CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, Double-blind, Randomized Study of BGB-290 versus Placebo as Maintenance Therapy in Patients with Inoperable Locally Advanced or Metastatic Gastric Cancer that Responded to Platinum-based First-line Chemotherapy
Protocol Identifier:	BGB-290-303
EudraCT Number:	2017-003493-13
Phase:	2
Date of Original Protocol:	25 October 2017
Date of Protocol Amendment	13 February 2020, Version 1.0
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1900 Powell Street, 5th Fl., Suite 500 Emeryville, CA 94608 USA
Sponsor Medical Monitor:	[redacted]

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PROTOCOL APPROVAL SHEET

Protocol Title: A Phase 2, Double-blind, Randomized Study of BGB-290 versus Placebo as Maintenance Therapy in Patients with Inoperable Locally Advanced or Metastatic Gastric Cancer that Responded to Platinum-based First-line Chemotherapy

Protocol Identifier: BGB-290-303, Version 1.0, 13 February 2020

BeiGene Ltd., Approval:

[redacted]

14 Feb 2020

Date

SYNOPSIS

Name of Sponsor/Company:	BeiGene, Ltd.
Name of Finished Product:	BGB-290 capsule
Name of Active Ingredient:	BGB-290
Title of Study:	A Phase 2, Double-blind, Randomized Study of BGB-290 versus Placebo as Maintenance Therapy in Patients with Inoperable Locally Advanced or Metastatic Gastric Cancer that Responded to Platinum-based First-line Chemotherapy
Protocol No:	BGB-290-303
Number of Patients:	Approximately 128 patients will be enrolled
Study Centers:	Approximately 110 centers
Study Phase:	2
Treatment Duration:	Patients will receive daily treatment during the study until occurrence of progressive disease (PD), unacceptable toxicity, death, withdrawal of consent, lost to follow-up, or study termination by sponsor.

Objectives:

Primary:

- To evaluate the efficacy of maintenance therapy with BGB-290 versus placebo in patients with inoperable locally advanced or metastatic gastric cancer with a complete response (CR) or confirmed partial response (PR) after first-line platinum-based chemotherapy, as measured by:
    - Progression-free survival (PFS) by investigator assessment

Secondary:

- To further evaluate the efficacy of maintenance therapy with BGB-290 versus placebo in patients with inoperable locally advanced or metastatic gastric cancer with a CR or confirmed PR after first-line platinum-based chemotherapy, as measured by:
    - Overall survival (OS)
    - Time to second subsequent treatment (TSST) by investigator assessment
    - Objective response rate (ORR; CR or PR) by investigator assessment
    - Duration of response by investigator assessment
    - Time to response by investigator assessment
- To evaluate safety and tolerability of BGB-290 versus placebo, as measured by:
    - Incidence, timing, and severity of treatment-emergent adverse events (TEAEs), graded according to National Cancer Institute-Common Terminology Criteria for Adverse

Events (NCI-CTCAE) Version 4.03

Exploratory:

- To confirm the pharmacokinetics (PK) of BGB-290, as measured by:
  - Lowest observed plasma concentrations (C_{trough}) at steady-state and other PK parameters for patients who received BGB-290
- To assess patient-reported outcomes on health-related quality of life, as measured by:
  - European Quality of Life 5-Dimensions 5-Levels Health Questionnaire (EQ-5D-5L)
  - European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire (EORTC QLQ-C30)
  - EORTC QLQ gastric cancer module (EORTC QLQ-STO22)
- To explore potential biomarkers associated with the pharmacodynamics, response, and resistance to BGB-290:
  - Including, but not limited to, expression and mutations of genes in the DNA damage response pathway, genomic loss of heterozygosity (LOH), and relationship to efficacy and resistance to BGB-290

Study Design:

This is a double-blind, placebo-controlled, randomized, multicenter, global Phase 2 study comparing the efficacy and safety of single-agent poly (ADP-ribose) polymerase (PARP) inhibitor BGB-290 to placebo as maintenance therapy in patients with advanced gastric cancer who have completed first-line platinum-based chemotherapy.

To be eligible for participation in the study, patients must have histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction with inoperable locally advanced or metastatic disease. Patients must have achieved a PR that is maintained for ≥ 4 weeks or a CR as determined by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 with platinum-based first-line chemotherapy. The primary endpoint of the study is PFS by investigator assessment. Sufficient tumor tissue (archival biopsy) must be provided for central laboratory determination of homologous recombination deficiency (HRD) status for randomization and exploratory biomarker analyses.

Patients will be randomized ≤ 8 weeks after the last platinum dose of first-line chemotherapy. Central interactive response technology will be used to randomize patients in a 1:1 ratio and assign eligible patients to 1 of 2 arms: Arm A – BGB-290 or Arm B – Placebo. Patient randomization will be stratified by HRD status (LOH_{high} versus LOH_{low} versus unknown), region (China/Hong Kong/Taiwan versus Australia/Europe/North America versus Japan/South Korea versus rest of world [ROW]), and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1).

Cycles will be 28 days in length.

Safety assessments will occur on Day 1 of each cycle, on Day 15 of Cycles 1 and 2, and as needed. Dose modifications will be made if appropriate. Adverse events (AEs) will be followed and documented during the treatment period and for approximately 30 days after the last dose of study drug or until initiation of new anticancer therapy, whichever occurs first. AEs will be graded according to NCI-CTCAE Version 4.03. An external independent data monitoring committee will periodically review safety data.

To confirm PK properties of BGB-290, blood samples will be taken at various time points.

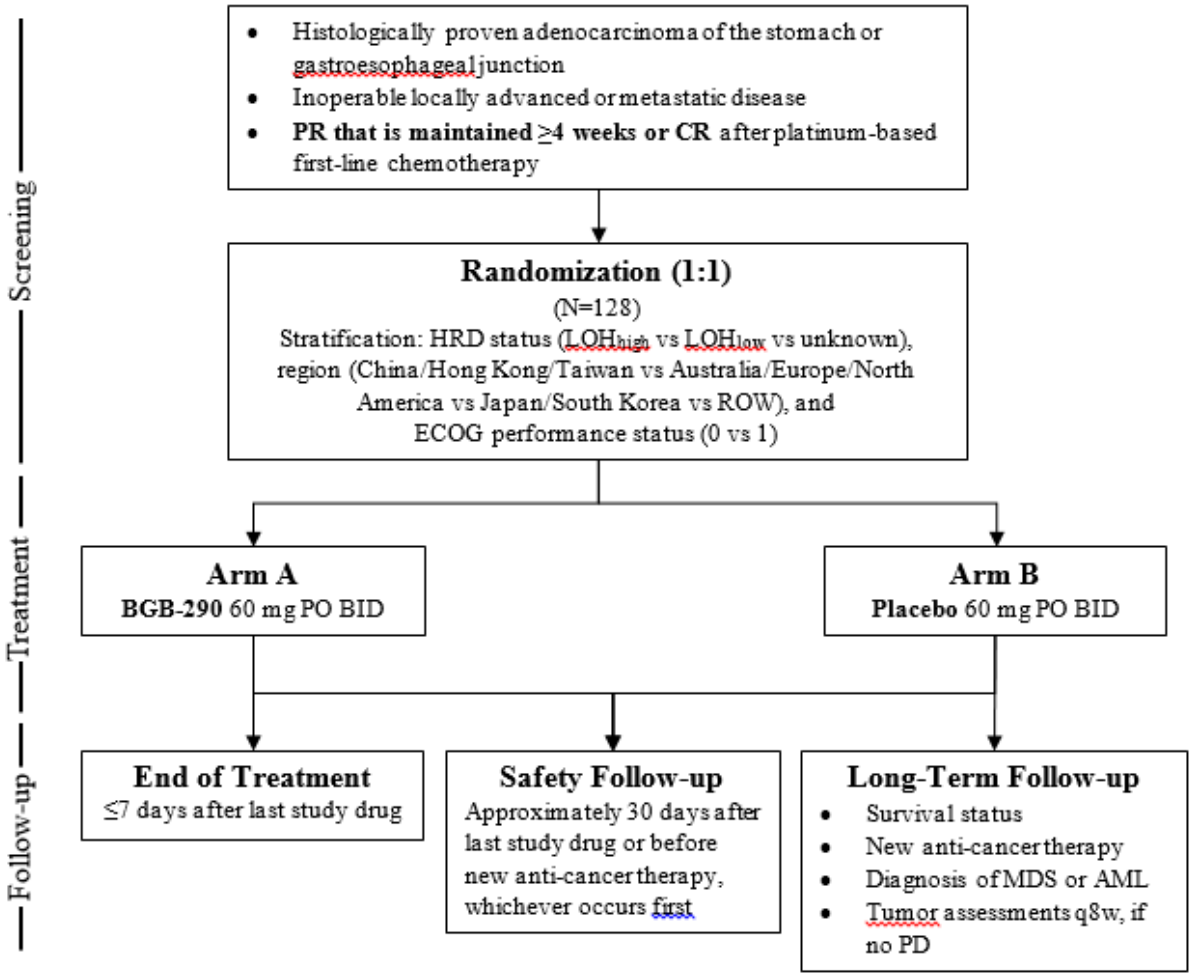
Additionally, tumor tissue and blood samples will be obtained to explore biomarkers of pharmacodynamics, response, and resistance to BGB-290 in gastric cancer.

Disease status will be assessed by the investigator using RECIST Version 1.1. Patients will undergo tumor assessments at screening and then every 8 weeks (±7 days), or as clinically indicated.

Administration of BGB-290 or placebo will continue until PD, unacceptable toxicity, death, or another discontinuation criterion is met. Once the treatment phase has been completed, an end of treatment visit should occur within 7 days of stopping BGB-290 or placebo with subsequent phases of safety and long-term follow-up.

Long-term follow-up will include tumor assessments every 8 weeks (±7 days) for those patients without PD, survival status, new anticancer therapy, and diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukemia. Long-term follow-up will continue until the patient dies or another criterion for discontinuation from study is met.

Study Schema



Abbreviations: AML, acute myeloid leukemia; BID, twice daily; CR, complete response; ECOG, Eastern Cooperative Oncology Group; LOH, loss of heterozygosity; HRD, homologous recombination deficiency; MDS, myelodysplastic syndrome; PD, progressive disease; PO, oral; PR, partial response; q8w, every 8 weeks; ROW, rest of world; vs, versus.
Note: Key assessments during treatment phase: tumor assessments and patient-reported outcomes every 8 weeks, adverse events, hematology, and chemistry every 4 weeks. BGB-290 and placebo are to be administered continuously.

Key Eligibility Criteria:

The population under study is adult patients (>18 years of age) with histologically proven adenocarcinoma of the stomach or gastroesophageal junction, inoperable locally advanced or with metastatic disease. Patients with gastric cancer overexpressing HER2 or who received irradiation as part of prior first-line treatment are not allowed. All patients are required to have a PR that is maintained for ≥ 4 weeks or CR to platinum-based first-line chemotherapy; archival tumor tissue for central laboratory determination of HRD status for stratification and exploratory biomarker analyses is also required.

Test product, dose and mode of	BGB-290: 60 mg will be administered orally (PO) twice daily (BID)

administration:	
Reference therapy, dose, and mode of administration:	Placebo: 60 mg will be administered PO BID

Dose Modifications:

Dosing of BGB-290 or placebo can be withheld for up to approximately 28 days consecutively. A maximum of 2 dose reductions is allowed before the patient must be permanently withdrawn from study drug. If drug is planned to be held > 28 days, the medical monitor should be contacted before 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, supplements, and intravenous medications and fluids, taken by or administered to the patient within 28 days before randomization and 30 days after the last day of BGB-290 or placebo will be recorded.

Patients are not allowed to receive other anticancer therapy, including surgery, radiation therapy, immunotherapy, investigational agents, cytotoxic, biologic or hormone therapy, anticancer Chinese medicine, or herbal remedies ≤ 14 days (or ≤ 5 half-lives, if applicable, whichever is shorter) prior to randomization and during the study. Hormone replacement therapy is allowed. Bisphosphonate and denosumab use is permitted if the patient had already been receiving it at a stable dose > 28 days prior to randomization.

The primary metabolic pathway for BGB-290 involves the CYP3A isoform. Administration of strong/moderate inhibitors of CYP3A or strong CYP3A inducers is not allowed. In addition, careful monitoring should be used when co-prescribing CYP2C9 substrates with a narrow therapeutic index, such as phenytoin and warfarin.

Criteria for Evaluation:

Efficacy:

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 Day 1. Any measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Patients who do not have PD at the time of BGB-290 or placebo permanent discontinuation but meet other discontinuation criteria will continue to have tumor assessments per protocol. PFS will be assessed by the investigator. Response and duration of response will be assessed by the 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 provided 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, electrocardiograms (ECGs), and clinical laboratory tests.

Statistical Methods:

Analysis Set:

- Intent-to-Treat (ITT) Analysis Set includes all randomized patients who are assigned to study drug (BGB-290 or placebo). The ITT Analysis Set will be used for all efficacy analyses unless otherwise specified in the statistical analysis plan.
- Safety Analysis Set includes all patients in the ITT Analysis Set who receive any dose of study drug (BGB-290 or placebo). The Safety Analysis Set will be used for all safety analyses.
- Per-Protocol (PP) Analysis Set includes all patients in the ITT Analysis Set without major protocol deviations that impact assessment of efficacy. Criteria for exclusion from the PP Analysis Set will be determined and documented before the final analysis of PFS. The PP Analysis Set will be used to perform sensitivity analysis for the PFS and OS endpoints.
- PK Analysis Set includes all patients who receive BGB-290 and for whom valid BGB-290 PK parameters can be estimated.

Efficacy Analyses:

All efficacy analyses will be conducted using the ITT Analysis Set unless otherwise specified. Primary efficacy analysis of PFS will use the investigator assessment of PD according to RECIST Version 1.1. Secondary efficacy analyses of ORR, time to response, and duration of response will use the investigator assessments of response and PD according to RECIST Version 1.1. All stratified efficacy analyses will incorporate the stratification factors used at randomization (HRD status [LOH_{high} versus LOH_{low} versus unknown], ECOG performance status [0 versus 1], and region [China/Hong Kong/Taiwan versus Australia/Europe/North America versus Japan/South Korea versus ROW]), unless otherwise specified.

Primary Efficacy Analysis:

A stratified 1-sided log-rank test at a 0.1 significance level incorporating the randomized stratification factors will be used to compare treatment groups using the ITT Analysis Set for the PFS primary endpoint. The hazard ratio [HR] and its 2-sided 95% confidence interval (CI) will be estimated using the stratified Cox-proportional hazards model.

Secondary Efficacy Analyses:

A stratified log-rank test incorporating the randomized stratification factors will be used to compare treatment groups using the ITT Analysis Set for the OS secondary endpoint. The HR and its 2-sided 95% CI will be estimated using the stratified Cox-proportional hazards model. The median OS for each treatment group will be estimated using the Kaplan-Meier method and the 95% CI will be calculated using the Brookmeyer-Crowley method.

A sensitivity analysis of OS will be conducted using the PP Analysis Set.

Other secondary time-to-event endpoints, such as TSST and DOR will be analyzed in a similar manner.

The ORR and its exact 2-sided 95% CI will be reported for each treatment group of the ITT Analysis Set. A Cochran-Mantel-Haenszel score test will be used to compare treatment groups.

Only patients with a response of CR or PR during the study will be included in time to response and duration of response analyses.

Pharmacokinetic Analyses:

BGB-290 C_{trough} at steady-state will be summarized. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Population PK analysis may be carried out to include plasma concentrations from this study in an existing

model. 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 post-dose (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.

Exploratory Efficacy Analyses:

Patient-reported outcomes will be assessed using the EORTC QLQ-C30 and QLQ-STO22 questionnaires and the EQ-5D-5L health questionnaire. The scores from these questionnaires will be summarized by study visit using descriptive statistics.

Correlative biomarker analyses in tumor tissues and blood will be performed. A separate statistical analysis plan will outline details of the biomarker analyses.

Safety Analysis:

All TEAEs including, serious AEs (SAEs), deaths, ≥ Grade 3 TEAEs, study drug-related TEAEs, and TEAEs that led to study drug withholding or permanent discontinuation, will be summarized. Study drug exposure, vital sign measurements, ECG results, and clinical laboratory results will also be summarized.

Sample Size:

This study is designed to provide 80% power for PFS. The following assumptions are used in determining the sample size for this study:

- Overall type I error rate: 0.1 (1-sided)
- Randomization: 1:1
- Median PFS for placebo group: 6.0 months
- PFS HR (BGB-290/placebo): 0.63

A sample size of approximately 128 patients (64 per treatment group) is required to achieve 85 PFS events within the planned study duration of approximately 26 months after the first patient is randomized to study, assuming an estimated accrual period of 20 months.

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Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATM_{low}	low or undetectable levels of ATM
AUC	area under the plasma concentration-time curve (drug exposure)
AUC_{0-12}	area under the plasma concentration-time curve from 0 to 12 hours postdose
AUC_{0-last}	area under the plasma concentration-time curve from 0 to the last measurable concentration
BGB-290	study drug code
BID	twice daily
C	Cycle
CFR	Code of Federal Regulations
CI	confidence interval
CIN	chromosomal instability
CL/F	apparent clearance
C_{max}	maximum concentration
CNS	central nervous system
CNV	copy number variation
CR	complete response
CT	computed tomography
C_{trough}	lowest observed plasma concentration
CYP	cytochrome P450
DLT	dose-limiting toxicity (or toxicities)
EBV	Epstein-Barr virus
E/C	etoposide and carboplatin
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire
EORTC QLQ-STO22	European Organisation for Research and Treatment of Cancer Quality of Life gastric cancer module

Abbreviation	Definition
EOT	end of treatment
EQ-5D-5L	European Quality of Life 5-Dimensions 5-Levels Health Questionnaire
FDA	Food and Drug Administration
FDG	fluorine-18 [F-18]fluorodeoxyglucose
GCP	Good Clinical Practice
h	hour(s)
HCP	health care provider
Hgb	hemoglobin
hERG	human ether-à-go-go related gene
HR	hazard ratio
HRD	homologous recombination deficiency
IB	investigator brochure
IC_{50}	half-maximal inhibition concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	intravenous
LOH	loss of heterozygosity
MDRD STUDY EQ	Modification of Diet in Renal Disease study equation
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	not evaluable
ORR	objective response rate
OS	overall survival
PAR	poly (ADP-ribose)
PARP	poly (ADP-ribose) polymerase
PBMCs	peripheral blood mononuclear cells

Abbreviation	Definition
PD	progressive disease
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PLT	platelet (count)
PO	oral (orally)
PP	Per-Protocol
PR	partial response
PT	preferred term
q8w	every 8 weeks
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	rest of world
SAE	serious adverse event
SCLC	small cell lung cancer
SD	stable disease
SEM	standard error of the mean
SOC	system organ class
SSBs	single-strand DNA breaks
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TSST	time to second subsequent treatment
ULN	upper limit of normal
US	United States
vs	versus

1. INTRODUCTION

1.1. Inoperable Locally Advanced and Metastatic Gastric Cancer

There were an estimated 17.5 million cancer cases and 8.7 million cancer deaths in 2015 worldwide. Gastric cancer alone contributed about 1.3 million cases with 800,000 deaths. It is the fifth most common cancer worldwide and the second leading cause of cancer death together with colorectal and liver cancer (Global Burden of Disease Cancer Collaboration, 2017). More than half of gastric cancer cases and deaths are estimated to occur in China, with approximately 680,000 cases and approximately 500,000 deaths in 2015 (Chen et al, 2016). Predicted gastric cancer deaths for the European Union in 2017 are approximately 55,000 (Malvezzi et al, 2017). For the United States (US), estimates for gastric cancer in 2017 are approximately 28,000 cases with 11,000 deaths (Siegel et al, 2017).

Adenocarcinoma is the major histologic subtype representing approximately 90% of gastric cancer (Smyth et al, 2016). About two-thirds are true gastric cancers (non-cardia) and the remainder are gastroesophageal junction cancers (cardia) (Colquhoun et al, 2015). The most common anatomical subsites differ in world regions due to differences in risk factors. Distal and antral gastric cancers are more common in East Asia and tumors of the proximal stomach or gastroesophageal junction are more common in non-Asian countries (Forman and Burley, 2006; World Cancer Research Fund International/American Institute for Cancer Research, 2017). Patients with newly diagnosed inoperable locally advanced or metastatic disease generally receive chemotherapy regimens containing a platinum and a fluoropyrimidine (Smyth et al, 2016; NCCN 2017). Triplet regimens may provide additional clinical benefit, as suggested in a meta-analysis for the addition of an anthracycline (Okines et al, 2009). Because of their added toxicities, however, they have not been uniformly adopted and are recommended only for medically fit patients with good performance status and access to frequent toxicity evaluations. In Western countries, approximately two-thirds of patients present with advanced disease. Response rates for first-line chemotherapy regimens are around 30% to 50% with median progression-free survival (PFS) ranging from 5 to 7 months. Median overall survival (OS) is less than 12 months, and less than 10% of patients are still alive after 5 years (Chau et al, 2004; Cunningham et al, 2008; Kang et al, 2009; Koizumi et al, 2008; Van Cutsem et al, 2006; Wagner et al, 2006). Approximately 12% to 20% of gastric adenocarcinomas are HER2-positive (Van Cutsem et al, 2015). For these patients, a unique treatment paradigm has been established that combines first-line platinum- and fluoropyrimidine-based chemotherapy with the anti-HER2 antibody trastuzumab (Bang et al, 2010).

The duration of first-line chemotherapy typically does not exceed 6 months, either because of progressive disease (PD) or due to the cumulative toxicities of chemotherapy (Cunningham et al, 2008; Van Cutsem et al, 2006; Hess et al, 2016). Therefore, for patients who have achieved maximum tumor reduction with first-line chemotherapy, the concept of further treatment with a regimen of good tolerability is appealing. However, there are currently no approved drugs for maintenance treatment after first-line therapy. There are few data for monotherapy with a fluoropyrimidine, and they do not support that this approach provides clinical benefit compared with best supportive care (Li et al, 2017; Qiu et al, 2014). The concept of further therapy with a

different regimen (switch maintenance) is currently being explored in several studies. The Phase 3 JAVELIN Gastric 100 study is comparing the anti-PD-L1 antibody avelumab to continued platinum-based chemotherapy after a short induction phase of only 12 weeks with a platinum doublet (ClinicalTrials.gov identifier: NCT02625610). Similarly, the ARMANI Phase 3 trial is comparing paclitaxel plus ramucirumab to continued platinum doublet after 12 weeks of induction chemotherapy (ClinicalTrials.gov identifier: NCT02934464). The Phase 2 trial MANTRA allows up to 6 months of platinum-based chemotherapy before randomization to either regorafenib or placebo (Aprile et al, 2016).

In the second-line setting, several single-agent chemotherapy options are available, including irinotecan, docetaxel, or paclitaxel, that have been shown to improve OS compared with best supportive care (Ford et al, 2014; Hironaka et al, 2013; Kang et al, 2012; Roy et al, 2013; Thuss-Patience et al, 2011). The anti-VEGFR-2 antibody ramucirumab is another option for second-line therapy since it has shown, as monotherapy, a survival benefit comparable with chemotherapy, and, when combined with paclitaxel, a survival benefit over paclitaxel alone (Fuchs et al, 2014; Wilke et al, 2014). More recently, immunotherapy with anti-PD1 antibodies pembrolizumab and nivolumab has resulted in durable remissions for a subset of patients (Le et al, 2016; Muro et al, 2016). ONO-12 (ATTRACTION 2), a randomized Phase 3 study comparing nivolumab with placebo in patients with advanced gastric cancer who had received at least 2 prior chemotherapy regimens, showed that PD1 inhibition can lead to a survival improvement in heavily pretreated gastric cancer patients. Median OS was 5.32 months (95% confidence interval [CI], 4.63%-6.41%) with nivolumab versus 4.14 months (95% CI, 3.42%-4.86%) with placebo (hazard ratio [HR] 0.63; 95% CI, 0.50%-0.78%; P <0.0001), suggesting that a subset of patients may derive longer-term benefit from PD1 inhibition (Kang et al, 2017). Phase 3 studies for second- and third-line patients are now ongoing to determine the efficacy of anti-PD1 and PD-L1 antibodies compared to single-agent chemotherapy (Kelly, 2017).

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

In the clinic, PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, have demonstrated sustained antitumor responses as a single agent in patients with BRCA1- or BRCA2-mutated tumors, while achieving a favorable safety profile. Olaparib has been approved in the US as single agent for advanced ovarian cancer patients with a deleterious germline BRCA mutation; whereas, rucaparib has been approved for patients with a deleterious germline or somatic BRCA mutation (Lynparza [olaparib] prescribing information 2017; Rubraca [rucaparib] prescribing information 2017).

Aside from BRCA1 or BRCA2 mutations, other alterations can also result in HRD, which is characterized by 'BRCA-like" genomic scarring. HRD does not only make cancer cells sensitive to PARP inhibitors but also to platinums, and shared mechanisms of resistance suggest that both classes of drugs have similar antitumor effects in cancers with HRD (Edwards et al, 2008; Sakai et al, 2008; Sakai et al, 2009). This concept is supported by clinical data for the PARP inhibitor olaparib in patients with BRCA-mutated ovarian cancer demonstrating that platinum sensitivity correlated with response and platinum refractoriness with an almost complete lack of response to olaparib (Fong et al, 2010; Gelmon et al, 2011). In addition, rucaparib has been shown to be effective in platinum-sensitive ovarian cancer with BRCA-mutated patients deriving most benefit, followed by nonBRCA HRD and non-HRD patients (Swisher et al, 2017).

The strongest evidence that platinum sensitivity can predict clinical benefit from PARP inhibition is provided by 2 studies for ovarian cancer. The NOVA study for the PARP inhibitor niraparib in patients with platinum-sensitive ovarian cancer demonstrated that patients had significantly improved median PFS with niraparib compared with placebo regardless of BRCA mutation or HRD status (Mirza et al, 2016). Median PFS for niraparib in patients with germline BRCA-mutations was 21.0 versus 5.5 months for placebo (HR 0.27; $P < 0.001$). An exploratory analysis for patients who were biomarker negative (germline BRCA-wild-type and HRD negative) showed a median PFS of 6.9 versus 3.8 months (HR 0.58, $P = 0.02$). This led to the approval of niraparib for the maintenance treatment of patients who are in a complete response (CR) or partial response (PR) to platinum-based chemotherapy (Zejula [niraparib] prescribing information 2017). Similar results were recently reported for rucaparib in the ARIEL3 study. Median PFS for rucaparib in patients with BRCA-mutant (germline or somatic) ovarian cancers was 16.6 versus 5.4 months for placebo (HR 0.23; $P < 0.0001$). In an exploratory analysis for patients who were biomarker negative (BRCA-wild-type and HRD negative), median PFS was 6.7 versus 5.4 months (HR 0.58, $P = 0.0049$) (Coleman et al, 2017).

1.3. Biology of Gastric Cancer and PARP Inhibitors

Gastric cancers have been classified, using the Lauren system, as intestinal, diffuse, or indeterminate — the vast majority of these being adenocarcinomas. The World Health Organization has also applied an alternative system dividing gastric cancer into tubular, papillary, mucinous (colloid), or poorly cohesive carcinomas (Hu et al, 2012); however, these classification systems have provided little clinical utility. Gastric cancer is largely associated with infectious agents such as the *Helicobacter pylori* bacterium and Epstein-Barr virus (EBV), yet the frequencies of histological subtypes and distribution of associated *H. pylori* or EBV infections vary greatly by

geographical regions. Recently, The Cancer Genome Atlas group profiled a global population of 295 primary gastric cancers (Cancer Genome Atlas Research Network, 2014) and identified 4 different subtypes according to various molecular characteristics. These were EBV-positive tumors, microsatellite unstable tumors, genomically stable tumors, and tumors with chromosomal instability (CIN). These subtypes were found in 9%, 22%, 20%, and 50% of gastric cancers, respectively. The CIN subgroup is distinguished by a high frequency of p53 defects and copy number variation (CNV), characteristic of DNA repair deficiency. While present across all histologies, the CIN subtype was most enriched in the intestinal subtype at the gastroesophageal junction.

PARP inhibitors are particularly effective in tumors that have defects in DNA repair, specifically those that have HRD. Many genes are involved in homologous recombination repair including BRCA1/2, RAD51, PALB2, ATR, and ATM (Lord and Ashworth, 2016). Defects in these genes lead to HRD and large scale CNV. Assessment of these "genomic scarring" patterns, including genomic loss of heterozygosity (LOH), by using next generation sequencing techniques have recently demonstrated the ability to identify ovarian cancer patients who clinically benefit from PARP inhibitors. In the ARIEL2 single-arm Phase 2 study, serous ovarian cancer patients with platinum-sensitive relapsed disease were treated with rucaparib and in a prespecified analysis it was demonstrated that patients with HRD (including non-BRCA tumors) had a significantly improved clinical outcome compared with biomarker-negative patients (Swisher et al, 2017). Moreover, in the NOVA and ARIEL3 randomized, switch-maintenance Phase 3 trials, platinum-sensitive high-grade serous ovarian cancer patients treated with niraparib or rucaparib, respectively, had a significant clinical benefit compared with placebo. A further improvement in clinical benefit was also seen in the HRD patients treated with the PARP inhibitors compared with placebo (Mirza et al, 2016; Coleman et al, 2017).

Since platinum-based therapy leads to DNA damage, it follows that platinum-sensitive tumors likely have a higher level of HRD and, thus, are more likely to respond to PARP inhibitors. This has been shown for BRCA-mutant patients where PARP inhibitor benefit is higher for those who are platinum sensitive compared with platinum-resistant patients (Fong et al, 2010). Indeed, acquisition of secondary mutations that restore the functionality of homologous recombination proteins including BRCA1, BRCA2, RAD51C, and RAD51D have been found in both platinum- and PARP inhibitor-resistant disease (Norquist et al, 2011; Pennington et al, 2014; Patch et al, 2015; Quigley et al, 2017; Kondrashova et al, 2017).

In gastric cancer, a recent study assessing LOH in platinum-treated patients indicated that patients with HRD may have improved clinical outcome (Cafferkey et al, 2016). Whereas this was a small study, there was a trend to improved OS in those patients with a high level of LOH. The cutoff chosen in this study identified 14% of patients that had LOH_{high} tumors. In addition, a BRCA mutational signature has been identified in gastric cancer with a frequency of approximately 7% to 12% (Alexandrov et al, 2015). Loss of ATM expression, as defined by immunohistochemistry (IHC), has also been explored as an approach for identifying patients who may be sensitive to PARP inhibitors. Preclinically, there is an association with ATM deficiency and PARP inhibitor response

(Kubota et al, 2014). Interestingly, this is related to loss of ATM expression but not mutational status. ATM expression is lost in approximately 13% to 21% of gastric cancers (Kim et al, 2013). Accordingly, Bang et al, 2015 assessed the clinical benefit of olaparib in a gastric cancer population enriched for ATM loss. Approximately half of the patients had loss of ATM expression as defined by a validated IHC assay. In a randomized Phase 2 study in 123 second-line metastatic gastric cancer patients, the combination of olaparib and paclitaxel significantly improved OS versus placebo and paclitaxel; whereas, the best improvement in OS was seen in patients with tumors with low or undetectable levels of ATM (ATM_{low}) (HR 0.35; 80% CI, 0.22%-0.56%; $P = 0.002$; median OS, not reached versus 8.2 months, respectively). The subsequent randomized Phase 3 GOLD study did not recapitulate these findings as it did not meet its primary endpoint. However, the proportion of patients with ATM_{low} tumors was significantly lower than the Phase 2 study potentially diluting the treatment effect (Smyth et al, 2016). Together, these data suggest that a molecular subtype of gastric cancer exists that displays HRD and, thus, may be particularly sensitive to PARP inhibitor therapy.

1.4. PARP Inhibitor BGB-290

1.4.1. Nonclinical Data for BGB-290

BGB-290 is a potent and selective inhibitor of PARP1 and PARP2 that sets itself apart from other PARP inhibitors by combining potent PARP-trapping activity with significant brain penetrance.

1.4.1.1. Nonclinical Safety Data

The nonclinical toxicity and toxicokinetic profile of BGB-290 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 (hERG) channel activity assays and in vivo studies of cardiovascular function in dogs, as well as central nervous system (CNS) and respiratory system function tests in rats.

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

BGB-290 was not mutagenic in the in vitro Ames (bacterial reverse mutation) assay, but clastogenic in the in vitro chromosomal aberration assay in 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. BGB-290 interacts with and inhibits the enzymatic repair machinery that carries out detection and repair of SSBs.

In the general toxicity studies in rats and dogs, no gross lesions or histopathological changes were noted in male and female reproductive organs. No embryo-fetal toxicity studies were planned or conducted because of the already established genotoxicity and bone marrow inhibition by BGB-290.

There was no apparent inhibition of BGB-290 on hERG channel as the value of half-maximal inhibition concentration (IC_{50}) was 12.4 µM; for comparison, the IC_{50} of the positive control amitriptyline was 1.9 µM. No effects on blood pressure, heart rate, or electrocardiogram (ECG) findings were noted in telemetry-instrumented conscious dogs. No effects on CNS or respiratory functions were noted in Sprague-Dawley rats. No abnormal changes in the cardiovascular, CNS, or 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.

In summary, all available toxicological studies and data are adequate to support clinical development of BGB-290 for treatment of patients with advanced cancer. Please refer to the investigator's brochure (IB) for additional information (BGB-290 Investigator's Brochure).

1.4.1.2. Nonclinical Activity Data

Biochemical and Cellular Inhibition of PARP Activity by BGB-290

BGB-290 potently inhibits enzyme activity of PARP1 and PARP2, with IC_{50}s of 1.3 and 0.92 nM, respectively (Table 1). 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 BGB-290 was measured by a fluorescence polarization binding assay, similar to the method described in the literature (Murai et al, 2012). BGB-290 showed potent PARP-trapping activity (with a half-maximal effective concentration [EC_{50}] of 13 nM), similar to olaparib (EC_{50} = 16 nM), and 30-fold more potent than veliparib.

Table 1: PARP Enzyme Inhibition and PARP Trapping Activity of PARP Inhibitors

Enzyme	BGB-290 (nM)	Olaparib (nM)	Veliparib (nM)
PARP1 (Full length), IC_{50}	1.3 ± 0.058 (n=3)	1.9 ± 0.12 (n=3)	5.4 ± 0.70 (n=3)
PARP2 (aa2-583), IC_{50}	0.92	0.92	3.2
PARP trapping, EC_{50}	13	16	400

Source: BGB-290 Investigator's Brochure

Abbreviations: EC_{50}, half-maximal effective concentration; IC_{50}, half-maximal inhibitory concentration; PARP, poly (ADP-ribose) polymerase.

Cellular assays confirmed that BGB-290 can potently inhibit intracellular PARP activity in hydrogen peroxide-treated HeLa cells, with an IC_{50} of 0.24 nM. BGB-290 was more potent than veliparib and olaparib, which had IC_{50}s of 2.66 nM and 0.47 nM, respectively.

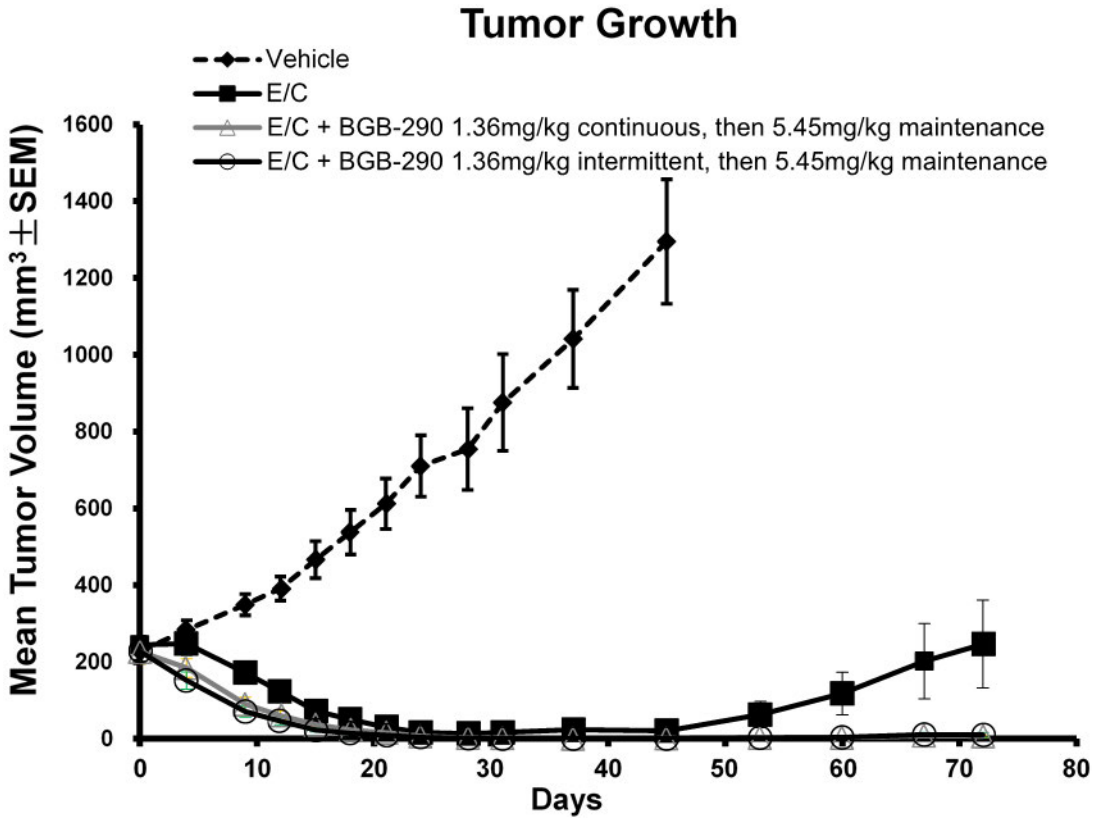
Single Agent Antitumor Activity of BGB-290

BGB-290 as a single agent has demonstrated excellent in vitro activity against tumor cell lines with defects of the homologous recombination pathway. In vivo, BGB-290 has shown strong antitumor activity against a BRCA1 mutant mouse xenograft model (MDA-MB-436 breast cancer) and was 16-fold more potent than olaparib. In a pharmacokinetic (PK)/pharmacodynamic study, oral (PO) administration of BGB-290 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 BGB-290.

Antitumor Activity of BGB-290 Monotherapy in the Maintenance Setting

BCLU-053 is a primary human small cell lung cancer (SCLC) xenograft model derived from a patient who experienced a PR with first-line carboplatin and etoposide treatment. In the mouse model, the tumor was also sensitive to this combination with 6 PRs and 4 CRs in 10 mice. However, 7 of 10 mice showed progression after discontinuation of chemotherapy. In contrast, addition of BGB-290 (continuously or intermittently) during chemotherapy and as subsequent single-agent maintenance therapy resulted in CRs in all mice and no relapses during BGB-290 monotherapy (Figure 1). Thirty days after completion of maintenance treatment (Day 72), most animals were still tumor-free with mean tumor volumes of 6 and 10 mm^3 in the continuous and intermittent dosing groups, respectively.

Figure 1: BGB-290 Activity with Etoposide and Carboplatin and as Maintenance Monotherapy in BCLU-053 Small Cell Lung Cancer Xenograft Model

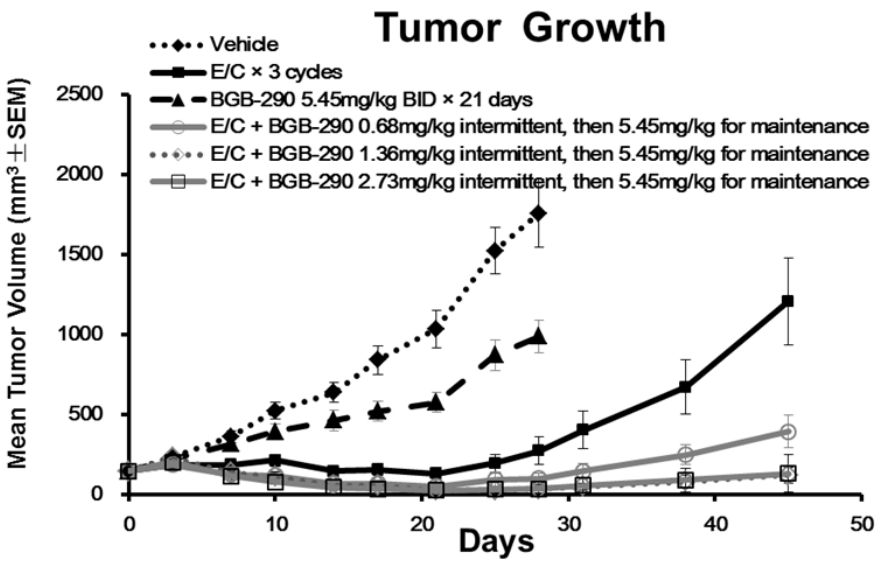


Source: BGB-290 Investigator's Brochure
Abbreviations: BID, twice daily; E/C, etoposide and carboplatin; SEM, standard error of the mean.
Data are presented as mean tumor volume ± SEM of 10 animals in each group. E/C treatment: etoposide at 12 mg/kg (Days 1-3) + carboplatin at 60 mg/kg (Day 1) of each 7-day cycle, for 3 cycles; continuous BGB-290: 1.36 mg/kg BID; intermittent BGB-290: 1.36 mg/kg BID on Days 1-4 of each 7-day cycle, for 3 cycles; maintenance BGB-290: 5.45 mg/kg BID from Day 22 to Day 42.

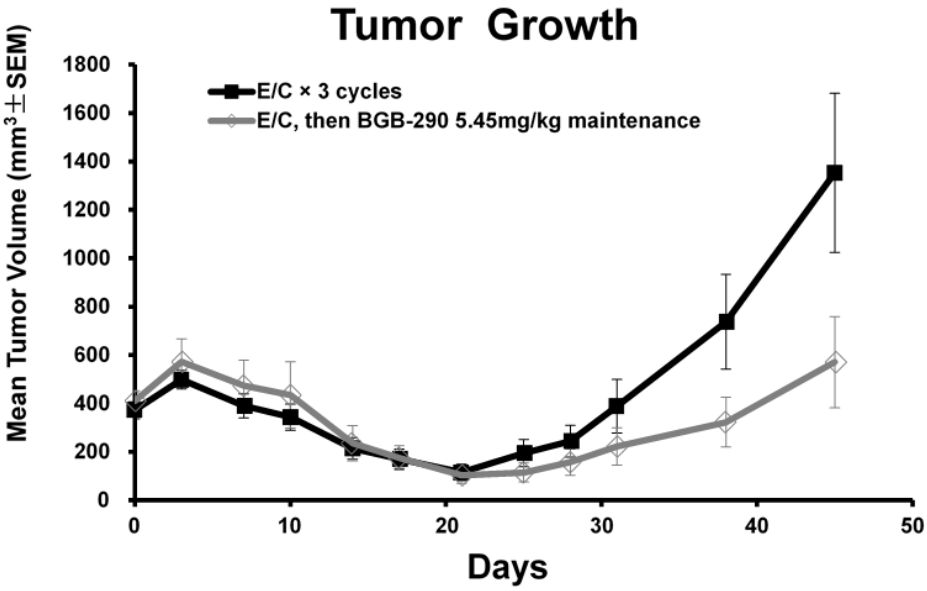
BCLU-080 is another primary human SCLC xenograft model derived from a patient who experienced a PR with first-line carboplatin and etoposide treatment. In the mouse model, the tumor was also sensitive to this combination with PR rates of 33% to 60%. However, all mice showed progression after discontinuation of chemotherapy. In the combination plus maintenance setting, addition of intermittent BGB-290 0.68, 1.36, or 2.73 mg/kg twice daily (BID) during chemotherapy and as subsequent single-agent maintenance therapy increased objective response rates (ORR; PR+CR) in all dose levels and significantly delayed relapses during BGB-290 monotherapy (Figure 2A). After completion of maintenance treatment, 6 out of 9 animals were still tumor-free on Day 45 in the intermittent BGB-290 2.73 mg/kg BID group. In the maintenance only setting, treatment with BGB-290 after completion of chemotherapy significantly delayed relapses, demonstrating more sustained tumor growth inhibition compared with no further treatment after chemotherapy (Figure 2B).

Figure 2: BGB-290 Activity with Etoposide and Carboplatin and as Maintenance Monotherapy in BCLU-080 Small Cell Lung Cancer Xenograft Model

2A



2B



Source: BeiGene VIVO-123 (Study No.: BCLU-080-1401)
Abbreviations: BID, twice daily; E/C, etoposide and carboplatin; SEM, standard error of the mean.
Data are presented as mean tumor volume ± SEM of 9-10 animals in each group. E/C treatment: etoposide at 12 mg/kg (Days 1-3) + carboplatin at 60 mg/kg (Day 1) of each 7-day cycle, for 3 cycles; intermittent BGB-290: 0.68, 1.36 or 2.73 mg/kg BID on Days 1-4 of each 7-day cycle, for 3 cycles; maintenance BGB-290: 5.45 mg/kg BID from Day 22 to Day 45.

1.4.2. Clinical Data for BGB-290

BGB-290 is currently being studied in two Phase 1a studies (BGB-290-AU-002 in Australia, n = 53 [as of 30 September 2016] and BGB-290-102 in China, n = 8 [as of 13 March 2017]), as well as one Phase 1 study, BGB-A317/BGB-290_Study_001, for the combination of BGB-290 with BGB-A317, an anti-PD-1 antibody (n = 41 [as of 02 February 2017]). The study data from BGB-290-AU-002 are the most mature and key interim results are summarized below.

1.4.2.1. Pharmacokinetics Data for BGB-290-AU-002

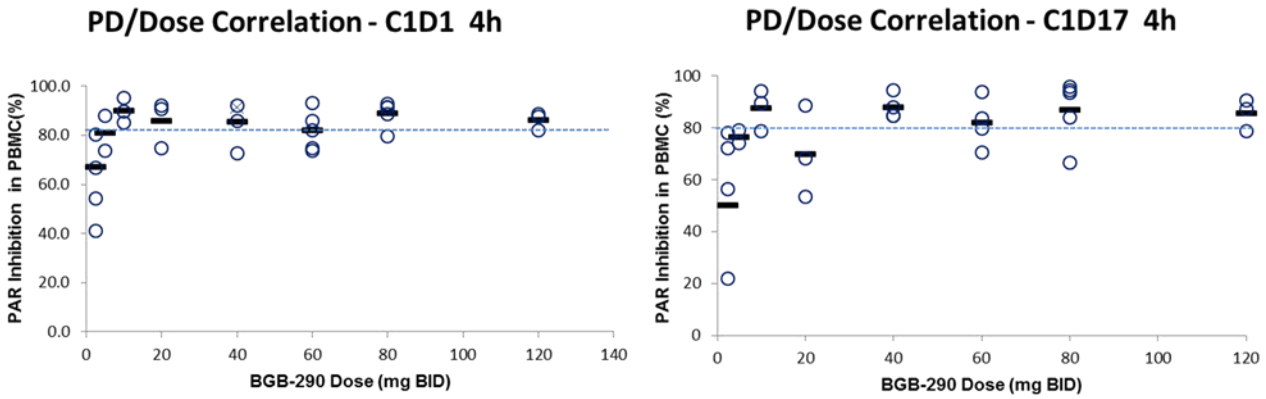
In the first-in-human Phase 1 study, interim PK data of BGB-290 showed that BGB-290 is rapidly absorbed and eliminated after PO administration. The maximum serum concentration and the drug exposure (AUC) increased in a nearly dose proportional manner from 2.5 to 120 mg BID both after the single-dose administration and at steady-state. The terminal half-life was determined to be approximately 13 hours, with a range of 5.5 to 34 hours. At steady-state, from 2.5 to 120 mg BID, drug exposure was increased in a dose-dependent manner.

The impact of administration of a high-fat meal on the PK of BGB-290 after a 60 mg dose is being assessed. Preliminary data from 6 patients show that after administration with a high-fat meal, the rate of absorption was slower, as indicated by a delay in time to maximum concentration (T_{max}) and lower maximum concentration (C_{max}), but overall there was minimum impact on the extent of absorption. The mean Fed:Fasted ratios for C_{max} and area under the plasma concentration-time from time 0 to the last measurable concentration ($AUC_{0\text{-}last}$) were 0.63 (individual ratios ranged from 0.49 to 0.85) and 0.85 (individual ratios ranged from 0.71 to 0.95), respectively. Based on pharmacodynamic data (Section 1.4.2.2) with an apparent flat exposure-response for PAR inhibition and objective responses observed at lower dose levels, the decrease in C_{max} and the modest decrease of 15% in overall exposure with high-fat meal is not considered to be clinically significant. Thus, BGB-290 can be administered without regard to food intake, which is expected to increase patient convenience with the BID dosing schedule.

1.4.2.2. Exploratory Biomarker Data

The PAR formation from peripheral blood mononuclear cells (PBMCs) was detected by enzyme-linked immunosorbent assay to explore the pharmacodynamic activity in the Phase 1 study BGB-290-AU-002. Blood samples for PK and isolation of PBMCs were obtained at baseline on Day 1 (predose) and 4 hours postdose on Days 1 and 17 of Cycle 1. The pharmacodynamic activity at 4 hours postdose on Days 1 and 17 was reported as percentage of predose PAR inhibition. PK/pharmacodynamic correlation analyses were conducted in 30 patients who received doses of 2.5, 5, 10, 20, 40, 60, 80, and 120 mg BID. Robust PAR inhibition in PBMCs was observed at the first dose level of 2.5 mg BID. The pharmacodynamic activity increased in a dose-dependent manner from 2.5 to 10 mg BID. Sustained PAR inhibition in PBMCs was observed at steady-state for patients treated at 10 mg BID or higher dose levels (Figure 3).

Figure 3: Correlation of PAR Inhibition in Peripheral Blood Mononuclear Cells with BGB-290 Dose



Abbreviations: BID, twice daily; h, hours.

1.4.2.3. Clinical Safety and Preliminary Efficacy for BGB-290-AU-002

BGB-290-AU-002 is a first-in-human study evaluating BGB-290 to characterize the safety, the MTD, preliminary antitumor activity, and the PK of BGB-290 given as a monotherapy in a 3+3 dose escalation scheme. BGB-290 was administered in doses ranging from 2.5 to 120 mg PO BID.

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

The preliminary safety data indicate that the most frequent nonhematologic adverse events (AEs) (≥ 10% of patients) assessed as related to BGB-290 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 BGB-290 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 BGB-290: 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 BGB-290: 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 BGB-290 dose. All deaths were due to complications of the underlying malignancy, and none was considered related to BGB-290.

Four patients experienced AEs that were considered dose-limiting toxicities (DLTs): Grade 2 nausea that persisted despite optimal standard medical therapy in 2 patients; Grade 2 anorexia and Grade 2 nausea in 1 patient, and Grade 2 nausea and Grade 2 paresthesia in 1 patient. Based on the encountered DLTs and the overall safety profile of BGB-290, the MTD of BGB-290 was determined to be 80 mg PO BID (160 mg/day).

Myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) are recognized AEs in patients receiving PARP inhibitors (Ricks et al, 2015). To date, no cases of MDS or AML have been observed in any study that includes BGB-290.

Ten patients achieved either a CR (n = 2) or PR (n = 8); all responses were observed in patients with gynecological cancers.

1.5. Rationale for Selection of BGB-290 Dose

Based upon the overall safety, efficacy, and PK profile of BGB-290, the dose of BGB-290 60 mg PO BID was selected using available clinical data from Study BGB-290-AU-002 (Section 1.4.2.3). The study determined the MTD of BGB-290 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 BGB-290 Investigator's Brochure):

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

1.6. Study Rationale

Inoperable locally advanced and metastatic gastric cancer continues to be an incurable disease with 5-year survival rates below 10% despite various available treatment regimens, necessitating the exploration of additional and different therapeutic approaches. First-line platinum-based therapy can result in response rates around 30% to 50%. Treatment with a platinum doublet or triplet, however, typically does not last longer than 6 months due to accumulating chemotherapy toxicities, and there is no evidence that further treatment with a fluoropyrimidine as single agent provides clinical benefit. The time point of maximum tumor response to platinum-based therapy provides a unique opportunity to further improve on clinical benefit rather than wait for PD and initiation of second-line therapy.

PARP inhibitors, in general, have favorable attributes that make them an interesting drug class for maintenance therapy as they are oral agents and tolerated well, in particular when compared with first- or second-line chemotherapy. BGB-290 is a promising PARP inhibitor to study in the gastric

cancer maintenance setting as it is a potent and selective inhibitor of PARP1 and PARP2. It has excellent PARP trapping activity that is likely to be more important for antitumor activity than catalytic PARP inhibition. In the clinic, BGB-290 has shown favorable PK properties, has been tolerated well, and has achieved maximum pharmacodynamic target modulation in PBMCs at a dose level well below the recommended Phase 2 dose (10 versus 60 mg BID).

The rationale for developing the PARP inhibitor BGB-290 in gastric cancer is several fold. The biology of gastric cancer indicates that a large subset of these tumors should be sensitive to PARP inhibition because of abnormalities that have been linked to PARP inhibitor sensitivity in various tumor types. This includes CIN and evidence of HRD, such as loss of ATM expression or BRCA mutational signatures. There is a significant overlap between cancers with platinum sensitivity and biomarkers for PARP inhibitors. Furthermore, activity of PARP inhibitors is not limited to biomarker-positive cancers but also includes biomarker-negative cancers with demonstrated platinum sensitivity. Gastric cancer is a cancer type for which platinum sensitivity has been clearly established, predicting that PARP inhibitors may have significant activity in patients with a CR or PR. Finally, other PARP inhibitors have shown activity in gastric cancer, particularly in cases with loss of ATM.

In summary, BGB-290 is an excellent candidate to determine the effects of PARP inhibition in this unmet medical need of patients with platinum-sensitive disease, as demonstrated by a CR or PR, but have no further treatment options to consolidate or maintain the clinical benefit derived from first-line chemotherapy.

1.7. Risk-Benefit Assessment

BGB-290 has been studied in nonclinical toxicity and Phase 1 clinical studies. BGB-290 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 mutation (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 BGB-290. 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.

Given that patients with advanced gastric cancer currently have no treatment options after completion of first-line therapy, the risk of BGB-290 toxicities appears acceptable considering the strong rationale for exploring PARP inhibition in the maintenance setting.

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 Regulatory Authorities and in accordance with Good Clinical Practice (GCP) standards.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To evaluate the efficacy of maintenance therapy with BGB-290 versus placebo in patients with inoperable locally advanced or metastatic gastric cancer with a CR or confirmed PR after first-line platinum-based chemotherapy, as measured by:
    - PFS by investigator assessment

2.2. Secondary Objectives

- To further evaluate the efficacy of maintenance therapy with BGB-290 versus placebo in patients with inoperable locally advanced or metastatic gastric cancer with a CR or confirmed PR after first-line platinum-based chemotherapy, as measured by:
    - OS
    - Time to second subsequent treatment (TSST) by investigator assessment
    - ORR (CR or PR) by investigator assessment
    - Duration of response by investigator assessment
    - Time to response by investigator assessment
- To evaluate safety and tolerability of BGB-290 versus placebo, as measured by:
    - Incidence, timing, and severity of treatment-emergent adverse events (TEAEs), graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03

2.3. Exploratory Objectives

- To confirm the PK of BGB-290, as measured by:
    - Lowest observed plasma concentrations (C_{trough}) at steady-state and other PK parameters for patients who received BGB-290
- To assess patient-reported outcomes on health-related quality of life, as measured by:
    - European Quality of Life 5-Dimensions 5-Levels Health Questionnaire (EQ-5D-5L)
    - European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire (EORTC QLQ-C30)
    - EORTC QLQ gastric cancer module (EORTC QLQ-STO22)
- To explore potential biomarkers associated with the pharmacodynamics, response, and resistance to BGB-290:
    - Including, but not limited to, expression and mutations of genes in the DNA damage response pathway, LOH, and relationship to efficacy and resistance to BGB-290

3. STUDY DESIGN

3.1. Summary of Study Design

This is a double-blind, placebo-controlled, randomized, multicenter, global Phase 2 study comparing the efficacy and safety of single-agent poly (ADP-ribose) polymerase (PARP) inhibitor BGB-290 to placebo as maintenance therapy in patients with advanced gastric cancer who have completed first-line platinum-based chemotherapy.

To be eligible for participation in the study, patients must have histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction with inoperable locally advanced or metastatic disease. Patients must have achieved a PR that is maintained for ≥ 4 weeks or a CR as determined by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 with platinum-based first-line chemotherapy. The primary endpoint of the study is PFS by investigator assessment. Sufficient tumor tissue (archival biopsy) must be provided for central laboratory determination of HRD status for randomization and exploratory biomarker analyses.

Patients will be randomized ≤ 8 weeks after the last platinum dose of first-line chemotherapy. Cycles will be 28 days in length. Once the treatment phase has been completed, an end of treatment (EOT) visit should occur with subsequent phases of safety and long-term follow-up.

Central randomization (1:1) will be used to assign eligible patients to 1 of the following 2 arms.

Arm A: BGB-290 60 mg PO BID

Arm B: Placebo 60 mg PO BID

Patient randomization will be stratified by HRD status (LOH_{high} versus LOH_{low} versus unknown), region (China/Hong Kong/Taiwan versus Australia/Europe/North America versus Japan/South Korea versus rest of world [ROW]), and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1).

Safety assessments will occur on Day 1 of each cycle, on Day 15 of Cycles 1 and 2, and as needed. Dose modifications will be made as outlined in Section 6.1.4. AEs will be followed and documented during the treatment period and for approximately 30 days after last study drug or until initiation of new anticancer therapy, whichever occurs first (Section 9 and Appendix 1). AEs will be graded according to NCI-CTCAE Version 4.03. An external independent data monitoring committee (IDMC) will periodically review safety data.

To confirm PK properties of BGB-290, blood samples will be taken at various time points as outlined in Section 7.6 and Appendix 1. Additionally, tumor tissue and blood samples will be obtained (as outlined in Section 7.7 and Appendix 1) to explore biomarkers of pharmacodynamics, response, and resistance to BGB-290 in gastric cancer.

Disease status will be assessed by the investigator using RECIST Version 1.1 (Appendix 2). Patients will undergo tumor assessments at screening and then every 8 weeks (±7 days), or as clinically indicated.

There is no fixed duration of treatment.

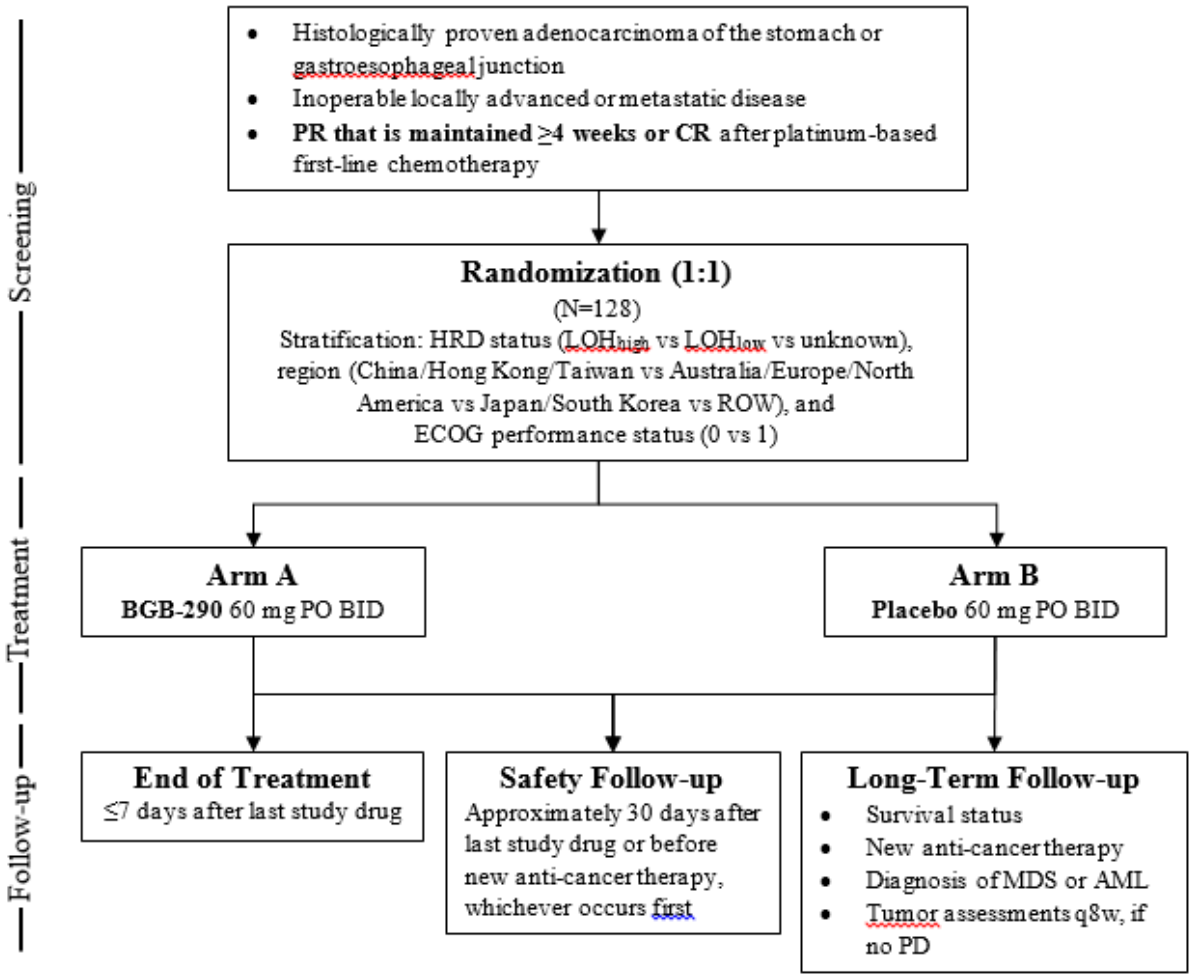
Administration of BGB-290 or placebo will continue until PD, unacceptable toxicity, death, or another discontinuation criterion is met (Sections 5.5 and 5.7). Once the treatment phase has been completed, an EOT visit should occur within 7 days of stopping BGB-290 or placebo with subsequent phases of safety and long-term follow-up.

Long-term follow-up will include tumor assessments every 8 weeks (±7 days) for those patients without PD, survival status, new anticancer therapy, and diagnosis of MDS or AML. Long-term follow-up will continue until the patient dies or another criterion for discontinuation from study is met (Section 5.7).

Once the study is completed and the study results are available, this study will be unblinded. For patients who have received BGB-290, the sponsor will continue providing the drug either on this study or through other options, ie, a roll-over study. Subjects who are on the Placebo arm will discontinue the study treatment.

Study procedures and assessments are detailed in Section 7 and Appendix 1. The study schema is provided in Figure 4.

Figure 4: Study Schema



Abbreviations: AML, acute myeloid leukemia; BID, twice daily; CR, complete response; ECOG, Eastern Cooperative Oncology Group; LOH, loss of heterozygosity; HRD, homologous recombination deficiency; MDS, myelodysplastic syndrome; PD, progressive disease; PO, oral; PR, partial response; q8w, every 8 weeks; ROW, rest of world; vs, versus.
Note: Key assessments during treatment phase: tumor assessments and patient-reported outcomes every 8 weeks, adverse events, hematology, and chemistry every 4 weeks. BGB-290 and placebo are to be administered continuously.

3.2. Independent Data Monitoring Committee

Regular safety monitoring (at least every 6 months) and efficacy monitoring will be performed by an IDMC. The IDMC will review SAE reports for the first 40 patients enrolled in the study and review aggregate safety data approximately 3 months after the 40th patient started on study drug to assess the benefit/risk. The IDMC may recommend study modification including termination of the study due to safety and/or efficacy concerns. The function and membership of the IDMC will be described in the IDMC charter.

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

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

3.3. Blinding

Site staff and blinded sponsor team members will be blinded to treatment allocation (BGB-290 or placebo).

Unblinding of a patient's treatment assignment may be performed at any time and without restrictions based on the investigator's (or other non-study treating physician's) clinical judgement if the knowledge of the treatment arm is essential for the further management of the patient.

The investigator can access the IRT system using assigned credentials to immediately perform unblinding. Following unblinding, the system will notify the sponsor of unblinding of the patient without revealing the patient's treatment assignment. In the event that the investigator is not available to perform unblinding, each randomized patient is provided with a patient information card that includes a global phone number linked to an after-hours physician-staffed emergency medical service. Additionally, the card provides a unique, blinded number that links to the subject's treatment arm.

Any physician treating a patient that is participating in the study (eg, emergency room physician or other health care provider [HCP] unaffiliated with the study) can contact the emergency medical service to unblind the patient using the information located on the patient information card. The emergency service will perform this unblinding and inform the treating physician/HCP of the patient's treatment assignment. If unblinding occurs, the service will provide notification to the sponsor of the patient-specific unblinding without revealing the patient's treatment assignment.

3.4. Duration of the Study

The duration of the study from first enrolled patient until final analysis is estimated to be 2.5 years.

4. STUDY POPULATION

4.1. Inclusion Criteria

Patients must meet all of the following criteria to be eligible for the study:

1. Signed informed consent form (ICF)
2. Age ≥ 18 year
3. Histologically proven adenocarcinoma of the stomach or gastroesophageal junction, inoperable locally advanced or with metastatic disease
    a. Patients with gastric cancer overexpressing HER2 are not allowed.

- Negative result for HER2, as determined by local assessment, must be documented in order for a patient to be eligible.

b. Irradiation as part of prior first-line treatment is not allowed.

4. Availability of archival tumor tissue for central laboratory determination of HRD status for randomization and exploratory biomarker analyses
   - Tumor tissue needs to originate from core or punch biopsy.
   - Tumor tissue from fine-needle aspiration is not acceptable.
5. Received platinum-based first-line chemotherapy with a total of ≥ 8 platinum-containing 14-day cycles, ≥ 5 platinum-containing 21-day cycles, or ≥ 4 platinum-containing 28-day cycles for ≤ 28 weeks
6. Confirmed PR that is maintained for ≥ 4 weeks or CR as determined by the investigator per RECIST Version 1.1 (Appendix 2)
7. Ability to be randomized ≤ 8weeks after last dose of platinum
8. ECOG performance status ≤ 1 (Appendix 3)
9. Ability to swallow whole capsules
10. Ability to comply with study requirements and complete study questionnaires independently
11. Adequate hematologic and end-organ function, as defined by the following laboratory results (obtained ≤ 14 days before randomization):
    a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
    b. Platelet count ≥ 100×10^9/L
    c. Hemoglobin ≥ 9 g/dL (≥ 14 days after growth factor support or transfusion)
    d. Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease study equation (MDRD STUDY EQ; www.mdrd.com or Appendix 11)
    e. Total serum bilirubin ≤ 1.5 × upper limit of normal (ULN)
       - ≤ 4 × ULN, if Gilbert's syndrome or if indirect bilirubin concentrations suggestive of extrahepatic source of elevation
    f. Aspartate and alanine aminotransferase (AST and ALT) ≤ 3 × ULN
12. Females of childbearing potential, nonsterile males, and female partners of nonsterile male study patients must agree to practice highly effective methods of birth control (Appendix 4) for the duration of the study and for at least 6 months after last study drug. Nonsterile males must avoid sperm donation for the duration of the study and for at least 6 months after last study drug.

4.2. Exclusion Criteria

Patients will be excluded from 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, biologic therapy, immunotherapy, investigational agent, anticancer Chinese medicine, or herbal remedies ≤ 14 days (or ≤ 5 half-lives, whichever is shorter) before randomization
    - Bisphosphonate and denosumab use is allowed on study, if administered at a stable dose > 28 days before randomization.
4. Major surgical procedure, open biopsy, or significant traumatic injury ≤ 14 days before randomization, 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 > 2 years ago with no current evidence of disease and no therapy ≤ 2 years before randomization
7. Leptomeningeal disease or brain metastasis
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 before randomization
    b. Symptomatic pulmonary embolism ≤ 28 days before randomization
    c. Any history of acute myocardial infarction ≤ 6 months before randomization
    d. Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 5) ≤ 6 months before randomization

e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before randomization

f. Any history of cerebral vascular accident ≤ 6 months before randomization

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 before randomization
12. Use ≤ 10 days (or ≤ 5 half-lives, whichever is shorter) before randomization or anticipated need for food or drugs known to be strong or moderate cytochrome P450 (CYP) 3A inhibitors or strong CYP3A inducers (Appendix 6)
13. Pregnancy or nursing
    a. Females of childbearing potential require a negative serum pregnancy test ≤ 7 days before randomization.
14. Significant intercurrent illness that may result in the patient's death before death from gastric cancer
15. Known history of intolerance to the excipients of the BGB-290 capsule

5. STUDY PHASES FROM SCREENING TO END OF STUDY

5.1. Screening

As part of the screening visit, study center personnel will explain to the potential patient all aspects of the study, obtain signed informed consent, and document the informed consent process in the patient's source documents before any study-specific procedures are conducted.

The signed ICF initiates screening that must occur within 28 days of randomization (Day -28 to Day -1). Study center personnel will access the Interactive Response Technology (IRT) system to obtain a screening identification number for the potential patient.

Required screening assessments, some with shorter screening windows, are listed in Appendix 1. Assessments obtained within 7 days of Day 1 do not have to be repeated on Day 1. Patient registration and randomization may occur as late as Day 1 before any study treatment. Results of standard of-care tests or examinations performed before obtaining informed consent and within the screening windows may be used and do not have to be repeated as long as they meet protocol specifications.

The investigator and site radiologist will assess the potential patient for eligibility. Repeating screening assessments within the original screening window is allowed if the patient did not

previously meet certain eligibility criteria. Screen failures and consent withdrawals will be documented in the patients' source documents.

5.2. Enrollment

After consent has been obtained, each patient will be assigned a unique patient number by the IRT system that cannot be reassigned to any other patient. After determination of eligibility, the investigator will complete the randomization request form and supporting documentation and provide them to the sponsor and/or designee for review and subsequent approval in the IRT system. No eligibility waivers will be granted.

After medical monitor approval, the investigator or delegate will access the IRT system for randomization of the patient based on the protocol-specified stratification factors. The randomization list will be kept by the IRT vendor in their secure system and will not be accessible to the study center, responsible (or designee) monitors, project statisticians, or to the blinded project team at BeiGene, Ltd. (hereafter referred to as BeiGene). Blinded team members will not have access to unblinded information in IRT; this will be managed by clearly defined roles and permissions within the IRT system.

5.3. Treatment

Day 1 of Cycle 1 is the first day of study drug administration (there is no Day 0 in this protocol). Patients must initiate study treatment within 4 days after randomization.

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

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

Patient-reported outcome questionnaires should be completed before any other study activities occur.

5.4. Unscheduled Visit

Unscheduled visits may occur any time as necessary as per investigator decision or patient's request for reasons such as assessment or follow-up of AEs. Study activities of an unscheduled visit should be performed based on the reason for the unscheduled visit and are outlined in Appendix 1. If PD is suspected, imaging studies should be performed and blood for biomarkers should be obtained as appropriate.

5.5. Permanent Discontinuation of Study Drug

5.5.1. Reasons for Permanent Discontinuation of BGB-290 or Placebo

Patients may permanently discontinue BGB-290 or placebo for any of the following reasons:

- PD
- AEs
- Pregnancy
- Major protocol deviation
- 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 patient withdraws consent from the treatment phase only
- Investigator's discretion
- Start of new anticancer therapy

The reason for permanent discontinuation of BGB-290 or placebo will be recorded on the electronic case report form (eCRF). Patients may discontinue study drug for other reasons but these will result in premature discontinuation from study (Section 5.7) and, consequently, result in lack of an EOT visit.

5.5.2. End of Treatment Visit

The EOT visit should occur within 7 days after BGB-290 or placebo has been permanently discontinued. Required assessments are listed in Appendix 1. A visit should be scheduled as soon as possible, but the EOT visit may occur later after discussion with the medical monitor for specific circumstances, such as prolonged hospitalization. The visit at which tumor assessments showed PD may be used as the EOT visit providing all required assessments were performed. Tumor assessments 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 PD. An ECG does not have to be repeated if it was performed within 14 days of the EOT visit.

5.6. Follow-Up Phase

5.6.1. Safety Follow-up

All patients who permanently discontinue study drug and have not initiated new anticancer therapy will be followed for AEs and serious AEs (SAEs) as outlined in Section 9.3.1. Approximately 30 days after the last day of study drug or before initiation of new anticancer therapy, whichever occurs first, a safety follow-up will occur with the safety assessments outlined in Appendix 1. 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.

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 of contact are unsuccessful, the additional attempts detailed in Section 5.6.3 should be made.

5.6.2. 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 until death, withdrawal of consent, or the end of study, whichever occurs first (Appendix 1).

Patients who were permanently discontinued from study drug for reasons other than PD and meet criteria otherwise (eg, discontinued for AE and no new anticancer therapy) will be followed with tumor assessments every 8 weeks (±7 days) until PD or any other reason listed in Section 5.7, whichever occurs first. For efficacy assessments as per protocol, refer to Section 7.3.2 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.

5.6.3. Lost to Follow-up

If attempts to contact the patient by telephone are 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.

5.7. 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 5.6.3)
- Death
- Study termination by sponsor
- Other, as per the discretion of the sponsor or health authority

6. STUDY TREATMENT

6.1. Study Drug

6.1.1. Packaging and Labeling

BGB-290 is provided in 20-mg capsules or matching placebo. BGB-290 and placebo capsules will be provided in 30-count child-resistant high-density polyethylene bottles with an induction seal and bottle label. The contents of the label will be in accordance with all applicable local regulatory requirements. The label will include at a minimum: drug name, dose strength, contents, sponsor, protocol number, bottle number, directions for use, storage conditions, caution statements, retest or expiration date, and space to enter the patient number and name of investigator.

6.1.2. Handling and Storage

The instructions for drug ordering are in the pharmacy binder. The IRT system will also be used for drug supply management. The study drug 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. The investigator or pharmacist/designated personnel is responsible for maintaining the drug supply inventory and acknowledging receipt of all study drug shipments. All study drugs 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 study drug specific requirements.

The study drugs must be kept at the condition as specified on the labels. BGB-290 and placebo bottles must be stored at 15°C to 30°C (59°F to 86°F) and protected from light.

6.1.3. Dosage and Administration

Both BGB-290 and placebo capsules will be administered PO BID, once in the morning and once in the evening. The time difference between 2 consecutive doses should be approximately 8 to 12 hours.

Patients will be instructed to swallow the capsules whole, in rapid succession, with water. BGB-290 can be administered with or without food.

A dose of BGB-290 or placebo should be skipped if it is not taken within 2 hours of the scheduled time. An extra dose of BGB-290 or placebo 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, BGB-290 or placebo should be administered in the clinic in accordance with the schedule for the PK samples (Appendix 1).

6.1.4. Dose Hold and Modification

AEs should be assessed as best as possible regarding their relatedness to BGB-290 or placebo. Investigators should assess all patients as if they were receiving BGB-290. Regardless of

discontinuation of BGB-290 or placebo, patients should continue on study with follow-up as outlined in Sections 5.5 and 5.6.

Investigators should make every effort to maintain dose intensity in patients. Dosing of BGB-290 or placebo can be withheld for up to 28 days consecutively. If drug is planned to be held > 28 days, the medical monitor should be contacted before permanent patient discontinuation from the study drug.

Criteria for treatment modifications and suggested guidelines for the management of some toxicities related to BGB-290 or placebo are summarized below. These general guidelines may be modified at the discretion of the investigator based on discussions with the medical monitor and the best clinical judgment at that time; any decisions should be documented. Any toxicities related to BGB-290 or placebo 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 BGB-290 or placebo are summarized in Table 2. BGB-290 or placebo will be dose modified as outlined in Table 3.

Table 2: Dose Levels for BGB-290 and Placebo

Dose Level	BGB-290	Placebo
1	60 mg PO BID	60 mg PO BID
-1	40 mg PO BID	40 mg PO BID
-2	20 mg PO BID	20 mg PO BID

Abbreviations: PO, oral; BID, twice daily.
BGB-290 may be dose-reduced for a maximum of 2 dose reductions.

Table 3: Criteria for Modification of BGB-290 or Placebo Dosing for Related Adverse Events

Toxicity	Recommended Dose Modification[a]
Hematologic	
Anemia (hemoglobin, Hgb)	
Grade 2 (Hgb < 10 - 8 g/dL) *Only applies to patients with normal Hgb at baseline*	First occurrence: continue dosing at current dose level Second and subsequent occurrences: hold BGB-290 or placebo until resolved to ≤ Grade 1 or baseline • If resolved ≤ 14 days, then maintain dose levels • If resolved > 14 days, then ↓ BGB-290 or placebo by 1 dose level
Grade 3 (Hgb < 8 g/dL)	Hold BGB-290 or placebo until resolved to ≤ Grade 1 or baseline • If resolved ≤ 14 days, then maintain dose levels • If resolved > 14 days, then ↓ BGB-290 or placebo by 1 dose level
Grade 4 (life-threatening consequences; urgent intervention indicated)	Hold BGB-290 or placebo until resolved to ≤ Grade 1 or baseline and ↓ BGB-290 or placebo by 1 dose level
Neutropenia (absolute neutrophil count, ANC)	
Grade 3 (ANC < 1.0 - 0.5 × 10^9/L)	Hold BGB-290 or placebo until resolved to ≤ Grade 2 or baseline • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ BGB-290 or placebo by 1 dose level
Grade 4 (ANC < 0.5 × 10^9/L)	Hold BGB-290 or placebo until resolved to ≤ Grade 1 or baseline and ↓ BGB-290 or placebo 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 BGB-290 or placebo until resolved and ↓ BGB-290 or placebo by 1 dose level
Thrombocytopenia (platelet count, PLT)	
Grade 3 (PLT < 50 - 25 × 10^9/L)	Hold BGB-290 or placebo until resolved to ≤ Grade 1 or baseline • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ BGB-290 or placebo by 1 dose level
Grade 4 (PLT < 25 × 10^9/L)	Hold BGB-290 or placebo until resolved to ≤ Grade 1 or baseline and ↓ BGB-290 or placebo by 1 dose level
Renal	
Estimated glomerular filtration rate (MDRD STUDY EQ; www mdrd.com or Appendix 11)	
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 BGB-290 or placebo until resolved to ≥ 60 mL/min/1.73 m^2 • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ BGB-290 or placebo by 1 dose level
Regardless of baseline: < 15 mL/min/1.73 m^2	Permanently discontinue BGB-290 or placebo

Table 3: Criteria for Modification of BGB-290 or Placebo Dosing for Related Adverse Events

Toxicity	Recommended Dose Modification[a]
Hepatic	
Bilirubin	
Grade 2 (> 1.5 - 3.0 × ULN) *Only applies to patients with normal bilirubin at baseline*	Hold BGB-290 or placebo until resolved to ≤ Grade 1 or baseline • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ BGB-290 or placebo by 1 dose level
Grade 3 (> 3.0 - 10.0 × ULN)	Hold BGB-290 or placebo until resolved to ≤ Grade 1 or baseline • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ BGB-290 or placebo by 1 dose level
Grade 4 (> 10.0 × ULN)	Permanently discontinue BGB-290 or placebo 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 ↓ BGB-290 or placebo by 1 dose level and continue treatment at the discretion of the investigator in discussion with the medical monitor
Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)	
Grade 3 (> 5 and ≤ 20 × ULN)	Hold BGB-290 or placebo until AST and/or ALT resolved to ≤5 × ULN or baseline • If ≤5 × ULN within 14 days, then ↓ BGB-290 or placebo by 1 dose level • If second episode, permanently discontinue BGB-290 or placebo • If persistent for >14 days, permanently discontinue BGB-290 or placebo
Grade 4 (> 20 × ULN)	Permanently discontinue BGB-290 or placebo
Pancreatic	
Pancreatitis	
Grade 3 or 4	Permanently discontinue BGB-290 or placebo
Cardiac	
Cardiac - Prolonged QTc interval	
QTcF > 500 msec	• Obtain triplicate ECGs (2 to 3 minutes apart) ~1 hour after initial ECG • If mean QTcF > 500 ms, hold BGB-290 or placebo until evaluation of ECGs by cardiologist o Cardiology evaluation as soon as practical but within 7 days of initial abnormal ECG • If mean QTcF > 500 ms confirmed by cardiologist, permanently discontinue BGB-290 or placebo
Cardiac - General	
Grade 3	Hold BGB-290 or placebo until resolved to ≤ Grade 1 or baseline and ↓ BGB-290 or placebo by 1 dose level
Grade 4	Permanently discontinue BGB-290 or placebo

Table 3: Criteria for Modification of BGB-290 or Placebo Dosing for Related Adverse Events

Toxicity	Recommended Dose Modification[a]
Other adverse events	
Grade 3	Hold BGB-290 or placebo until resolved to ≤ Grade 1 or baseline and ↓ BGB-290 or placebo by 1 dose level No dose reduction required for asymptomatic laboratory abnormalities
Grade 4	Permanently discontinue BGB-290 or placebo

Abbreviations: ECG, electrocardiogram; MDRD, Modification of Diet in Renal Disease; QTcF, QT interval corrected for heart rate using Fridericia's formula; ULN, upper limit of normal.

a. Dosing of BGB-290 or placebo can be withheld for up to 28 days consecutively.

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 BGB-290 or placebo accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain BGB-290 or placebo accountability records throughout the course of the study. This person will document the amount of BGB-290 or placebo 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 BGB-290 or placebo 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 Nondrug 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, supplements, and intravenous (IV) medications and fluids, taken by or administered to the patient within 28 days before randomization and 30 days after the last day of BGB-290 or placebo will be recorded.

6.2.2. Prohibited Medications

Patients are not allowed to receive other anticancer therapy, including surgery; radiation therapy; immunotherapy; investigational agents; cytotoxic, biologic, or hormone therapy; anticancer Chinese medicine; or herbal remedies ≤ 14 days (or ≤ 5 half-lives, if applicable, whichever is shorter) prior to randomization and during the study. Hormone replacement therapy is allowed. Bisphosphonate and denosumab use is permitted if the patient had already been receiving it at a stable dose >28 days before randomization.

The primary metabolic pathway for BGB-290 involves the CYP3A isoform. Administration of strong/moderate inhibitors of CYP3A or strong CYP3A inducers is not allowed. 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 allowed. Consumption of grapefruit and Seville oranges or their juices are not allowed throughout the study. No other dietary restrictions will apply.

6.2.3. Medications to Be Used with Caution

Based on preliminary in vitro screening assays, BGB-290 is not a strong inhibitor of other human CYP isoenzymes tested. It is a moderate inhibitor of CYP2C9 (IC_{50} = 6.48 μM). Investigators need to be aware that BGB-290 has the potential to interfere with the appropriate metabolism of medications that rely on CYP2C9 and follow the prescribing information recommendations for use with CYP2C9 inhibitors. Therefore, careful monitoring should be used when co-prescribing CYP2C9 substrates with a narrow therapeutic index, such as phenytoin and warfarin.

Examples of these medications are listed in Appendix 7 and these should be used cautiously with drug concentration monitoring where appropriate.

In addition to CYP3A, BGB-290 can also be metabolized by CYP2C8 in human liver microsomes, but to a lesser extent. See Appendix 7 for medications that should be used with caution for that reason.

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 Demographics and Other Baseline Characteristics

7.2.1. Demographics

Demographic data will include gender, date of birth (or age), and race/ethnicity.

7.2.2. Medical History

Clinically significant medical history findings (eg, previous diagnoses, diseases, or surgeries) that were present before signing the ICF and considered relevant for the patient's study eligibility will be collected and captured, including baseline severity if the finding is ongoing, in the eCRF. Clinically significant is defined as any events, diagnoses, or laboratory values that require treatment or 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 gastric cancer history, the date of initial diagnosis and current disease status, staging, sites of disease, smoking history, prior anticancer therapies and dates administered, responses, and duration of response to these treatments will also be recorded.

7.2.3. Other Baseline Characteristics

Information will also be collected regarding smoking history, prior medications/significant nondrug therapies, childbearing potential (Appendix 4), and any other assessments that are performed for the purpose of eligibility for inclusion in the study (Section 5), such as physical examination, vital signs, hematology, chemistry, pregnancy test, and ECG.

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 Day 1. Any measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Patients who do not have PD at the time of BGB-290 or placebo permanent discontinuation but meet criteria otherwise will continue to have tumor assessments per protocol as outlined in Section 5.6.2. PFS, response, and duration of response will be assessed by the investigator using RECIST Version 1.1 (Appendix 2).

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 provided it meets the requirements (Section 7.3.1.2).

7.3.1.1. Determination of Eligibility

The investigator and site radiologist will review tumor assessments to determine whether the patient achieved PR that is maintained for ≥ 4 weeks or a CR with platinum-based first-line chemotherapy as defined in Section 4.1.

For a patient at study entry to confirm response, the following tumor assessments must be documented:

- Tumor assessment that determined baseline disease state before initiation of first-line chemotherapy
- Subsequent tumor assessments that demonstrate a CR or a confirmed PR to the first-line chemotherapy

7.3.1.2. Screening Tumor Assessment

The baseline tumor assessment should include the following:

- Diagnostic-quality, contrast-enhanced CT scans of the chest, abdomen, and pelvis (Day -14 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.
- PET or whole-body radionuclide bone scan to evaluate for bone metastases, if clinically indicated (Day -14 to -1)
    - Only to be performed at screening if the patient has known bone metastases or has symptoms that could be due to bone metastases
- CT scan of the neck, if clinically indicated (Day -14 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.

7.3.1.3. On-study Tumor Assessments

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

- Diagnostic-quality, contrast-enhanced CT scans of the chest, abdomen, and pelvis (every 8 weeks ±7 days)
  - 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)

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.

7.3.2. Survival Assessments

Survival status of patients will be monitored through all phases of the study as outlined in Section 5 and Appendix 1. The date and cause of death will be recorded.

7.3.3. Quality of Life Assessments

Patients will complete 3 questionnaires in the clinic on Day 1 of Cycle 1, then on the same schedule as tumor assessments, and at the EOT visit before any other study activities occur (Appendix 1). Patients should be given sufficient instruction, space, time, and privacy for completion of the questionnaires. A study center team member should check for completeness of answers and encourage the patient to complete any missing answers. The questionnaires are validated instruments to measure the health status of patients (EQ-5D-5L; Appendix 8), the quality of life of cancer patients (EORTC QLQ-C30; Appendix 9), and gastric cancer-specific symptoms or problems (EORTC QLQ-STO22; Appendix 10).

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 drug, 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, Weight, and Height

A complete or limited physical examination, vital signs (systolic and diastolic blood pressure; pulse rate; and oral, temporal, or tympanic 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. Electrocardiograms

Single 12-lead ECGs with assessment of PR interval, QRS duration, and QT interval corrected for heart rate (QTc) will be obtained at the following timepoints: screening; predose and 2 hours postdose on Cycle 1 Day 1, Cycle 1 Day 15; and EOT. Additional ECGs will be performed if clinically indicated. To minimize postural variability, it is important that patients are resting and in a semirecumbant or supine position for ≥ 5 minutes before each ECG collection. Blood draws and other procedures should be avoided during the period immediately before ECG measurement, and activity should be controlled as much as possible to minimize variability because of the effects of physiologic stress. Screening ECG must be performed within 14 days of randomization. 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

On-study clinical laboratory evaluations starting from screening shall be performed by a central laboratory, as regionally available. An investigator may obtain safety laboratory results from their local laboratory as clinically indicated (eg, on the day of a patient's visit before results are available from the central laboratory for dose modifications or AE/SAE monitoring). Results from the central laboratory will serve as the official study laboratory result, where available. If required by local regulations, clinical laboratory evaluations performed by a local, instead of a central, laboratory are acceptable.

A detailed description of the procedures for sample collection, handling, storage, and shipment of the laboratory samples and all material such as test tubes and labels is provided in the study manual.

Laboratory assessments will be performed at the time points specified in Appendix 1 and may also be performed as medically necessary. Laboratory assessments should be performed before BGB-290 or placebo administration. Screening blood tests must be performed within 14 days of randomization. If tests were performed within 7 days of Day 1, they do not need to be repeated on Day 1.

7.5.1. Hematology

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

7.5.2. Chemistry

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

7.5.3. Urinalysis

Urinalysis includes blood, protein, ketones, glucose, red blood cells, and white blood cell.

7.5.4. Pregnancy Testing

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical studies include for females with childbearing potential the use of highly effective forms of birth control (Appendix 4). For women of childbearing potential, a screening serum pregnancy test must be obtained within 7 days before randomization and may be performed by a local laboratory. For subsequent pregnancy testing, if clinically indicated, urine pregnancy tests are allowed and may be performed by a local laboratory. If a urine pregnancy test is positive, a confirmatory serum pregnancy test is required.

7.6. Pharmacokinetics

PK samples will be collected from patients at the following time points (Appendix 1): predose (within 30 minutes before dose) and 2 hours (±30 minutes) postdose on Cycle 1 Day 1 and Cycle 1 Day 15. The time of study drug administration on the day before Day 15 (Cycle 1 Day 14) must be recorded on the eCRF. Details concerning collection, handling, and processing of the PK plasma samples will be provided in the study manual. PK samples collected from patients assigned to placebo treatment will not be analyzed for BGB-290 concentrations.

7.7. Biomarkers

Blood samples for biomarker testing will be collected from patients at the time points specified in Appendix 1. Patients are required to provide tumor tissue for central laboratory determination of HRD status for randomization and the analysis of candidate predictive biomarkers. Archival tumor tissue shall be sent to the central laboratory for biomarker testing (either a formalin-fixed paraffin embedded block with tumor tissue [preferred] or, ideally, up to 15 unstained slides). The most recent tumor block is preferred.

Candidate markers will include, but are not limited to, those related to pharmacodynamics, response, or resistance to PARP inhibitors (eg, HRD signatures, ATM expression, LOH).

Patients will also provide blood samples to be processed into plasma and cell fractions for the analysis of genetic defects associated with gastric cancer, such as, but not limited to, HRD signatures and DNA repair deficiency.

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

7.8. Appropriateness of Measurements

All efficacy, safety, and PK assessments used in this study are standard 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.

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 Medical Dictionary for Regulatory Activities (MedDRA®) Version 22.0 or higher. Concomitant medications will be coded using the World Health Organization Drug

Dictionary. Concomitant diseases/medical history will be coded using the MedDRA Version 22.0 or higher.

8.3. Quality Assurance

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

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 an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records before submission to the sponsor.

9.1.2. Assessment of Severity

The investigator will make an assessment of severity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI-CTCAE Version 4.03.

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

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

Note: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (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 9.2.

9.1.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, and other risk factors, and the temporal relationship of the AE or SAE to the study drug will be considered and investigated. The investigator will also consult the IB and/or product information for marketed products in the determination of his/her assessment.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always 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 in light of follow up information, amending the SAE report/eCRF accordingly.

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

- Temporal relationship of the AE to the administration of study drug/study procedure

- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility

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

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

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 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.

9.1.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, hematology or chemistry) or other abnormal assessments (eg, ECGs, x-rays, or vital signs) that are judged by the investigator as clinically significant will be

recorded as AEs or SAEs if they meet the definition of an AE (as defined in Section 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.

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.

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

- 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).

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 before 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 prior study drug.

9.3.2. Eliciting Adverse Events

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

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

9.4. Specific Instructions for Recording Adverse Events and Serious Adverse Events

9.4.1. Diagnosis versus Signs and Symptoms

If a diagnosis is known at the time of reporting, this should be recorded in the eCRF (and SAE report, as applicable), rather than the individual signs and symptoms (eg, record only hepatitis rather than elevated transaminases, bilirubin, or jaundice). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual AE should be recorded as an SAE or AE on the eCRF (and SAE report, if applicable). If a diagnosis is subsequently established, it should replace the individual signs and/or symptoms as the AE term on the eCRF (and SAE report, if applicable), unless the signs/symptoms are clinically significant.

9.4.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other AEs (eg, clinical sequelae or a cascade of AEs) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as the SAE or AE on the eCRF (and SAE report,

if applicable). However, if a patient initially has a nonserious AE, and it subsequently becomes an SAE, both AEs should be reported separately on the eCRF. The onset date of the nonserious AE should be recorded as the start date of the nonserious AE. The onset date of the SAE should be recorded as the start date when the nonserious AE becomes an SAE.

9.4.3. Persistent or Recurring Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such AEs should only be recorded once on the AE eCRF (and SAE report, if applicable). If a persistent AE worsens in grade, the worst grade should be recorded for the entire event.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded separately on the eCRF (and SAE report, if applicable).

9.4.4. Disease Progression

PD is measured as an efficacy endpoint and not considered to be an AE. However, if there are separate identifiable clinical sequelae that result from PD, 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 PD. The AE term should be reported as "pleural effusion" instead of PD 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 PD or brain metastasis. If a patient experienced multi-organ failure due to PD, the term "multi-organ failure" should be reported as the AE instead of PD. Deaths that are assessed by the investigator as solely due to PD 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 PD, 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 PD, it should be reported as an AE.

9.4.5. Death

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".

9.4.6. Myelodysplastic Syndrome and Acute Myeloid Leukemia

Events of MDS or AML should be treated as medically serious, even if the patient is not admitted to a hospital. These events should be reported to the sponsor irrespective of the time elapsed since the end of study treatment (see Section 9.7).

9.5. Prompt Reporting of Serious Adverse Events

9.5.1. Timeframes for Submitting Serious Adverse Events

SAEs will be reported promptly 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 Frame for Reporting Serious Adverse Events to the Sponsor or Designee

Type of SAE	Initial SAE Report	Document
All SAEs	Within 24 hours of first knowledge of the AE	eCRF

Abbreviations: AE, adverse event; eCRF, electronic case report form; 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 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 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, 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.

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. 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 US Food and Drug Administration (FDA). 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 FDA.

Expedited investigator safety reports are prepared according to the sponsor's policy and are forwarded to investigators as necessary. Reports that have been unblinded to placebo treatment will not be expedited. 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.

Expedited Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

BeiGene, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions involving the study drug to all regulatory authorities and participating investigators in accordance with International Council for Harmonisation (ICH) Guidelines and/or local regulatory requirements, as applicable. In addition, BeiGene or authorized designee will be responsible for the submission of safety letters to central independent ECs (IECs).

The sponsor will notify investigators of all reportable SAEs. This notification will be in the form of an expedited safety report. Upon receiving such notices, the investigator must review and retain the notice with other study-related documentation.

The investigator and IRB/EC will determine whether the informed consent requires revision. The investigator should also comply with the IRB/EC procedures for reporting any other safety information.

Suspected serious adverse reactions and other significant safety issues reported from the investigational product development program will be reported by the sponsor or its designated representative—either as expedited safety reports and/or in aggregate reports—to the relevant, competent health authorities in all concerned countries.

9.6. 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.

Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

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

9.7. Poststudy Adverse Events

A poststudy AE or SAE is defined as any AE that occurs outside of the AE/SAE reporting period, as defined in Section 9.3.1.

Investigators should follow-up patients for poststudy period cases of MDS and AML. If the investigator learns of any study drug-related SAE, including a death, at any time after a patient has been discharged from the study, he/she should notify the sponsor using the SAE procedure.

9.8. Expedited Reporting to Health Authorities, Ethics Committees, and Investigators

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

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the BGB-290 IB.

10. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

Details of the statistical analyses will be included in the statistical analysis plan (SAP).

10.1. Analysis Set

- Intent-to-Treat (ITT) Analysis Set includes all randomized patients who are assigned to study drug (BGB-290 or placebo). The ITT Analysis Set will be used for all efficacy analyses unless otherwise specified in the statistical analysis plan.
- Safety Analysis Set includes all patients in the ITT Analysis Set who receive any dose of study drug (BGB-290 or placebo). The Safety Analysis Set will be used for all safety analyses.
- Per-Protocol (PP) Analysis Set includes all patients in the ITT Analysis Set without major protocol deviations that impact assessment of efficacy. Criteria for exclusion from the PP Analysis Set will be determined and documented before the final analysis of PFS. The PP Analysis Set will be used to perform sensitivity analysis for the OS and PFS endpoints.

- PK Analysis Set includes all patients who receive BGB-290 and for whom valid BGB-290 PK parameters can be estimated.

10.2. Covariates

The following covariates may be used to examine efficacy and/or safety in subgroups or covariate analyses if deemed appropriate:

- Geographic region (China/Hong Kong/Taiwan vs Australia/Europe/North America vs Japan/South Korea vs ROW)
- EGOG performance status at baseline (0, 1)
- HRD status (LOH_{high} vs LOH_{low} vs unknown)
- Age at baseline: $< 65, \geq 65; < 75, \geq 75$
- Race: White vs Asian vs others; Chinese vs Japanese vs White vs others
- Measurable disease at baseline (yes, no)
- IRT values and CRF values will be used for primary analyses and sensitivity/subgroup analyses, respectively

10.3. Efficacy Analyses

All efficacy analyses will be conducted using the ITT Analysis Set unless otherwise specified. Primary efficacy analysis of PFS will use the investigator assessment of PD according to RECIST Version 1.1. Secondary efficacy analyses of ORR, time to response, and duration of response will use the investigator assessments of response and PD according to RECIST Version 1.1. All stratified efficacy analyses will incorporate the stratification factors used at randomization: HRD status (LOH_{high} versus LOH_{low} versus unknown), region (China/Hong Kong/Taiwan versus Australia/Europe/North America versus Japan/South Korea versus ROW), and ECOG performance status (0 versus 1), unless otherwise specified.

10.3.1. Primary Efficacy Analyses

PFS is defined as the time from randomization to PD per RECIST Version 1.1 by investigator assessment or death due to any cause, whichever occurs first.

The null and alternative hypotheses for the final PFS analysis are as follows:

H_0: HR (BGB-290/placebo) = 1

H_a: HR (BGB-290/placebo) < 1

The final PFS analysis will be performed when 85 PFS events have occurred (66% of target sample size). A stratified 1-sided log-rank test at a 0.1 significance level incorporating the randomized stratification factors will be used to compare treatment groups using the ITT Analysis Set. The HR and its 2-sided 95% CI will be estimated using the stratified Cox-proportional hazards model. The median PFS for each treatment group will be estimated using the Kaplan-Meier method, and the

2-sided 95% CI will be calculated using the Brookmeyer-Crowley method (Brookmeyer and Crowley, 1982).

PFS censoring rule will follow FDA Guidance for Industry, Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics (2007). Data for patients without PD per RECIST Version 1.1 or death at the time of analysis will be censored at the date of the last tumor assessment. Data for patients who started new anticancer therapy will be censored at the last tumor assessment date before the introduction of new anticancer therapy. Data for patients who had 2 or more consecutive missed scheduled tumor assessments immediately before PD will be censored at the last tumor assessment date before the 2 missed tumor assessments. Non-proportionality of hazard ratios between the treatment groups will be assessed and additional sensitivity analysis will be performed. Further details will be described in the statistical analysis plan.

10.3.2. Secondary Efficacy Analyses

A secondary analysis of PFS will be conducted using the PP Analysis Set.

OS is the key secondary efficacy endpoint and is defined as the time from randomization to death due to any cause.

A stratified log-rank test incorporating the randomized stratification factors will be used to compare treatment groups using the ITT Analysis Set. The HR and its 2-sided 95% CI will be estimated using the stratified Cox-proportional hazards model. The median OS for each treatment group will be estimated using the Kaplan-Meier method and the 95% CI will be calculated using the Brookmeyer-Crowley method (Brookmeyer and Crowley, 1982).

A sensitivity analysis of OS will be conducted using the PP Analysis Set.

TSST is defined as the time from randomization until the second subsequent anti-cancer therapy or death after next-line therapy. Subjects alive and without the 2nd anti-cancer therapy will be censored at last known alive.

TSST will be assessed using a stratified log-rank test in ITT Analysis Set. The HR and its 2-sided 95% CI will be estimated using the stratified Cox-proportional hazards model. The median for each treatment group will be estimated using the Kaplan-Meier method and the 95% CI will be calculated using the Brookmeyer-Crowley method (Brookmeyer and Crowley, 1982).

ORR is defined as the proportion of patients with a best overall response of CR or PR per RECIST Version 1.1 by investigator assessment for the ITT Analysis Set. The ORR and its exact 2-sided 95% CI will be reported for each treatment group. A Cochran-Mantel-Haenszel score test will be used to compare treatment groups.

The best overall response will be summarized by the following categories for the ITT Analysis Set, patients with measurable disease at baseline and patients with nonmeasurable disease at baseline.

- CR
- PR (for the ITT Analysis Set and patients with measurable disease)

- Stable disease
- PD
- Not evaluable

DOR is defined as the time from the first documented confirmed response of CR or PR to PD per RECIST Version 1.1 by investigator assessment or death due to any cause, whichever occurs first. Only patients with response of CR or PR during the study will be included in duration of response analysis. The median duration of response and its 2-sided 95% CI for each treatment group will be provided.

Time to response is defined as the time from randomization to the first documented confirmed response of CR or PR per RECIST Version 1.1 by investigator assessment. Only patients with response of CR or PR during the study will be included in time to response analysis. Descriptive statistics will be provided.

10.4. Pharmacokinetic Analyses

BGB-290 C_{trough} at steady-state will be summarized. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Population PK analysis may be carried out to include plasma concentrations from this study in an existing model. 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 post-dose (AUC_{0-12}) may be derived from the population PK if supported by data.

Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data. The results of the population PK and exposure-response analyses may be reported separately from the clinical study report. Details of the PK analyses will be provided in a separate SAP.

10.5. Exploratory Analyses

10.5.1. Health-related Quality of Life

Patient reported outcomes will be assessed using the EORTC QLQ-C30 and QLQ-STO22 questionnaires and the EQ-5D-5L health questionnaire. The scores from these questionnaires will be summarized descriptively.

10.5.2. Biomarkers

Correlative biomarker analyses in tumor tissues and blood will be performed. A separate statistical analysis plan will outline details of the biomarker analyses.

10.6. Safety Analyses

Safety will be assessed by monitoring and recording of all AEs. Laboratory values, vital signs, physical examinations, and ECG findings will also be used in determining the safety of the study treatment.

10.6.1. Extent of Exposure

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

The number (percentage) of patients requiring dose reductions, study drug holds, and permanent study drug discontinuation due to AEs will be summarized by treatment group. Frequency of dose reductions and study drug withholding will be summarized by categories.

10.6.2. Adverse Events

The AE will be coded using MedDRA Version 22.0 or higher and graded using the current version of NCI-CTCAE.

A TEAE is defined as an AE that had an onset date on or after first study treatment or was worsening in severity from baseline (pretreatment) up to 30 days following permanent study drug discontinuation or initiation of new anticancer therapy, whichever occurs first. All TEAEs will be included in summary tables and in-patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class (SOC) and preferred term (PT). A patient will be counted only once by the highest grade according to NCI-CTCAE Version 4.03 within an SOC and PT, even if the patient experienced more than one TEAE within a specific SOC and PT. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study treatment. Treatment-related AEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. Serious AEs, deaths, TEAE of Grade ≥3, study drug-related TEAEs, and TEAEs that led to study drug withholding or permanent discontinuation will also be summarized.

10.6.3. Laboratory Analyses

Clinical laboratory (eg, hematology and chemistry) values to be evaluated will be specified in the statistical analysis plan and collected in the EDC system. Collected values may be a subset of all the values obtained in the requested sampling, eg, a complete blood count with differential may be requested for the evaluation of neutrophils only. 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 will be summarized by NCI-CTCAE grade. Shift tables will be provided as appropriate.

10.6.4. Physical Examinations

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

10.6.5. Vital Signs

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

10.6.6. Electrocardiograms

The percentage of patients with abnormal and clinically significant ECG findings will be presented.

10.7. Sample Size Consideration

This study is designed to provide 80% power for PFS. The following assumptions are used in determining the sample size for this study:

- Overall type I error rate: 0.1 (1-sided)
- Randomization: 1:1
- Median PFS for placebo group: 6.0 months
- PFS HR (BGB-290/placebo): 0.63

A sample size of approximately 128 patients (64 per treatment group) is required to achieve 85 PFS events within the planned study duration of approximately 26 months after the first patient is randomized to study, assuming an estimated accrual period of 20 months.

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 that country.

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", ICH guidelines, and that the basic principles of "Good Clinical Practice," 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 subinvestigators 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 subinvestigator. The investigator and subinvestigator agree to notify BeiGene or its authorized representative of any change in 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 IND, 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 subinvestigator 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
- 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 before 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.

In addition, details of the study drug assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her patient(s).

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

Study Phase	**Screening[a]**	**Treatment[b]**					**Un-scheduled Visit[c]**	**End of treatment (EOT) Visit[d]**	**Safety Follow-up[e]**	**Long-term Follow-up[f]**
Day of Phase	**-28 to -1**	**Cycle 1**		**Cycle 2**		**Cycle ≥3**				
		Day 1	**Day 15**	**Day 1**	**Day 15**	**Day 1**				
Allowed time window			± 2	± 3	± 3	± 3				
Study Day	-28 to -1	1	15	29	43	57, 85, etc.	Varies	Varies	Varies	Varies
Informed consent	X									
Eligibility criteria	X									
Demographics, medical history, smoking status	X									
Complete physical examination	X							X		
Limited physical examination		X	X	X	X	X	X			
EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-STO22 questionnaires		X				X (q8w ±7d)		X		
Vital signs and weight[g]	X	X	X	X	X	X	X	X		
Height	X									
ECOG performance status	X	X	X	X	X	X	X	X		
12-lead ECG[h]	X (-14 to -1)	X	X				X	X		
Hematology[i]	X (-14 to -1)	X	X	X	X	X	X	X	X	
Chemistry[i]	X (-14 to -1)	X	X	X	X	X	X	X	X	
Urinalysis[i]	X (-14 to -1)	X					X	X		
Pregnancy testing[j]	X (-7 to -1)			X		X	X	X	X	

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Study Phase	**Screening[a]**	**Treatment[b]**					**Un-scheduled Visit[c]**	**End of treatment (EOT) Visit[d]**	**Safety Follow-up[e]**	**Long-term Follow-up[f]**
Day of Phase	**-28 to -1**	**Cycle 1**		**Cycle 2**		**Cycle ≥3**				
		Day 1	**Day 15**	**Day 1**	**Day 15**	**Day 1**				
Allowed time window			± 2	± 3	± 3	± 3				
Study Day	-28 to -1	1	15	29	43	57, 85, etc.	Varies	Varies	Varies	Varies
CT with IV contrast of chest, abdomen and pelvis[k]	X (-14 to -1)					X (q8w ±7d)	X	X		X (q8w ±7d)
PET or bone scan, if clinically indicated[l]	X (-14 to -1)					X (q8w ±7d)[l]	X	X[n]		X (q8w ±7d)[l]
MRI scan of brain, if clinically indicated[m]	X					X (q8w ±7d)[m]	X	X[o]		X (q8w ±7d)[m]
Patient registration and randomization via IRT	X[a]									
BGB-290 or placebo		Twice daily dosing continuously								
Study drug dispensing/accountability		X		X		X	X	X		
Adverse events[n]	X	X	X	X	X	X	X	X	X	X
Concomitant medication(s)[o]	X	X	X	X	X	X	X	X	X	X (~q12w)
Pharmacokinetics[p]		X	X							
Blood for biomarkers[q]		X		X		X[q] (C4 only)		X		
Tumor tissue[r]	X									
Survival follow-up[s]										X (~q12w)

Abbreviations: -7/-14/-28 to -1, Day -7/-14/-28 to Day -1 (day of randomization) of screening; AE, adverse event; BID, twice daily; C, Cycle; CT, computed tomography; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire; EORTC QLQ-STO22, European Organisation for Research and Treatment of Cancer Quality of Life gastric cancer module; EOT, end of treatment; EQ-5D-5L, European Quality of Life 5-Dimensions 5 Levels Health Questionnaire; HRD, homologous recombination deficiency; IRT, interactive response technology; IV, intravenous; MRI, magnetic resonance imaging; NCI-CTCAE; National Cancer Institute-Common Toxicity Criteria for Adverse Events; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; PET, positron-emission tomography; PK, pharmacokinetic; PO, oral; q8w ±7d, every 8 weeks ±7 days; ~q12w, approximately every 12 weeks;

RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event.

a. Screening must occur within 28 days of randomization. Some assessments have a narrower screening window as shown in the table. Assessments obtained within 7 days of Day 1 do not have to be repeated on Day 1. Patient registration and randomization may occur as late as Day 1 before any study treatment.

b. Patients must initiate study treatment within 4 days after randomization. Administration of BGB-290 or placebo will continue until PD, as assessed by investigator per RECIST Version 1.1, unacceptable toxicity, death, or another discontinuation criterion is met (Sections 5.5 and 5.7). A cycle is 28 days. Assessments shown for Cycle 3 apply to all subsequent cycles except for required tumor assessments that occur every 8 weeks ±7 days (every second cycle) and blood collection for biomarkers occurs only on Day 1 of Cycle 4 (not any other Day 1 of ≥ Cycle 3).

c. Unscheduled visits may occur any time as necessary as per investigator decision or patient's request for reasons such as assessment or follow-up of AEs. Study activities, as indicated by 'X,' should be performed based on the reason for the unscheduled visit. If PD is suspected, imaging studies should be performed and blood for biomarkers should be obtained as appropriate.

d. The EOT visit should occur within 7 days after BGB-290 or placebo has been permanently discontinued. A visit should be scheduled as soon as possible, but the EOT visit may occur later after discussion with the medical monitor for specific circumstances, such as prolonged hospitalization. The visit at which tumor assessments showed PD may be used as the EOT visit providing all required assessments were performed. Tumor assessments 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 PD. An ECG does not have to be repeated if it was performed within 14 days of the EOT visit.

e. Approximately 30 days after the last day of study drug or before initiation of new anticancer therapy, whichever occurs first, a safety follow-up will occur with the outlined safety assessments. If new anticancer therapy is initiated before this safety follow-up, a safety follow-up should be scheduled as soon as possible. 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 of contact are unsuccessful, the additional attempts detailed in Section 5.6.3 should be made.

f. Patients will be followed for survival, further anticancer therapy, and diagnosis of myelodysplastic syndrome or acute myeloid leukemia via telephone contact or other means (eg, clinic visit) approximately every 12 weeks until death, withdrawal of consent, or the end of study, whichever occurs first.

   Patients who were permanently discontinued from study drug for reasons other than PD and meet criteria otherwise (eg, discontinued for AE and no new anticancer therapy) will be followed with tumor assessments every 8 weeks (±7 days) until PD or any other reason listed in Section 5.7, 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.
   Should attempts of telephone contact be unsuccessful, the additional attempts detailed in Section 5.6.3 should be made. If a patient cannot be contacted despite all attempts, the patient will be considered lost to follow-up.

g. Vital signs (systolic and diastolic blood pressure; pulse rate; and oral, temporal, or tympanic temperature) will be measured before study drug administration and approximately 15 minutes before each collection of PK blood samples, if applicable, during the treatment period.

h. ECGs will be obtained at the following timepoints: screening; predose and 2 hours postdose on Cycle 1 Day 1 and Cycle 1 Day 15; and EOT. Additional ECGs will be performed, if clinically indicated.

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

   Chemistry includes albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, chloride, creatinine, glucose, lactate dehydrogenase, phosphate, potassium, sodium, total bilirubin, and total protein.

   Urinalysis includes blood, protein, ketones, glucose, red blood cells, and white blood cells.

j. For females of childbearing potential, a serum pregnancy test must be performed at a central or local laboratory within 7 days before randomization. For subsequent pregnancy testing, if clinically indicated, urine pregnancy tests, performed at a central or local laboratory, are allowed. If a urine pregnancy test is

positive, a confirmatory serum pregnancy test is required.

k. Following the screening tumor assessment within 14 days before randomization, tumor assessments will occur at the schedule of every 8 weeks (±7 days) after Day 1. 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. A documented standard-of-care tumor assessment may be used as the screening assessment provided it meets protocol requirements (Section 7.3.1.2). CT scan with IV contrast is the preferred imaging method for assessment of the chest, abdomen, and pelvis. Other imaging methods are allowed as outlined in Section 7.3.1.2. Imaging of other areas of disease should be performed as clinically indicated. Patients without PD at the EOT visit should be followed with tumor assessments every 8 weeks (± 7 days) during the long-term follow-up phase.

l. PET scan or whole-body radionuclide bone scan must be performed at screening if the patient has known bone metastases or has symptoms that could be due to bone metastases. If bone metastases are present at baseline, they must be followed on study using the same imaging method as at baseline.

m. MRI scan of the brain to assess for brain metastases must be performed at screening if the patient has symptoms that could be due to brain metastases. CT scan with IV contrast is acceptable if MRI is not available or the patient is claustrophobic.

n. AEs and laboratory safety measurements will be recorded at each study visit, graded per NCI-CTCAE Version 4.03, and assessed as outlined in Section 9. After the informed consent form has been signed, but before 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 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.

o. All concomitant medications taken by or administered to the patient within 28 days before randomization 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.

p. PK samples will be collected from patients at the following time points: predose (within 30 minutes before dose) and 2 hours (±30 minutes) postdose on Cycle 1 Day 1 and Cycle 1 Day 15. The time of study drug administration on the day before Day 15 must be recorded on the eCRF. Details concerning collection, handling, and processing of the PK plasma samples will be provided in the study manual.

q. One blood sample (8 mL) must be collected before initiation of study drug on Day 1 of Cycle 1 for the assessment of germline mutations. Two blood samples (10 mL each) must be collected for the assessment of plasma biomarkers of PARP inhibitor response/resistance before study drug administration on Day 1 of Cycles 1, 2, and 4, as well as at the EOT visit (unless they had been collected within 14 days). Instructions for the processing, storage, and shipping of samples will be provided in the study manual.

r. Archival tumor tissue shall be sent to the central laboratory for the determination of HRD status for randomization and the assessment of candidate predictive biomarkers.

s. Patients will be followed for survival via telephone contact approximately every 12 weeks or as further detailed in Sections 5.6.2 and 5.6.3.

APPENDIX 2. 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 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 magnetic resonance imaging (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 'not evaluable (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 3. 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. 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 5. 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 6. PROHIBITED MEDICATIONS

Strong and Moderate CYP3A Inhibitors and Strong CYP3A Inducers

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Strong CYP3A Inducers
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (*Hypericum perforatum*)
Moderate CYP3A Inhibitors
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole
Protease inhibitors: amprenavir, atazanavir, darunavir, fosamprenavir
Calcium channel blockers: diltiazem, verapamil
Tyrosine kinase inhibitors (anticancer): imatinib
Food products: grapefruit and juice (*Citrus paradisi*), Seville orange and juice (*Citrus aurantium*)
Herbal medications: *Schisandra sphenanthera*
Others: aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam

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

APPENDIX 7. MEDICATIONS TO BE USED WITH CAUTION

Sensitive CYP2C9 Substrates or CYP2C9 Substrates with Narrow Therapeutic Index

- Celecoxib[a]
- Phenytoin[b]
- Warfarin[b]

[a] Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when coadministered with a known potent inhibitor, where AUCi is the AUC of the substrate when coadministered with a known potent inhibitor and AUC is the AUC of substrate alone.

[b] Substrates with narrow therapeutic index: Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (eg, Torsade de Pointes).

Strong CYP2C8 Inhibitors

- Gemfibrozil

APPENDIX 8. EUROPEAN QUALITY OF LIFE 5-DIMENSIONS 5-LEVELS HEALTH QUESTIONNAIRE

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

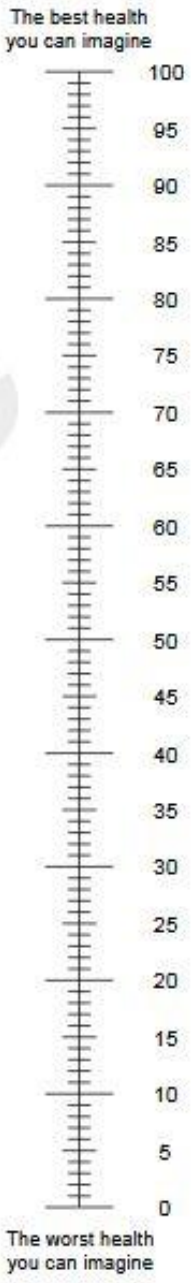
ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

2

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

YOUR HEALTH TODAY = ☐



3

APPENDIX 9. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE CANCER QUESTIONNAIRE QLQ-C30

EORTC QLQ-C30 (version 3)

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

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

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 10. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE GASTRIC CANCER MODULE QLQ-ST022

EORTC QLQ – STO22

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

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had problems eating solid foods?	1	2	3	4
32. Have you had problems eating liquidised or soft foods?	1	2	3	4
33. Have you had problems drinking liquids?	1	2	3	4
34. Have you had discomfort when eating?	1	2	3	4
35. Have you had pain in your stomach area?	1	2	3	4
36. Have you had discomfort in your stomach area?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
39. Have you had acid indigestion or heartburn?	1	2	3	4
40. Have you had trouble with belching?	1	2	3	4
41. Have you felt full up too quickly after beginning to eat?	1	2	3	4
42. Have you had trouble enjoying your meals?	1	2	3	4
43. Has it taken you a long time to complete your meals?	1	2	3	4
44. Have you had a dry mouth?	1	2	3	4
45. Did food and drink taste different from usual?	1	2	3	4
46. Have you had trouble with eating in front of other people?	1	2	3	4
47. Have you been thinking about your illness?	1	2	3	4
48. Have you worried about your weight being too low?	1	2	3	4
49. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4
51. Have you lost any hair?	1	2	3	4
52. Answer this question only if you lost any hair: If so, were you upset by the loss of your hair?	1	2	3	4

ENGLISH

APPENDIX 11. 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.

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

where:

Scr is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of Scr /κ or 1, and

max indicates the maximum of Scr /κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area.

The online calculator for CKD-EPI can be found here: https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/Pages/gfr-calculators.aspx

APPENDIX 12. SIGNATURE OF INVESTIGATOR

Protocol Title: **A Phase 2, Double-blind, Randomized Study of BGB-290 versus Placebo as Maintenance Therapy in Patients with Inoperable Locally Advanced or Metastatic Gastric Cancer that Responded to Platinum-based First-line Chemotherapy**

Protocol Identifier: BGB-290-303

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: _____

Signature Page for VV-CLIN-021346 v1.0

Approval	[redacted] Clinical Development 14-Feb-2020 20:44:19 GMT+0000

Signature Page for VV-CLIN-021346 v1.0