in this protocol, "women of childbearing potential" are female patients who are physiologically capable of becoming pregnant.
Conversely, "women of no childbearing potential" are defined as female patients meeting > 1 of the following criteria:

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

postmenopausal follicle-stimulating hormone concentration >30 IU/mL

Appendix 9 New York Heart Association Functional Classification

Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, eg, no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.
Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

Appendix 10 Signature of Investigator

Protocol Title: An Open Label, Multi-Center Phase 2 Study to Evaluate Efficacy and Safety of BGB-290 in the Treatment of Metastatic HER2-Negative Breast Cancer Patients with *BRCA* mutation in China

Protocol Identifier: BGB-290-201

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: _____