BeiGene

BGB-3111-206 (NCT03206970)

A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Efficacy and Safety of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Subjects With Refractory or Relapsed Mantle Cell Lymphoma (MCL)

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Clinical Study Protocol

Protocol Title:	**A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Efficacy and Safety of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Subjects with Relapsed or Refractory Mantle Cell Lymphoma (MCL)**
Protocol Number:	**BGB-3111-206**
Date and Version of Protocol:	**1 October 2016, Version 1.0** **5 January 2017, Version 2.0** **25 October 2017, Version 3.0** **6 September 2018, Version 4.0**
Clinical Study Phase:	**2**
Sponsor:	**BeiGene (Beijing) Co., Ltd** **No. 30 Science Park Road,** **Zhong-Guan-Cun Life Science Park** **Changping District, Beijing 102206** **China**
Leading Principle Investigator:	**Jun Zhu, Professor** **Beijing Cancer Hospital**
Sponsor Medical Monitor:	PPD [redacted]

FINAL PROTOCOL APPROVAL SHEET

A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Efficacy and Safety of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Subjects with Relapsed or Refractory Mantle Cell Lymphoma (MCL)

Protocol No.: BGB-3111-206 Version 4.0

BeiGene (Beijing) Co., Ltd Approval:

PPD

PPD

12 Sep 2018

PPD

Date

Medical Monitor

PROTOCOL AMENDMENT (VERSION 4.0)

Protocol BGB-3111-206 is amended primarily for the following reason:

1. To update tumor assessment schedule

Throughout are administrative updates, editorial changes, and/or style and formatting revisions made with the purpose of improving clarity and consistency throughout the document

Major changes to the protocol are as follows:

Synopsis, Section 4.1, Section 7.3 and Table 2: Revise text to clarify that, for patients with avid PET diseases at screening, PET and contrast CT should be repeated every 12 weeks for the first 96 weeks, and every 24 weeks thereafter until disease progression (PD) or end of study, whichever comes first. For subjects with non-avid PET diseases at screening, only contrast CT should be performed every 12 weeks for the first 96 weeks, and every 24 weeks thereafter until PD or end of study, whichever comes first.

SYNOPSIS

Name of Sponsor/Company:	**BeiGene (Beijing) Co., Ltd**
Name of Finished Product:	**BGB-3111**
Name of Active Ingredient:	**BGB-3111**
Title of Study:	A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Efficacy and Safety of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Subjects with Refractory or Relapsed Mantle Cell Lymphoma (MCL)
Protocol No:	BGB-3111-206
Treatment duration: Screening (maximum of 28 days). Subjects will receive daily treatment on study for up to 3 years or until disease progression, unacceptable toxicity or death, withdrawal of consent, lost to follow-up, or study termination by sponsor. Safety follow-up for 30 days after drug withdrawal; Survival follow-up until the end of study.	**Phase**: 2

Objectives:

Primary:

To evaluate the efficacy of BGB-3111 at a dose of 160 mg orally (PO) twice daily (BID) in subjects with centrally confirmed relapsed or refractory mantle cell lymphoma (MCL) as measured by overall response rate (ORR) assessed by an Independent Review Committee (IRC) in accordance with the 2014 modification of the International Working Group on Non-Hodgkin's lymphoma (NHL) Criteria (Cheson, 2014).

Secondary:

- To evaluate the efficacy of BGB-3111 as measured by progression-free survival (PFS), time to response (TTR) and duration of response (DOR) by IRC
- To evaluate the efficacy of BGB-3111 by investigator as measured by overall response rate.
- To evaluate the safety and tolerability of BGB-3111 in subjects with relapsed or refractory MCL

CCI [redacted]

Methodology:

This is a single-arm, open-label, multicenter Phase 2 study.

Planned number of subjects:	Approximately 80 subjects will be enrolled.
Study Population	Inclusion criteria: 1. Diagnostic report has to include evidence for morphological and cyclin D1 and B cell markers (eg, CD19, CD20 or PAX5) and CD5 co-expression or t (11; 14). The above results are detected by immunohistochemistry, cytogenetics or fluorescence in situ hybridization (FISH). After enrollment, tumor tissue (FFPE) block or unstained slides must be sent to central laboratory for immunohistochemical analysis to confirm MCL. The block or slides must have been obtained from within 2 years before treatment is to be started or, if not, must have been first sent to the central laboratory for confirmation of appropriateness for use for pathology examination and diagnosis.

	2. Men and women, 18-75 years of age. 3. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. 4. Measurable disease by computed tomography/magnetic resonance imaging (computerized tomography/magnetic resonance imaging (MRI). Measurable disease is defined as at least 1 lymph node > 1.5 cm in longest diameter and measurable in 2 perpendicular dimensions. 5. Received at least one but less than five prior regimens for MCL ($1 \leq$ the number of prior regimens < 5). 6. Documented failure to achieve any response, [stable disease (SD) or progressive disease during treatment] or documented progressive disease after response to the most recent treatment regimen. 7. Neutrophils $\geq 1 \times 10^9$/L independent of growth factor support within 7 days of study entry 8. Platelets $\geq 75 \times 10^9$/L independent of growth factor support or transfusion (Platelets $\geq 50 \times 10^9$/L with bone marrow involvement) within 7 days of study entry 9. Creatinine clearance of ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation or estimated glomerular filtration rate [eGFR] from the Modification of Diet in Renal Disease [MDRD]). 10. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN. 11. Total bilirubin $\leq 2 \times$ ULN (unless documented Gilbert's syndrome). 12. International normalized ratio (INR) ≤ 1.5 and activated partial thromboplastin time (APTT) $\leq 1.5 \times$ ULN. If a factor inhibitor is present with prolongation of the INR or APTT, a patient may be enrolled after consultation with the medical monitor. 13. Subjects may be enrolled who relapse at least 6 months after autologous stem cell transplant. To be eligible after transplant, subjects should have no active related infections. 14. Females of childbearing potential must agree to use highly effective forms of birth control throughout the course of the study and at least up to 90 days after last dose of study drug. Highly effective forms of birth control include abstinence, hysterectomy, bilateral oophorectomy with no menstrual bleeding for 6 months, intrauterine contraception, hormonal methods such as contraceptive injection, oral contraceptive, etc. Males must have undergone sterilization–vasectomy, or utilize a barrier method while the female partner utilizes the effective forms of birth control noted above. 15. Life expectancy of > 4 months. 16. Able to provide written informed consent and can understand and comply with the requirements of the study. Exclusion criteria: 1. Current or history of central nervous system (CNS) lymphoma. 2. Prior exposure to a BTK inhibitor before enrollment. 3. Prior corticosteroids in excess of prednisone 10 mg/day or its equivalent with antineoplastic intent within 7 days of the start of study drug. Prior chemotherapy, targeted therapy, or radiation therapy

within 3 weeks, antineoplastic therapy with Chinese herbal medicine or antibody based therapies within 4 weeks of the start of study drug.
4. Major surgery within 4 weeks of screening.
5. Toxicity must recover to ≤ Grade 1 from prior chemotherapy (except for alopecia, absolute neutrophil count (ANC) and platelet count). Please refer to Inclusion Criteria 7 and 8 for ANC and platelet count, respectively).
6. History of other active malignancies within 2 years of study entry, with exception of (1) adequately treated in-situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy controlled and treated locally (surgery or other modality) with curative intent.
7. Currently clinically significant active cardiovascular disease such as uncontrolled arrhythmia, uncontrolled hypertension, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association (NYHA) Functional Classification (Appendix 7), or history of myocardial infarction within 6 months of screening. Echocardiogram (ECHO) must demonstrate left ventricular ejection fraction (LVEF) less than 50% (AHA, 2016).
8. QTcF > 450 msecs or other significant ECG abnormalities including second degree atrioventricular (AV) block Type II, or third degree AV block.
9. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
10. Active infection including infections requiring oral or intravenous antimicrobial therapy.
11. Known infection with human immunodeficiency virus (HIV) or serologic status reflecting active hepatitis B or hepatitis C infection (detected positive by polymerase chain reaction [PCR]).

	Inclusion		Exclusion	
HIV	Antibody (-)		Antibody(+)	
HBV	HBsAg (-) and HBcAb (-)		HBsAg (+)	
	HBsAg (-) and HBcAb (+)	HBV DNA < 1000 IU/mL and anti-viral therapy during study treatment and perform monthly monitoring of HBV DNA	HBsAg(-) and HBcAb(+)	HBV DNA ≥ 1000 IU/ml
HCV	Antibody (-) or Antibody (+)	HCV RNA "Not detected" (<15 IU/mL) Perform monthly monitoring of HCV RNA	Antibody(+)	HCV RNA Detected

Abbreviations: HBcAb; hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV; hepatitis C virus; HIV, human immunodeficiency virus

12. Pregnant or lactating women.
13. Any life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, or put the study at risk.

	14. Inability to comply with study procedures. 15. Requires ongoing treatment with medications that are strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors or strong CYP3A inducers. 16. Has received allogenic hematopoietic stem cell transplantation prior to enrollment.
Test product, dose and mode of administration:	BGB-3111 160 mg (Two 80-mg white opaque capsules) PO BID
Reference therapy, dose, and mode of administration:	Not applicable

Study Treatment:

BGB-3111 160 mg will be administered PO BID. Daily treatment with BGB-3111 may be continued for up to 3 years until disease progression, unacceptable toxicity or death, withdrawal of consent, lost to follow up, or study termination by sponsor, whichever comes first. At the time of final analysis, subjects who still benefit from treatment will be considered for participation in the extension study upon approval from sponsor. A treatment cycle consists of 28 days.

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Criteria for Evaluation:

Response will be evaluated by IRC review using the 2014 modification of the International Working Group on Non-Hodgkin's lymphoma (NHL) Criteria (Appendix 3). All patients should undergo positron emission tomography (PET) and contrast CT at screening. For patients with avid PET diseases at screening, PET and contrast CT should be repeated every 12 weeks for the first 96 weeks, and every 24 weeks thereafter until disease progression (PD) or end of study, whichever comes first. For subjects with non-avid PET diseases at screening, only contrast CT should be performed every 12 weeks for the first 96 weeks, and every 24 weeks thereafter until PD or end of study, whichever comes first. Response will be assessed based on clinical and radiological evaluations. Bone marrow biopsy will be required for confirmation of complete response ([CR] at first occurrence of radiological and clinical evidence of CR) in subjects with bone marrow tumor involvement prior to study drug. Endoscopy is mandatory to confirm CR for any subject with a documented history of gastrointestinal involvement. Clinical suspicion of PD at any time will require a physical examination and radiological confirmation to be performed promptly, rather than waiting for the next scheduled radiological assessment.

The study will set up an IRC. The IRC will assess efficacy independently. Detailed IRC composition and procedures will be provided separately in an IRC charter.

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Subjects will be evaluated for AEs (all grades, according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version [v]4.03) (NCI, 2010) and serious adverse events (SAEs). Subjects who have an AE that leads to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the subject is lost to follow-up, or the subject starts a different antitumor therapy.

Endpoints:

Primary Endpoint:

The primary endpoint of the study is the rate of objective response, defined as the achievement of either a partial response (PR) or complete response (CR) as assessed by the IRC according to the 2014 modification of the International Working Group on Non-Hodgkin's lymphoma (NHL) Criteria (Cheson, 2014) (Appendix 3) at any time on study drug.

Secondary Endpoints:

Efficacy:

- PFS as assessed by the IRC in subjects with relapsed or refractory MCL after administration of BGB-3111: defined as time from treatment initiation to documentation of progression or death due to any cause, whichever happens first
- TTR as assessed by the IRC in subjects with relapsed or refractory MCL after administration of BGB-3111: defined as the time from treatment initiation to the first documentation of response
- DOR as assessed by the IRC in subjects with relapsed or refractory MCL after administration of BGB-3111: defined as the time from the first response documentation to the date that PD is documented after treatment initiation
- ORR as assessed by the investigator: defined as defined as the achievement of either a PR or CR as assessed by the Investigator at any time on study drug

Safety: To evaluate safety and tolerability of BGB-3111, endpoints include:

- Incidence, time and severity of treatment-emergent adverse events (TEAE) according to NCI CTCAE v4.03 (NCI, 2010).
- Incidence, severity, time and causation of adverse events leading to study drug discontinuation

CCI [redacted]

Statistical Methods:

Populations:

The Safety Population includes all subjects who received any dose of BGB-3111. This will be the population for the safety analysis.

The Revised Safety Population includes subjects with pathologically confirmed MCL among those in the Safety Population. This population is also the primary efficacy evaluable population.

The Per-protocol (PP) Population includes subjects who received any dose BGB-3111and had no major protocol deviations. Criteria for exclusion from the PP Population will be determined and documented before the database lock for the primary analysis. This will be the secondary analysis population for efficacy analysis.

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Primary Efficacy Analysis:

The ORR in this study is estimated as 70%, which is deemed a clinical meaningful improvement. Hence, the null and alternative hypotheses are set as follows:

H_0: ORR=40%

H_a: ORR $\geq$ 40%

A binomial exact test will be performed for hypothesis testing H_0: ORR=40% vs. H_a: ORR $\geq$ 40% in the Revised Safety Population. If the obtained 1-sided p-value is ≤ 0.025, it will be concluded that the single agent BGB-3111 statistically significantly increases ORR compared with the historical control. Therefore, the superiority of single agent BGB-3111 will be demonstrated.

Two-sided Clopper-Pearson 95% confidence interval (CI) of ORR will be constructed to assess the precision of the point estimate of ORR.

Best overall response (BOR) is defined as the best response recorded from the start of BGB-3111 until data cut or start of new anti-neoplastic treatment. Subjects with no post-baseline response assessment (due to any reason) will be considered non-responders for BOR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, PR, SD, and PD) will be presented.

CCI [redacted]

Secondary Efficacy Analysis:

Kaplan-Meier (KM) method will be used to estimate progression event-free curves and corresponding quantiles (including the median). A two-sided 95% CIs of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer, 1982). The PFS at 6 months, defined as the percentages of subjects in the analysis population who remain alive and progression-free at the specified time points, will be estimated using the KM method along with the corresponding 95% CI constructed using Greenwood's formula (Greenwood, 1926).

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

The DOR will be analysed using the KM method as described above. The KM estimates of DOR will be plotted over time. The TTR will be summarized using sample statistics, such as sample mean, median, and standard deviation

Sensitivity analysis will also be performed for the primary endpoint using the Safety Population and the PP Population.

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Safety Analysis:

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

Verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA®) terms and graded according to the NCI CTCAE v4.03 (NCI, 2010). All TEAEs will be summarized. A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the date of first dose of study drug up to 30 days following study drug discontinuation (Safety Follow-up visit) or initiation of new anticancer therapy, whichever comes first. Serious adverse events, deaths, TEAEs of Grade 3 or above, and TEAEs that led to treatment discontinuation, dose reduction, or dose interruption will be summarized.

Multiple occurrences of the same event will be counted once at the maximum severity within a system organ class (SOC) and preferred term (PT).

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

Sample Size:

Approximately 80 subjects will be enrolled. The sample size calculation was mainly based on the level of precision of the estimated ORR. CCI [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABC	Activated B-cell
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
ARF	Alternate reading frame
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
ATM	Ataxia telangiectasia mutated
ATP	Adenosine triphosphate
AUC	Area under plasma concentration-time curve
AUC_{0-12}	Area under the plasma concentration-time curve from 0 to 12 hours
AV	Atrioventricular
BCR	B-cell receptor
BID	Twice daily
BMI1	B lymphoma Mo-MLV insertion region 1 homolog
BOR	Best overall response
BP	Blood pressure
BTK	Bruton's tyrosine kinase
BUN	Blood urea nitrogen
CCND1	Oncogene that encodes cyclin D1 protein
CDK	Cyclin D-dependent kinase
CERT	Center for Education and Research on Therapeutics
CFDA	China Food and Drug Administration
CHK2	Checkpoint kinase 2
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	Confidence interval
CL	Total apparent clearance of the drug from plasma
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration

CMR	Complete molecular remission
CNS	Central nervous system
CR	Complete response
CRO	Contract research organization
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CYP3A	Cytochrome P450, family 3, subfamily A
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epithelial growth factor receptor
eGRF	Estimated glomerular filtration rate
EOT	End of treatment
F	Bioavailability (systemic availability of the administered dose)
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FGR	Garden-Rasheed feline sarcoma viral (v-fgr) oncogene homolog
FFPE	Formalin-fixed, paraffin-embedded
FL	Follicular lymphoma
FRK	fyn-related kinase
GCP	Good Clinical Practice
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High density lipoprotein
HDPE	High density polyethylene
HER	Human epidermal growth factor receptor

HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	50% maximum inhibitory concentration
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IND	Investigational new drug
INK4a	Inhibitor of kinase 4a
INR	International normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
ITK	Interleukin-2-inducible T cell kinase
IV	intravenous
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
JAK3	Janus kinase 3
KM	Kaplan-Meier
LCK	Lymphocyte-specific protein tyrosine kinase
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LVEF	Left ventricular ejection fraction
MCL	Mantle cell lymphoma
MDRD	Modification of Diet in Renal Disease
MedDRA®	Medical Dictionary for Regulatory Activities
MIPI	Mantle Cell Lymphoma International Prognostic Index
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NHL	Non-Hodgkin's lymphoma
nM	nanomolar
NTI	Narrow therapeutic index
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival

PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PI3K	Phosphatidylinositol 3-kinase
PK	Pharmacokinetics
PLCβ2	Phospholipase C-beta-2
PLT	Platelet
PO	Per os (orally)
PP	Per-protocol
PR	Partial response
PT	Preferred term or prothrombin time
QD	Once daily
QT	Interval between the beginning of the QRS complex to the end of the T wave
QTcF	Interval between the beginning of the QRS complex to the end of the T wave as corrected by corrected for heart rate using Fridericia's method
RB1	Retinoblastoma 1
RBC	Red blood cell
R-CHOP	Rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)
RNA	Ribonucleic acid
R/R	Relapsed or refractory
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Stable disease
SLL	Small lymphocytic lymphoma
SMC	Safety Monitoring Committee
SOC	System organ class
SOP	Standard operating procedure
SYK	Spleen tyrosine kinase
TEAE	Treatment-emergent adverse event
TEC	Tyrosine kinase expressed in hepatocellular carcinoma
TMD8	A DLBCL cell line

TTR	Time to response
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WM	Waldenström's macroglobulinemia
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

1.1 Current Status of Mantle Cell Lymphoma Care

Mantle cell lymphoma (MCL) is diagnosed in 0.51-0.55/100,000 persons per year in the United States (US), making up 6% of all non-Hodgkin's lymphoma (NHL); while the incidence is slightly lower in China. This translates into approximately 4,500 new patients each year, similar to global incidence (Smedbya, 2011; Wang, 2015). MCL is a cancer of older persons with a median age at diagnosis of approximately 60 years with a male preponderance (Barista, 2001; Smedbya, 2011). Patients often present with advanced disease; 70% are diagnosed in stage IV. Most commonly, there is generalized lymphadenopathy and organomegaly. Approximately 10-20% of patients present with bone marrow involvement, and B symptoms (fever, night sweats, and weight loss) are present in approximately 40% of patients. Extra-nodal involvement of the gastrointestinal tract, particularly the colon, is relatively common. Central nervous system (CNS) involvement is uncommon (Skarbnik, 2015).

The pathognomonic feature of MCL is over expression of cyclin D1, which is a consequence of juxtaposition of the proto-oncogene CCND1 on chromosome 11q13 to the immunoglobulin (Ig) heavy chain gene at chromosome 14q32. Cyclin D1 can be confirmed by immunohistochemistry in almost 100% of specimens. The molecular consequence of cyclin D1 over-expression is deregulation of cell cycle control by overcoming the suppressor effect of the retinoblastoma 1 (RB1) and the cell cycle inhibitor p27. Frequent companion anomalies include secondary chromosomal and molecular alterations targeting proteins that regulate the cell cycle and senescence (B lymphoma Mo-MLV insertion region 1 homolog (BMI1), inhibitor of kinase 4a (INK4a), alternate reading frame (ARF), cyclin D-dependent kinase (CDK)4, and RB1), and interfere with the cellular response to deoxyribonucleic acid (DNA) damage (ataxia telangiectasia mutated (ATM), checkpoint kinase 2 (CHK2) and p53) (Rickert, 2013). Concomitantly, β2 microglobulin and lactate dehydrogenase (LDH) are increased by 56% and 45%, respectively, of patients; these markers should be monitored for disease activity and are also prognostic.

The Mantle Cell Lymphoma International Prognostic Index (MIPI) composites the parameters of the Eastern Cooperative Oncology Group (ECOG) performance status, age, leukocyte count, and LDH, and classifies patients into low, intermediate, and high risk groups, with corresponding median overall survival time of 6 years, 51 months, and 29 months, respectively (Vose, 2013). The histological pattern of MCL is also prognostic, with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) complete response (CR) rates for mantle-zone/nodular/diffuse patterns of

73%, 25%, and 19%, respectively, and 3-year survival rates of 100%, 50%, and 55%, respectively (Barista, 2001). Another prognostic factor is the Ki-67 expression; 60% of patients have over 10% of their tumors staining positive for Ki-67, with highly proliferative cases showing a much poorer outcome than tumors with low proliferation.

Management of MCL has been with chemo-immunotherapeutic combinations, most commonly rituximab-CHOP (R-CHOP) combinations that result in high response rates. Duration of response (DOR) ranges from 18 to 30 months, but patients invariably relapse. Younger, fit patients have the option of chemotherapy containing middle and high dose of cytarabine, followed by stem cell transplantation, with improved outcome. In the past few years, targeting the B-cell receptor through Bruton's tyrosine kinase (BTK) and phosphatidylinositol 3-kinase (PI3K) inhibition has opened up a new era of B-cell malignancy control.

Treatment with BTK inhibitors can incur transient increase in lymphocytes in over 70-97% of chronic lymphocytic leukemia (CLL) and 40-70% of MCL patients. ALCs generally peak around 4-8 weeks, and take 4-8 months to return to baseline (Tam, 2015). This transient lymphocytosis is generally asymptomatic, requires no medical management and drug therapy, and does not signify progressive disease (PD), so treatment with the B cell inhibitors should be continued.

1.2 BGB-3111

BGB-3111 is a novel second generation small molecule oral BTK inhibitor, which forms an irreversible covalent bond at Cys481 within the adenosine triphosphate (ATP) binding pocket of the BTK protein. BGB-3111 is highly potent against BTK; however, as opposed to ibrutinib, BGB-3111 has significantly less epithelial growth factor receptor (EGFR)/Janus kinase 3 (JAK3)/tyrosine kinase expressed in hepatocellular carcinoma (TEC)/interleukin-2-inducible T cell kinase (ITK) inhibitory activity, thus potentially reducing the side effects seen with ibrutinib and allowing increased exposure which may translate into improved efficacy (NCCN, 2016; Smith, 2015).

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2 OBJECTIVES

2.1 Primary Objective

To evaluate the efficacy of BGB-3111 at a dose of 160 mg orally (PO) twice daily in subjects with centrally confirmed relapsed or refractory mantle cell lymphoma as measured by overall response rate (ORR) assessed by an Independent Review Committee (IRC) in accordance with the 2014 modification of the International Working Group on NHL Criteria (Cheson, 2014).

2.2 Secondary Objectives

- To evaluate the efficacy of BGB-3111 as measured by progression-free survival (PFS), time to response (TTR), and duration of response (DOR) by IRC.
- To evaluate the efficacy of BGB-3111 by investigator as measured by overall response rate.
- To evaluate the safety and tolerability of BGB-3111 in subjects with relapsed or refractory MCL

CCI [redacted]

- CCI [redacted]

[redacted]

[redacted]

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint of the study is the rate of objective response, defined as the achievement of either a partial response (PR) or CR as assessed by the IRC according to the 2014 modification of the International Working Group on NHL Criteria (Cheson, 2014) (Appendix 3) at any time on study drug.

3.2 Secondary Endpoints

Efficacy (using response assessment as determined by IRC)

- Progression-free survival (PFS) as assessed by the IRC in subjects with relapsed or refractory MCL after administration of BGB-3111: defined as time from treatment initiation to documentation of progression or death due to any cause, whichever happens first

- TTR as assessed by the IRC in subjects with relapsed or refractory MCL after administration of BGB-3111: defined as the time from treatment initiation to the first documentation of response
- DOR as assessed by the IRC in subjects with relapsed or refractory MCL after administration of BGB-3111: defined as the time from the first response documentation to the date that PD is documented after treatment initiation
- ORR as assessed by the investigator: defined as the achievement of either a PR or CR as assessed by the Investigator at any time on study drug.

Safety

- Incidence, time and severity of treatment-emergent adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version (v)4.03 (NCI, 2010).
- Incidence, severity, time and causation of adverse events leading to study drug discontinuation.

3.3 Exploratory Endpoints

- CCI [redacted]

3.4 Rationale for Endpoint Selection

Efficacy: The proposed endpoints have been chosen based on relevant pathophysiology and clinical manifestations of mantle cell lymphoma, and the known pharmacology of BGB-3111 as a BTK inhibitor. The objective of this study is to exemplify the benefit/risk ratio of BGB-3111. All of the endpoints have been explored in prior studies of mantle cell lymphoma treatment, and data derived from this Phase 2 trial can be compared with historical data with acceptable reliability and accuracy.

Safety and tolerability: Small molecules TKIs have been known to induce QT prolongation but BGB-3111 did not incur any such toxicity in its first 171 subjects enrolled in the Phase 1 study in Australia; however, continued vigilance is necessary. Off target inhibition caused impaired platelet function and bleeding is another adverse event of special interest. In addition, the hematological toxicity with Grade 3/4 neutropenia and infection needs to be documented.

4 STUDY DESIGN

4.1 Summary of Study Design

This is a single-arm, open-label, multi-center Phase 2 study in subjects with histologically documented MCL who have no response or relapse after ≥ 1 but < 5 prior treatment regimen(s). The study is composed of an initial screening phase (up to 28 days), a single-arm treatment phase, and a follow-up phase. Subjects who have not progressed at the time of the final analysis and/or study closure, or subjects who had PD but are still benefitting from BGB-3111 treatment in the assessment of the investigator, will be considered to participate in the extension study for continued treatment upon approval from the sponsor.

Approximately 80 subjects will be enrolled. The primary efficacy analysis will be conducted at mature data of overall response rate, no later than 12 months after the last subject received the first dose of study drug, and final analysis will be conducted at mature data of secondary endpoints. For the primary efficacy analysis, response will be evaluated by an IRC based on central imaging using the 2014 modification of the International Working Group on NHL Criteria (Cheson, 2014) (Appendix 3). All subjects should undergo positron emission tomography (PET) and contrast computerized tomography (CT) at screening. For patients with avid PET diseases at screening, PET and contrast CT should be repeated every 12 weeks for the first 96 weeks, and every 24 weeks thereafter until disease progression or end of study, whichever comes first. For subjects with non-avid PET diseases at screening, only contrast CT should be performed every 12 weeks for the first 96 weeks, and every 24 weeks thereafter until disease progression or end of study, whichever comes first. The PET and contrast CT are required for confirmation of CR for all subjects. Endoscopy is mandatory to confirm CR for any subject with a documented history of gastrointestinal involvement. Bone marrow biopsy will be required for confirmation of CR in subjects with bone marrow tumor involvement prior to study drug.

All subjects will be followed for adverse events (AEs) for 30 additional days after the last dose of study drug. All treatment-related AEs and SAEs will be followed until resolution or stabilization.

Screening phase: Screening evaluations will be performed within 28 days prior to the first dose of study drug. Subjects will sign the informed consent form prior to any screening evaluations. Please refer to Table 2 for details on screening procedures. Screening evaluations can be repeated within the screening period.

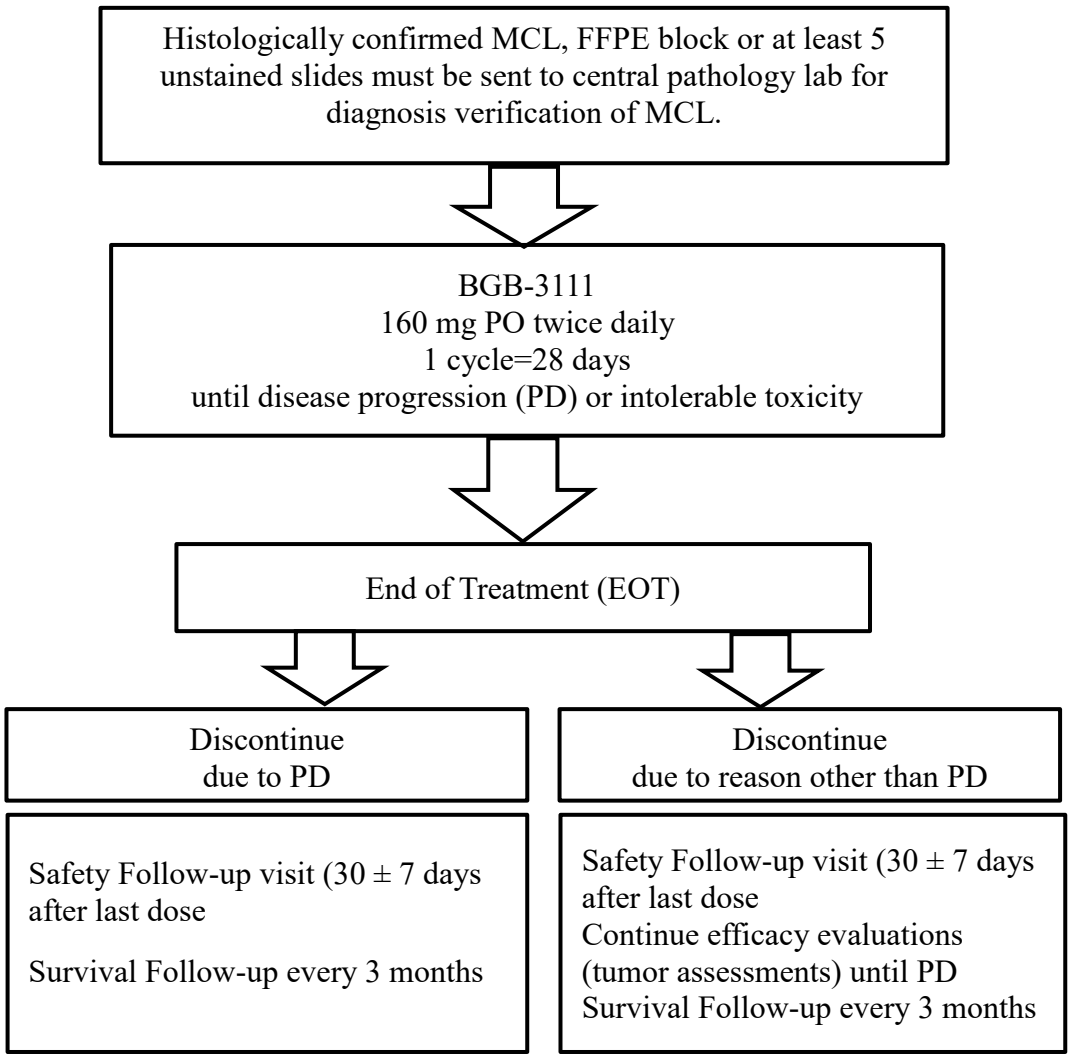
Treatment phase: Subjects will receive the first dose of BGB-3111 at Cycle 1 Day 1. All subjects

will be treated with 160 mg, administered orally, twice daily and will continue to be treated until disease progression, unacceptable toxicity, death, withdrawal of consent, or the study is terminated by the sponsor for final analysis. A treatment cycle consists of 28 days.

Follow-up phase: Subjects will return 30 ± 7 days after the last dose of study drug for safety follow-up visit. Assessments to be performed are presented in Table 2. Radiological assessments will continue until documented disease progression. If a subject discontinues study drug due to reasons other than PD, radiological assessments will continue until subject exhibits first progression, withdrawal of consent, death, lost to follow-up, or study termination by sponsor, whichever occurs first.

Survival phase: Subjects will be followed for survival via phone contact (with subject's guardian, if applicable) every 3 months after the subject's last visit until withdrawal of consent, lost to follow-up, death, or the date of data cutoff for the final analysis.

Figure 1 Schema for Study BGB-3111-206



Abbreviations: EOT, end of treatment; FFPE, formalin-fixed, paraffin-embedded (tumor tissue); MCL, mangle cell lymphoma; PD, progressive disease

5 STUDY POPULATION

5.1 Inclusion Criteria

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

1. Diagnostic report has to include evidence for morphological and cyclin D1 and B cell markers (eg, CD19, CD20, or PAX5) and CD5 co-expression or t (11; 14). The above results are detected by immunohistochemistry, cytogenetics or fluorescence in situ hybridization (FISH). After enrollment, tumor tissue (formalin-fixed, paraffin-embedded [FFPE]) block or unstained slides must be sent to central laboratory for immunohistochemical analysis to confirm MCL. The block or slides must have been obtained from within 2 years before treatment is to be started or, if not, must have been first sent to the central laboratory for confirmation of appropriateness for use for pathology examination and diagnosis.
2. Men and women, 18-75 years of age.
3. ECOG performance status of 0-2.
4. Measurable disease by CT/magnetic resonance imaging (MRI). Measurable disease is defined as at least one lymph node > 1.5 cm in longest diameter and measurable in 2 perpendicular dimensions.
5. Received at least one but less than five prior regimens for MCL ($1 \leq$ the number of prior regimens < 5).
6. Documented failure to achieve any response, [stable disease (SD) or progressive disease during treatment] or documented progressive disease after response to the most recent treatment regimen.
7. Neutrophils $\geq 1 \times 10^9$/L independent of growth factor support within 7 days of study entry.
8. Platelets $\geq 75 \times 10^9$/L independent of growth factor support or transfusion within 7 days of study entry (Platelets $\geq 50 \times 10^9$/L with bone marrow involvement).
9. Creatinine clearance of ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation or estimated glomerular filtration rate [eGFR] from the Modification of Diet in Renal Disease [MDRD]).
10. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ upper limit of normal (ULN).
11. Total bilirubin $\leq 2 \times$ ULN (unless documented Gilbert's syndrome).

12. International normalized ratio (INR) ≤ 1.5 and activated partial thromboplastin time (APTT) ≤ 1.5 × ULN. If a factor inhibitor is present with prolongation of the INR or APTT, a patient may be enrolled after consultation with the medical monitor.
13. Subjects may be enrolled who relapse at least 6 months after autologous stem cell transplant. To be eligible after transplant, subjects should have no active related infections.
14. Females of childbearing potential must agree to use highly effective forms of birth control throughout the course of the study and at least up to 90 days after last dose of study drug. Highly effective forms of birth control include abstinence, hysterectomy, bilateral oophorectomy with no menstrual bleeding for 6 months, intrauterine contraception, hormonal methods such as contraceptive injection, oral contraceptive, etc. Males must have undergone sterilization–vasectomy, or utilize a barrier method while the female partner utilizes the effective forms of birth control noted above.
15. Life expectancy of > 4 months.
16. Able to provide written informed consent and can understand and comply with the requirements of the study.

5.2 Exclusion Criteria

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

1. Current or history of CNS lymphoma.
2. Prior exposure to a BTK inhibitor before enrollment.
3. Prior corticosteroids in excess of prednisone 10 mg/day or its equivalent with antineoplastic intent within 7 days of the start of study drug. Prior chemotherapy, targeted therapy, or radiation therapy within 3 weeks, antineoplastic therapy with Chinese herbal medication or antibody-based therapies within 4 weeks of the start of study drug.
4. Major surgery within 4 weeks of screening.
5. Toxicity must recover to ≤ Grade 1 from prior chemotherapy (except for alopecia, absolute neutrophil count (ANC), and platelet count). Please refer to Inclusion Criteria 7 and 8 for ANC and platelet count, respectively),
6. History of other active malignancies within 2 years of study entry, with the exception of (1) adequately treated in-situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy controlled and treated locally (surgery or other modality) with curative intent.

7. Currently clinically significant active cardiovascular disease such as uncontrolled arrhythmia, uncontrolled hypertension, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association (NYHA) Functional Classification (Appendix 7), or history of myocardial infarction within 6 months of screening. Echocardiogram (ECHO) must demonstrate left ventricular ejection fraction (LVEF) less than 50% (AHA, 2017).

8. QTcF > 450 msecs or other significant ECG abnormalities including second degree atrioventricular (AV) block Type II, or third degree AV block.

9. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.

10. Active infection including infections requiring oral or intravenous antimicrobial therapy.

11. Known infection with human immunodeficiency virus (HIV), or serologic status reflecting active hepatitis B or hepatitis C infection as follows.

	Inclusion		Exclusion	
HIV	Antibody (-)		Antibody(+)	
HBV	HBsAg (-) and HBcAb (-)		HBsAg (+)	
	HBsAg (-) and HBcAb (+)	HBV DNA < 1000 IU/mL and anti-viral therapy during study treatment and perform monthly monitoring of HBV DNA	HBsAg(-) and HBcAb (+)	HBV DNA≥1000 IU/ml
HCV	Antibody (-) or Antibody (+)	HCV RNA "Not detected" (<15 IU/mL) Perform monthly monitoring of HCV RNA	Antibody(+)	HCV RNA Detected

Abbreviations: HBcAb; hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV; hepatitis C virus; HIV, human immunodeficiency virus

12. Pregnant or lactating women.

13. Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, or put the study at risk.

14. Inability to comply with study procedures.

15. Requires ongoing treatment with medications that are strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors or strong CYP3A inducers.

16. Has received allogenic hematopoietic stem cell transplantation prior to enrollment.

6 STUDY TREATMENT

6.1 Study Treatment

Subjects will receive BGB-3111 160 mg (two 80-mg white opaque capsules) orally twice daily. It is recommended that the capsules be taken approximately 12 hours apart, ± a 2-hour time window. The capsules should be swallowed whole with a glass of water. The capsules should not be chewed, but in case of breakage, additional water should be imbibed to rinse out the mouth.

6.2 Study Treatment Preparation and Dispensation

6.2.1 Packaging and Labeling

The capsules of BGB-3111 will be provided in a child-resistant high density polyethylene (HDPE) bottle with induction seal and bottle label. The label will include at least space to enter the subject number, name of investigator, content and quantity of BGB-3111, protocol number, batch number, directions for usage, storage conditions, and precautions.

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

6.2.2 Handling and Storage

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.

Study drug must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or administer study drug. 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 drug must be kept at the condition as specified on the labels, or according to the current IB.

6.2.3 Compliance and Accountability

Compliance will be assessed by the investigator and/or study personnel at each subject visit and information provided by the subject and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each subject visit.

The investigator is responsible for study drug accountability, reconciliation, and record

maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain study drug accountability records throughout the course of the study. This person will document the amount of study drug received from the sponsor, the amount supplied, and/or administered to and returned by subjects (if applicable).

6.2.4 Disposal and Destruction

After completion of the study, all unused BGB-3111 will be inventoried and packaged for return shipment by the hospital pharmacist or other designated study center personnel. The inventoried supplies will be returned to the sponsor or destroyed on site or depot, after receiving written sponsor approval.

6.3 Subject Number and Treatment Assignment

6.3.1 Subject Number

Subjects will be identified by subject number. Each subject enrolled in this study will receive a unique subject number which will be assigned when the subject is screened or enrolled in the study. Subject will be assigned in chronological order starting with the lowest number. Once a subject number has been assigned to a subject, it cannot be reassigned to any other subject. Subject can be re-screened if the subject did not previously meet the inclusion and exclusion criteria. Re-screening is defined as repeating the screening procedures or tests within the original screening window. A new informed consent is not required and subject shall maintain the same subject number as originally assigned.

6.3.2 Treatment Assignment

All subjects in the study will receive BGB-3111.

6.3.3 Treatment Blinding

This is an open-label study.

6.4 Dosage and Administration

BGB-3111 will be dispensed by the study center personnel on Day 1 of each cycle (every 4 weeks) during the first year and Day 1 of every other cycle thereafter (every 8 weeks starting on Cycle 13). Subjects will be provided with an adequate supply of study drug for self-administration at home. The investigator should instruct the subject to take the study drug exactly as prescribed. Subjects will be requested to bring their unused medication including empty packaging to the center at each

visit. All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the appropriate electronic case report form (eCRF).

Subjects are highly recommended to take 160 mg (two 80-mg capsules) with water at the same time every day, twice daily. BGB-3111 will be taken daily from Cycle 1 Day 1 until disease progression, unacceptable toxicity or death, withdrawal of consent, or the study is terminated by the sponsor for final analysis.

CCI [redacted].

Subjects will be advised that if a dose of the study drug is not taken at the scheduled time, they should take the missed dose as soon as they remember and return to the normal schedule for the next dose. Subjects should skip the missed dose if it is less than 4 hours to the next scheduled dose. An extra dose of the study drug should not be taken to make up for the missed dose.

CCI [redacted]

CCI [redacted]

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

CCI [redacted]	[redacted]	[redacted]	[redacted]
			[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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6.7.1 Discontinuation of Treatment

Subjects may discontinue study drug for one of the following reasons:

- Death
- Disease progression
- Unmanageable and unacceptable toxicity attributed to BGB-3111
- Pregnancy
- Subject misses > 28 consecutive days of dosing.
- Subject withdrew consent, permitted at any time during the trial.

All subjects who discontinue study drug will have a safety follow-up visit 30 ± 7 days after the last dose of study drug to collect AEs and SAEs that may have occurred after the subject discontinued from the treatment. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug. A laboratory assessment will only be performed if the subject had an ongoing laboratory abnormality at the previous visit which the investigator considered to be related to study drug. If the subject is unable to return to the clinic and no laboratory assessment is necessary, the investigator or his/her designee will contact the subject or caregiver to collect this information.

Subjects who are discontinued from study drug for any reason (ie, AE or administrative reasons etc.) other than disease progression should not be considered withdrawn from the study. They will continue to be followed for efficacy evaluations per schedule outlined in Table 2 until subject exhibits first progression, withdrawal of consent, death, lost to follow-up, or study termination from sponsor, whichever occurs first. If subjects refuse to return for these visits or are unable to do so, every effort should be made to contact them or obtain information by telephone to determine the subject's disease status and survival.

6.7.2 Premature Withdrawal

Subjects will be withdrawn from the study prematurely for one of the following reasons:

- Study termination by sponsor
- Significant protocol deviation
- Lost to follow up

If the subject is lost to follow up, investigators should try best to contact with the patient to determine the reason for withdrawal. The information should be recorded in the source document and eCRF.

Subjects may voluntarily withdraw from the study (ie, withdraw consent) or withdrawn at the discretion of the investigator at any time. Subjects lost to follow up should also be recorded on the CRF. For subjects who are lost to follow-up, the investigator should show “due diligence” by documenting in the source documents steps taken to contact the subject, eg, dates of telephone calls, registered letters, etc.

7 STUDY ASSESSMENTS

7.1 Study Flow and Visit Schedule

The study-specific assessments and procedures are shown in Table 2. Pharmacokinetics and specimen collection are shown in Table 3.

Table 2 Study Assessments and Procedures Schedule for Study BGB-3111-206

	Pre-treatment	Treatment All Cycles Are 28 Days (4 Weeks) in Duration				End of Study Assessments		
	Screening[1]	Cycle 1	Cycle 2	Cycle 3 to Cycle 13 (Every 4 Weeks)	Cycle 15, Cycle 17, Cycle 19, etc… (Every 8 Weeks)	EOT	Safety Follow-up Visit	Survival Follow-up
Day of cycle	**-28 to -1**	**Day 1**	**Day 1 (± 4 Days)**	**Day 1 (± 4 days)**	**Day 1 (± 7 Days)**	**(Within 7 Days After Stopping Treatment)**	**30 ± 7 Days After Last Dose of Study Drug**	**Every 3 Months (± 7 Days)**
Visit	0	1	2	3, 4, 5, etc.…				
Informed consent	X [2]							
Inclusion/exclusion criteria	X [3]							
Demography	X [4]							
Medical/surgical history/current medical conditions	X [5]							
Diagnosis and status of disease	X [6]							
Prior antineoplastic therapy	X							
12-lead ECG [7]	X	X	X			X		
Lipid panel	X [8]							
Tumor tissue sample [9]	X							
ECOG performance status	X	X	X	X	X	X	X	
Height (cm)	X							
Weight (kg)	X	X	X	X	X	X	X	
Vital signs and physical examination (including assessment of B symptoms and liver and spleen enlargement)	X [10]	X	X	X	X	X	X	
Hematology [11]	X	X	X	X	X	X		
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Coagulation [11]	X	X						

	Pre-treatment	Treatment All Cycles Are 28 Days (4 Weeks) in Duration				End of Study Assessments		
	Screening[1]	Cycle 1	Cycle 2	Cycle 3 to Cycle 13 (Every 4 Weeks)	Cycle 15, Cycle 17, Cycle 19, etc… (Every 8 Weeks)	EOT	Safety Follow-up Visit	Survival Follow-up
Day of cycle	**-28 to -1**	**Day 1**	**Day 1 (± 4 Days)**	**Day 1 (± 4 days)**	**Day 1 (± 7 Days)**	**(Within 7 Days After Stopping Treatment)**	**30 ± 7 Days After Last Dose of Study Drug**	**Every 3 Months (± 7 Days)**
CCI								
CCI								
Hepatitis B/C testing and HIV testing [11]	X							
CCI								
CCI								
Study drug administration [13]		X	X	X	X			
Bone marrow biopsy/aspiration [14]	X	At time of CR						
Endoscopy [15]		At time of CR						
Echocardiogram [16]	X							
Radiological test [17]								
CT scan with contrast of neck/chest/abdomen and pelvis (or MRI)	X	Weeks 12, 24, 36, 48, 60, 72, 84 and 96, then every 24 weeks thereafter, and at CR						
PET scan	X	Weeks 12, 24, 36, 48, 60, 72, 84 and 96, then every 24 weeks thereafter, and at CR						
Brain CT/MRI scan with contrast	As clinically indicated							
Concomitant medications	Throughout the study							
AE/SAE	Throughout the study [18]							
Antineoplastic therapies since discontinuation of study drug							X	X
CCI								

	Pre-treatment	Treatment All Cycles Are 28 Days (4 Weeks) in Duration				End of Study Assessments		
	Screening[1]	Cycle 1	Cycle 2	Cycle 3 to Cycle 13 (Every 4 Weeks)	Cycle 15, Cycle 17, Cycle 19, etc… (Every 8 Weeks)	EOT	Safety Follow-up Visit	Survival Follow-up
Day of cycle	-28 to -1	Day 1	Day 1 (± 4 Days)	Day 1 (± 4 days)	Day 1 (± 7 Days)	(Within 7 Days After Stopping Treatment)	30 ± 7 Days After Last Dose of Study Drug	Every 3 Months (± 7 Days)

Abbreviations: AE, adverse event; APTT, activated partial thromboplastin time; CR, complete response; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EOT, End of Treatment; HBcAb; hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; Ig, immunoglobulin; IHC, immunohistochemistry; IV, intravenous; MCL, mantle cell lymphoma; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PET, positron emission tomography; PK, pharmacokinetic; SAE, serious adverse event

Time windows: Assessment shall be completed in designated date; if it cannot be fulfilled due to weekends, holidays or emergency, assessment shall be completed in the scheduled time windows, including ECOG, weight, vital signs, physical examination (including B symptoms), hematology, clinical chemistry, lipid panel, urinalysis, serum Ig, concomitant medications, AE/SAE, pregnancy test, pharmacokinetics, and study drug administration.
Assessments scheduled on Cycle 1 Day 1 should be performed prior to the administration of the first dose of BGB-3111. Screening blood and urine tests performed within 72 hours of the first administration of study drug do not need to be repeated on Cycle 1 Day 1.

1. Screening evaluations will be performed and completed within 28 days prior to the first dose of BGB-3111. Bone marrow aspirate/biopsy is allowed to be completed within 60 days prior to first dose. The results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to the Cycle 1 Day 1.
2. Written informed consent form(s) must be signed by the subject before any study-specific procedures are performed.
3. The investigator will review and ensure that the subject meets all of the inclusion and none of the exclusion criteria.
4. Demography includes gender and date of birth (or age).
5. Relevant medical history (ie, previous diagnoses, diseases or surgeries) not pertaining to the study indication, started before signing the informed consent, and considered relevant for the subject's study eligibility, and current medical conditions.
6. Diagnosis and extent of cancer. Subjects with confirmed MCL are required to provide diagnostic report, which has to include evidence of morphological and cyclin D1 or t (11; 14). After enrollment, other background information including history of disease and current disease status, staging, bone marrow involvement, sites of disease, prior anticancer therapies, and prior medications/significant non-drug therapies will be collected.
7. Perform a 12-lead ECG in triplicate at following time points: screening and end of treatment. CCI [redacted] Subjects should be in the

semi-recumbent or supine position.

8. Lipid panel includes cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides performed at screening only.
9. All subjects must provide at least 5 unstained slides or tumor tissue (may be newly collected sample or past biopsy specimen from within 2 years before starting treatment) and send to central pathological laboratory for immunohistochemical analysis (including but not limited to Cyclin D1 and Ki-67), and to conduct central pathological diagnosis of MCL. If the archived sample is not from within 2 years of starting treatment, it should be first sent to the central pathology laboratory to confirm it is appropriate for it to be used for pathology examination and diagnosis. Furthermore, upon approval of subject, past tumor tissue or newly collected sample (within 2 years of starting treatment) will be collected for biomarkers analyses. Either a formalin-fixed paraffin-embedded block with tumor tissue or at least 5 unstained slides should be sent to the central laboratory for biomarker analysis, including but not limited to IGVH and TP53.
10. A complete or targeted physical examination, vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, temperature, and respiratory rate), weight, and B symptoms examination will be performed at the time points specified. Complete physical examination includes assessments of cardiovascular, respiratory, abdominal and neurological systems as well as lymph nodes /spleen, skin, oropharynx, and extremities. Targeted physical examinations should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymph nodes, liver, and spleen), and those systems associated with clinical signs/symptoms. Clinical suspicion of disease progression at any time will require a physical examination to be performed promptly, rather than waiting for the next scheduled radiological assessment. B symptoms includes unexplained weight loss > 10% over previous 6 months, fever (> 38°C), and/or drenching night sweats. If the physical examination is not completed ± 7 days of the radiological tumor assessment, a separate physical examination should be performed.
11. CCI

CCI [redacted]

13. Subjects will receive BGB-3111 at a dosage of 160 mg (two 80-mg white opaque capsules) orally twice daily. BGB-3111 will be administered on a 28-day cycle and will continue for until disease progression, unacceptable toxicity, death, withdrawal of consent, or discontinuation from the study for any reason. All subjects will have an end of treatment (EOT) visit within 7 days after stopping study drug. All subjects will have a follow-up visit 30 ± 7 days after the last dose of the study drug to collect AE and SAE that may have occurred after the subject discontinued from the study. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug.
14. A bone marrow aspiration and biopsy (cytology and IHC) will be performed at screening for all subjects. Bone marrow assessment is allowed to be conducted within 60 days prior to the first dose of BGB-3111. In those subjects who had evidence of bone marrow disease at the time of enrollment, upon achieving a possible CR (eg, physical examination or CT scan indicating a possible CR), a bone marrow aspirate and biopsy will be obtained to confirm the CR.
15. Gastrointestinal endoscopy must be performed to confirm CR for any subject with a documented history of gastrointestinal involvement.
16. Cardiac ECHO to evaluate cardiac function; left ventricular ejection fraction must be ≥50%, investigation up to 30 days before enrollment acceptable
17. CT scans should encompass neck, chest, abdomen, and pelvis and include oral and IV contrast. A brain scan is required if clinically indicated. In all cases, an MRI may be used in place of CT only for anatomic lesions which cannot be adequately visualized by CT, or for subjects who cannot undergo CT. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is kept constant throughout a subject's course on study. Tumor response will be assessed according to 2014 modification of the International Working Group on Non-Hodgkin's lymphoma (NHL) Criteria (Cheson, 2014) (Appendix 3). The screening CT scan may be conducted within 30 days prior to the first dose of BGB-3111. Tumor assessment by PET and contrast CT scan will occur every 12 weeks for first 96 weeks (if in special case, time window for first 48-week CT scan can be expanded to ± 1 week), and then every 24 weeks ± 1 week thereafter until disease progression or end of study, whichever comes first. All subjects should have PET and contrast CT on screening. In subjects with PET-avid disease, a PET will be repeated at the same timepoints as CT scans and complete response should be confirmed by PET scan or an integrated PET/CT. Unscheduled response assessments may be performed based on physical examination or laboratory findings, at the discretion of the investigator. Results of PET and contrast CT scan in 30 days prior to first dose can be used for assessment on screening. Clinical suspicion of disease progression at any time will require radiological confirmation to be performed promptly, rather than waiting for the next scheduled radiological assessment. As far as possible, radiological confirmation is encouraged for any visible or palpable lesions by physical examination. De-identified copies of all scans and radiology reports (including those from screening) must be provided to the Sponsor or designee (eg, central imaging vendor). NOTE: PET/CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality, adheres to the specified slice thickness/scan parameters, and includes the use of IV contrast. Also, the CT images must be separated from the PET data prior to submitting the data, and cannot be transmitted as fused CT/PET images. If using a hybrid machine to acquire both PET and CT, the PET must be performed prior to the CT with IV contrast as to not compromise PET results. If independent CT and PET scanners are used, and the subject is receiving both scans on the same day, the PET must be performed prior to the CT with IV contrast.
18. After informed consent has been signed but prior to the administration of the study drug, only SAEs will be reported. After initiation of study drug, all AEs and SAEs will be reported until 30 days after the last study treatment of BGB-3111. After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment.
19. CCI [redacted]

Table 3 Pharmacokinetics and Specimen Collection

Flow	Cycle 1 Day 1			Cycle 2 Day 1		
Hours	Pre-dose (-0.5)	2 (± 0.5)	4-6	Pre-dose (-0.5)	2 (± 0.5)	4-6
Vital signs	X[1]	X		X	X	
ECG	X[1]	X		X	X	
CCI						

Caution: CCI

Abbreviations: AE, adverse event; DDI, drug-drug interaction; DLT, dose-limiting toxicity; ECG, electrocardiogram; min, minutes; PK, pharmacokinetic.

7.2 Subject Demographics/Other Baseline Characteristics

7.2.1 Demography

Demographic data will include gender, date of birth (or age).

7.2.2 Medical History

Medical history findings (ie, previous diagnoses, diseases or surgeries) not pertaining to the study indication, started before signing the informed consent, and considered relevant for the subject's study eligibility will be collected and captured in the eCRF.

7.2.3 Other Baseline Characteristics

Other background information including history of disease and current disease status, staging (Table 4), bone marrow involvement, sites of disease, prior anticancer therapies, and prior medications/ significant non-drug therapies will be collected.

Combined biologic MCL International Prognostic Index (MIPI-b) will be calculated based on the

baseline values, age, ECOG, lactate dehydrogenase (LDH) as quotient to the upper limit of normal, and the WBC count per 10^{-6}L, and the percentage of Ki-67 positive cells based on local pathology report (Hoster, 2008; Hoster, 2014). If Ki-67 is not available, MCL International Prognostic Index (MIPI) will be used.

MIPI-b score will be calculated according to the following formula:

> MIPI-b score = 0.03535 x age (years) + 0.6978 (if ECOG > 1, otherwise 0) + 1.367 × $\log_{10}$ (LDH/upper limit of normal) + 0.9393 × $\log_{10}$ (WBC count per 10^{-6}L) + 0.02142 x Ki-67 (%)

MIPI score will be calculated according to the following formula if Ki-67 is not available:

> MIPI score = 0.03535 x age (years) + 0.6978 (if ECOG > 1, otherwise 0) + 1.367 × $\log_{10}$ (LDH/upper limit of normal) + 0.9393 × $\log_{10}$ (WBC count per 10^{-6}L)

Information will also be collected regarding child-bearing potential and any other assessments that are done for the purpose of eligibility for inclusion into the study (physical examination, vital signs, hematology and blood chemistry, urinalysis, pregnancy test, and ECG). For further details on eligibility assessments, please see Table 2.

Table 4 Revised Ann Arbor Staging Classification

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	Stage II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Cheson, 2014

7.3 Efficacy

Responses and disease progressions will be evaluated centrally by the IRC and locally by site investigators using the 2014 International Working Group in NHL criteria (Appendix 3).

Clinical evaluation and tumor assessments will be performed periodically, as is indicated in Table 2, based on physical examination, radiological assessment and bone marrow aspirate/biopsy (to confirm complete responses in subjects with bone marrow tumor involvement prior to study drug). For the first 96 weeks of study drug, tumor assessments will be performed every 12 weeks ± 1 week, then every 24 weeks ± 1 week thereafter. Clinical suspicion of disease progression at any time will require a physical examination and radiological confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment. As far as possible, radiological confirmation is encouraged for any visible or palpable lesions by physical examination. In case of an unscheduled or delayed tumor assessment for any reason, subsequent tumor assessments must be performed according to the originally planned schedule from baseline, ie, every 12 weeks ± 1 week from baseline during the first 96 weeks and every 24 weeks ± 1 week thereafter.

All patients should receive PET scan at screening. For subjects who had PET-avid disease at screening, PET scan should be repeated every 12 weeks ± 1 week during the first 96 weeks and

every 24 weeks ± 1 week thereafter, and complete response should be confirmed by PET scan or an integrated PET/CT.

In subjects with bone marrow tumor involvement prior to study drug, CR should be confirmed by bone marrow aspirate/biopsy. In subjects with documented gastrointestinal tumor involvement at screening, CR should be confirmed by endoscopy.

7.3.1 Physical Examination

Evaluation of disease related B symptoms (unexplained fever of ≥ 38°C; unexplained, recurrent drenching night sweats; or unexplained loss of > 10% body weight within the previous 6 months) and enlargement of liver and spleen is included in the physical examination at each visit. If the physical examination is not completed ± 7 days of the radiological tumor assessment, a separate physical examination should be performed.

7.3.2 Radiological Tumor Assessment

Baseline radiological tumor assessment should be performed within 30 days prior to the first dose.

All subjects must have CT scan with contrast of neck, chest, abdomen, and pelvis and any other disease sites. CT of the brain is only indicated if clinical findings or symptoms suggest CNS involvement.

For screening, all patients must undergo PET and contrast CT. For subjects with PET avid disease at screening, PET and contrast CT have to be repeated every 12 weeks for the first 96 weeks, and every 24 weeks thereafter, until PD or end of study, whichever comes first. For subjects without PET avid disease, contrast CT is to be repeated every 12 weeks for the first 96 weeks, and every 24 weeks thereafter, until there is PD according to the 2014 modification of the International Working Group on Non-NHL Criteria (Appendix 3) (Cheson, 2014). The Investigator can determine further subject management after confirmation of disease status by local radiologist.

A CT scan of diagnostic quality performed as part of PET/CT is acceptable, provided bi-dimensional nodal and liver/spleen measurements can be made. An MRI may be used in place of CT only for anatomic lesions which cannot be adequately visualized by CT, or for subjects who cannot undergo CT. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is kept constant throughout a subject's course on study.

All CT scans, MRIs, PET scans, and PET/CT scans obtained during the study will be collected and archived. De-identified copies of all scans and radiology reports (including those from screening) must be provided to the sponsor or designee (eg, central imaging vendor).

7.3.3 Bone Marrow Assessment

A unilateral bone marrow aspirate and biopsy (cytology and immunohistochemistry [IHC]) will be performed at screening within 60 days prior to the first dose for all subjects, provided there has been no intervening therapy between the time of the biopsy and start of study drug. In those subjects who had evidence of bone marrow disease at screening, upon achieving a possible CR (eg, physical examination or CT scan indicating a possible CR), a bone marrow aspirate and biopsy should be obtained to confirm the CR.

Testing will be performed at the study center's local laboratory. De-identified copies of all bone marrow biopsy/aspirate results must be provided to the sponsor or designee.

7.3.4 Endoscopy

Gastrointestinal endoscopy must be performed to confirm CR for any subject with a documented history of gastrointestinal involvement.

7.3.5 Missed Evaluations

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible unless it is too close in time to the next scheduled evaluation. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

7.4 Safety

Safety assessments should be performed at all visits to the study center and throughout the study. The list of events and the time when they will be performed are presented in Table 2.

7.4.1 Adverse Events

All AEs and SAEs, regardless of the relationship to the study drug, will be collected from the time of start of study drug. All subjects will be followed for safety 30 additional days after the last dose of study drug. All treatment-related AEs and SAEs will be followed until resolution or stabilization.

The accepted regulatory definition for an AE is provided in Section 9.1.1. In addition, SAEs will be reported after informed consent has been signed but prior to the administration of the study drug, and, after the 30 days after the last dose of study drug, the investigator should report any SAEs that are believed to be related to prior study drug treatment. Important additional requirements for reporting SAEs are explained in Section 9.9.

In this study, lymphocytosis will be defined as a ≥ 50% increase in lymphocyte count over baseline, and absolute lymphocytosis of ≥ 5×10^9/L, in addition, at least 1 disease parameter (including lymph node size, spleen size, hematological parameters [hemoglobin or platelet count]) shows significant concurrent improvement.

As a result of the known mechanism of action of BTK inhibitors, increase in lymphocyte count after using such drugs is predictable, and will occur with high frequency. In this study, asymptomatic lymphocytosis will not be recorded or reported as an adverse event (including increase in WBC caused by it), and will not impact further therapy with the BTK inhibitor.

In this study, asymptomatic treatment-related lymphocytosis not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study related procedures.

7.4.2 Physical Examination, Vital Signs, Height, and Weight

A complete or targeted physical examination, vital signs (sitting blood pressure, pulse rate, body temperature, and respiratory rate), weight, and B symptoms examination will be performed at each study visit. Height (cm) is determined at screening/baseline only. B symptoms include unexplained weight loss > 10% over previous 6 months, fever (> 38°C), and/or drenching night sweats.

A complete physical examination includes assessments of cardiovascular, respiratory, abdominal and neurological systems as well as lymph nodes/spleen, skin, oropharynx and extremities. Targeted physical examinations should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymph nodes, liver, and spleen), and those systems associated with clinical signs/symptoms. A targeted physical examination will be conducted at all visits except screening/baseline, at which a complete physical exam is required.

If the physical examination is not completed ± 7 days of the radiological tumor assessment, a separate physical examination should be performed.

7.4.3 ECOG Performance Status

Eastern Cooperative Oncology Group performance status will be assessed at the Screening Visit, each visit during study treatment, and at End of Treatment Visits. Appendix 6 will be used to assess performance status.

7.4.4 Echocardiogram

Echocardiography is to be performed at screening within 30 days prior to first dose.

7.4.5 Laboratory Evaluations

Laboratory assessments should be performed at a local certified laboratory. Clinical chemistry, hematology, coagulation, urinalysis, serum β2 microglobulin and serum Ig will be performed at the time points specified in Table 2 and may also be performed as medically necessary. On Cycle 1 Day 1, laboratory assessments should be done before the study drug administration. Screening blood and urine tests were performed within 72 hours of the first study drug administration do not need to be repeated on Cycle 1 Day 1.

7.4.5.1 Hematology

Hematology includes hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, WBC count with differential including neutrophils (including bands), lymphocytes, monocytes, eosinophils, and basophils. In the event of neutropenia (absolute neutrophil count $< 0.75 \times 10^9$/L) or thrombocytopenia (platelets $< 50 \times 10^9$/L), these assessments will be conducted as frequently as the investigator feels it necessary and until toxicity resolves to ≤ Grade 2 or baseline.

7.4.5.2 Serum Chemistry

Clinical chemistry includes albumin, alkaline phosphatase, AST, ALT, CO_2, blood urea nitrogen (BUN) or urea, calcium, chloride, creatinine, fasting glucose, LDH, magnesium, phosphorus (optional), potassium, sodium, total bilirubin, total protein, and uric acid. In the event of ≥ Grade 3 clinical chemistry toxicity, these assessments will be conducted as frequently as the investigator feels it necessary and until toxicity resolves to ≤ Grade 2.

7.4.5.3 Lipid Panel

The lipid panel includes cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides and will be performed at screening only.

7.4.5.4 Coagulation

The coagulation profile includes prothrombin time (PT), which will also be reported as INR, and APTT. The coagulation profile will be performed at screening and on Cycle 1 Day 1.

7.4.5.5 Urinalysis with Dipstick

Urinalysis will be assessed using urine dipstick. Urinalysis includes pH, glucose, protein, ketones, bilirubin, occult blood, and specific gravity. If urine protein is ≥ 2 by dipstick, a 24-hour urine for total protein and creatinine will be obtained and evaluated**.**

7.4.5.6 Serum Ig and β2 Microglobulin

Serum immunoglobulin (IgG, IgM, IgA) will be measured at following time points: pre-dose on Cycle 1 Day 1, every 3 cycles (Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1 and Cycle 13 Day 1), and then every 6 cycles (Cycle 19 Day 1, Cycle 25 Day 1, Cycle 31 Day 1, etc.) thereafter until the end of treatment.

7.4.5.7 Pregnancy Test

A serum pregnancy test will be performed at screening and end of treatment in women of childbearing potential. Any female subject who is pregnant will not be eligible for the study. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. A subject who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study.

7.4.5.8 Hepatitis B/C Testing

Hepatitis B/C serologic markers and/or viral load will be tested at screening. The hepatitis B testing includes hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis B surface antibody (HBsAb) as well as hepatitis B virus (HBV) DNA by polymerase chain reaction (PCR) if the subject is negative for HBsAg but HBcAb positive (regardless of HBsAb status). The hepatitis C testing includes hepatitis C virus (HCV) antibody as well as HCV RNA by PCR if the subject is HCV antibody positive. CCI

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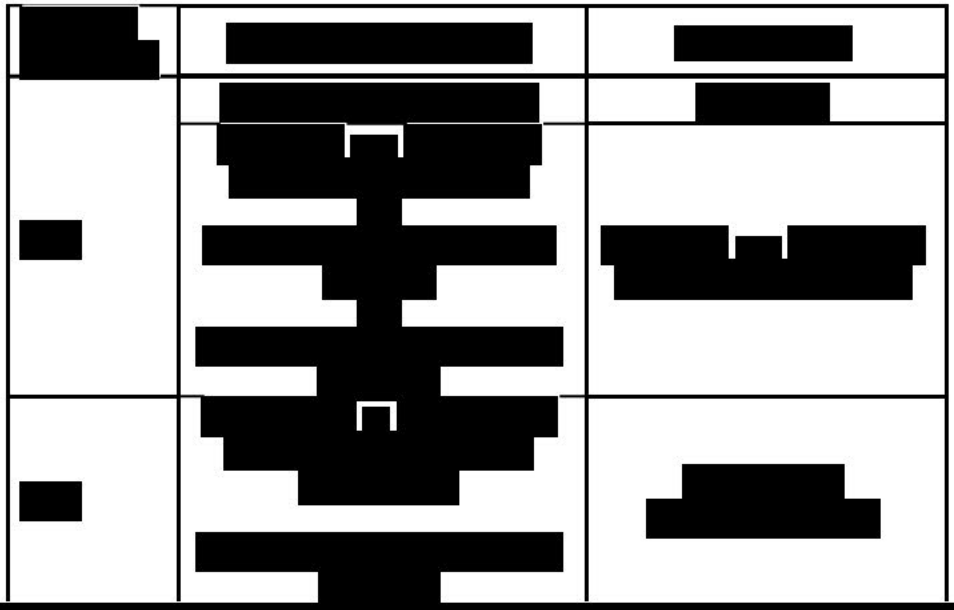

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7.5 Biomarkers

If available, previous tumor tissues or newly collected tumor specimen (within 2 years of starting treatment) will be collected. Either a formalin-fixed paraffin-embedded block with tumor tissue or at least 5 unstained slides should be sent to the central laboratory for biomarker analysis, including but not limited to IGVH and TP53.

7.6 Appropriateness of Measurements

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

8 DATA HANDLING AND QUALITY ASSURANCE

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedure (SOP), working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the contract research organization (CRO)'s qualified compliance auditing team (an independent function from the study team responsible for conduct of the study).

8.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by International Conference of Harmonisation (ICH) guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF.

Completed, original CRFs 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 software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

The Data Management Plan defines and documents the procedures necessary to ensure data quality. These activities must be followed to ensure that data are properly entered, validated, coded, integrated, reconciled, and reviewed.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 18.1 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Concomitant diseases/medical history will be coded using the MedDRA® Version 18.1 or higher.

8.3 Quality Assurance

To ensure compliance with Good Clinical Practice (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 detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During the study, when there is a safety evaluation, the investigator or study center personnel will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

9.1 Adverse Events

9.1.1 Definitions and Reporting

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

Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- Worsening of a chronic or intermittent pre-existing condition including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE)
- Significant failure of expected pharmacological or biological action.

Examples of an AE do not include:

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.2 Serious Adverse Events

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 event in which the subject was at risk of death at the time of the event. It does not refer to an event, 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 subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event 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 pre-existing condition that did not worsen from baseline 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

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also

be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Disease progression should not be reported as an AE/SAE, but symptoms meeting the definition of, and associated with, disease progression should be reported.

9.3 Lack of Efficacy

"Lack of efficacy" will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

9.4 Laboratory Test Abormaties or Other Abormaties

Abnormal laboratory findings (eg, clinical chemistry, hematology, coagulation, urinalysis) or other abnormal assessments (eg, ECGs, X-rays, vital signs, etc.) 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) 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 subject'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.

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

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

Subjects will be assessed for AEs and SAEs beginning immediately after signing the informed consent form and continuing through to follow-up which is 30 ± 7 days of last dose of investigation drug. 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?

All AEs and SAEs will be recorded in the source documents. All AEs and SAEs will be reported in the eCRF.

9.6 Recording of Adverse Events and Serious Adverse Events

When a SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The Investigator will then record all relevant information regarding an SAE form. It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor or designee in lieu of completion of the appropriate SAE form. However, there may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to the Sponsor or designee.

Investigator must report all SAE to sponsor or the designee of sponsor with 24 hours after awareness of SAE which happened during the trial conduction. Investigator should finish SAE form and sign and specify the awareness date on SAE form, and then send it to sponsor or the designee of sponsor via fax or Email.

All AE should be recorded in eCRF. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE or SAE and not the individual signs/symptoms. Adverse events are independent components of the study.

9.7 Evaluation of AE and SAE

9.7.1 Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study. When applicable, AEs and SAEs should be assessed and graded based upon the NCI-CTCAE Version 4.03 (NCI, 2010).

9.7.2 Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other

risk factors, and the temporal relationship of the event to the study drug will be considered and investigated. The investigator will also consult the IB, for marketed products, in the determination of his/her assessment.

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

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

- Definitely related: There is clear evidence to suggest a causal relationship that there is reasonable temporal relationship; the positive of de-challenge result (When necessary the positive of re-challenge result); the occurrence of AE that could be attributed to the pharmacological effect of study treatment.
- Probably related: This causality assessment will be applied for AE that is regarded by the investigator as highly positive related to the study treatment that: There is reasonable temporal relationship; the occurrence of AE could not be explained by the subject's medical history, concurrent medical condition, or other the subject's signs or symptoms; the positive of de-challenge result; the positive of re-challenge result.
- Possibly related: There is some evidence to suggest a causal relationship (e.g., 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 (e.g., the subject's clinical condition, other concomitant AEs).
- Unlikely related: There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the AE.
- Unrelated: An AE will be considered "not related" to the use of the product if any of the following tests are met:
    - An unreasonable temporal relationship between administration of the product and the onset on the AE (e.g., the AE occurred either before, or too long after administration of the product for it to be considered product-related);
    - A causal relationship between the product and the AE is biologically implausible (e.g., death

as a passenger in an automobile accident);

- A clearly more likely alternative explanation for the AE is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related AE).

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

9.8 Follow Up of Adverse Event

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

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

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. 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 or designee 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 subject dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE form, with all changes signed and dated by the investigator. The updated SAE form should be resent to the sponsor or designee within the time frames outlined in Section 9.9.

9.9 SAE Reporting

9.9.1 Time Frames for Submitting Reports of Serious Adverse Events

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

All SAEs will be reported promptly to the sponsor or designee as described in Table 6 once the investigator determines that the AE meets the protocol definition of an SAE.

Table 6 Time Frame for Reporting Serious Adverse Events to the Sponsor or Designee

Type	Initial Report	Document	Follow-up SAE	Document
All SAEs	Within 24 hours of first knowledge of the AE	SAE form	As expeditiously as possible	Updated SAE

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

9.9.2 Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE (Section 9.2) has occurred in a subject, he/she will report the information to the sponsor within 24 hours as outlined in Section 9.9.1. The SAE report form will always be completed as thoroughly as possible with all available details of the SAE, signed by the investigator and forwarded to the sponsor within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the sponsor 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 9.7.2

Facsimile transmission of the SAE report form is the preferred 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 SAE report form sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE report form within the time frames outlined in Section 9.9.1. The sponsor will provide a list of project contacts for SAE receipt, fax numbers, telephone numbers, and mailing addresses.

9.10 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 9.2. 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 the appropriate project contact by the investigator for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

Expedited investigator safety reports are prepared according to the sponsor's policy and are forwarded to investigators as necessary. The purpose of the report is to fulfill specific regulatory and GCP requirements regarding the product under investigation.

When a study center receives an initial or follow-up report or other safety information (eg, revised IB) from the sponsor, the responsible person according to local requirements is required to promptly notify his/her IRB or IEC.

9.11 Post-study Adverse Event

A post-study AE or SAE is defined as any AE that occurs outside of the AE/SAE reporting period, defined in Section 9.5.

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

9.12 Serious Adverse Events Related to Study Participation

An SAE considered related to study participation (eg, procedures, invasive tests, a change in existing therapy), even if it occurs during the pre-or post-treatment period, will be reported promptly to the sponsor or designee（Section 9.9）.

9.13 Pregnancy Reporting

A subject who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study. All post-study assessments will be collected at the time of discontinuation as described in Table 2.

If a female subject or the partner of a male subject becomes pregnant while receiving investigational therapy or within 90 days for BGB-3111 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. The investigator, or his/her designee, will record pregnancy information on the

appropriate form and submit it to the sponsor within 2 weeks of learning of a subject's or male subject's female partner's pregnancy. The subject or male subject's female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

An abortion, whether accidental, therapeutic, or spontaneous, should be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a subject exposed to the study drug should be recorded and reported as an SAE. While the investigator is not obligated to actively seek this information in former subjects, he/she may learn of an SAE through spontaneous reporting.

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10 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Data will be listed and summarized using SAS® Version 9.3 or higher (SAS Institute, Inc., Cary, North Carolina) according to sponsor agreed reporting standards, where applicable. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

10.1 Primary, Secondary and Exploratory Study Endpoints

10.1.1 Primary Endpoint

The primary endpoint of the study is the rate of objective response, defined as the achievement of either a partial response (PR) or CR as assessed by the IRC according to the 2014 modification of the International Working Group on NHL Criteria (Cheson, 2014) (Appendix 3) at any time on study drug.

10.1.2 Secondary Endpoints

Efficacy (using response assessment as determined by IRC):

- Progression-free survival (PFS) as assessed by the IRC in subjects with relapsed or refractory MCL after administration of BGB-3111: defined as time from treatment initiation to documentation of progression or death due to any cause, whichever happens first
- TTR as assessed by the IRC in subjects with relapsed or refractory MCL after administration of BGB-3111: defined as the time from treatment initiation to the first documentation of response
- DOR as assessed by the IRC in subjects with relapsed or refractory MCL after administration of BGB-3111: defined as the time from the first response documentation to the date that PD is documented after treatment initiation
- ORR as assessed by the investigator: defined as the achievement of either a PR or CR as assessed by the Investigator at any time on study drug.

Safety:

- The incidence, time and severity of treatment-emergent adverse events according to NCI CTCAE v4.03 (NCI, 2010)

- The incidence, severity, time and causation of adverse events leading to study drug discontinuation.

CCI [redacted]

- CCI [redacted]

[redacted]

[redacted].

10.2 Statistical Analysis

10.2.1 Analysis Populations

The Safety Population includes all subjects who received any dose of BGB-3111. It will be the population for the safety analysis.

The Revised Safety Population includes subjects with pathologically confirmed MCL among those in the Safety Population. The population is also the primary efficacy evaluable population.

The Per-protocol (PP) Population includes subjects who received any dose BGB-3111and had no major protocol deviations. Criteria for exclusion from the PP will be determined and documented before the database lock for the primary analysis. This will be the secondary analysis population for efficacy analyses.

CCI [redacted]

10.2.2 Subject Disposition

The number of subjects enrolled, treated, prematurely discontinued from study drug (defined as those who discontinued study drug due to any reason except for PD) and those with major protocol deviations will be counted. The primary reason for study drug discontinued will be summarized according to the categories in the eCRF. The end of study status (alive, death, withdrew consent or lost to follow-up) at the data cutoff date will be summarized using the data from the eCRF.

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

10.2.3 Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the Safety Population using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial MCL diagnosis; categorical variables include sex, age group, disease stage, ECOG-PS, prior line of therapy for MCL, MCL international prognostic index, Ki-67 and blastoid histology.

10.2.4 Prior and Concomitant Therapy

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report (CSR) for this protocol. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose. A listing of prior and concomitant medications will be included in the CSR of this protocol.

10.2.5 Efficacy Analyses

10.2.5.1 Primary Efficacy Analysis

The primary efficacy endpoint is overall response rate (ORR) and will be assessed by an IRC using the 2014 modification of the International Working Group in NHL criteria (Cheson, 2014) (Appendix 3). The ORR is defined as the proportion of subjects achieving a best overall response (BOR) of CR or PR.

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The BOR is defined as the best response recorded from the start of BGB-3111 until data cut or start of new antineoplastic treatment. Subjects with no post-baseline response assessment (due to any reason) will be considered non-responders for BOR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, PR, SD, and PD) will be presented.

The primary efficacy analysis will be conducted at mature data of response rate, no later than 12 months after the first dose of the last subject, and final analysis will be conducted at mature data of secondary efficacy endpoints.

10.2.5.2 Secondary Efficacy Analysis

Progression-free survival (PFS) is defined as the time from the starting date of BGB-3111 to the date of first documentation of disease progression or death, whichever occurs first. Subjects who do not have disease progression will be censored at their last valid tumor assessment. Six-month progression-free survival rate is defined as no disease progression after treated with BGB-3111 for over six months (under control).

Kaplan-Meier (KM) method will be used to estimate progression event-free curves and corresponding quantiles (including the median). A two-sided 95% CIs of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer, 1982). The PFS at 12 months and 18 months, defined as the percentages of subjects in the analysis population who remain alive and progression-free at the specified time points, will be estimated using the KM method along with the corresponding 95% CI constructed using Greenwood's formula (Greenwood, 1926).

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

The DOR is defined as the time from the date that the response criteria are first met to the date that PD is objectively documented or death (whichever occurs first). Subjects who do not have disease progression will be censored at their last valid assessment. The TTR is defined as time from the starting date of BGB-3111 to the date the response criteria are first met.

The DOR will be analysed using the KM method as described above. The KM estimates of DOR

will be plotted over time. The TTR will be summarized by sample statistics such as sample mean, median, and standard deviation.

The ORR is defined as the proportion of subjects achieving a BOR of CR and PR.

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10.2.5.3 Exploratory Efficacy Analysis

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10.2.5.4 Subgroup Analysis

Primary and selected secondary endpoints will be summarized descriptively in the specified subgroups: sex, age group (< 65 vs. ≥ 65), race, disease stage, ECOG-PS (0 vs. ≥ 1), prior line of therapy for MCL (< 3 vs. ≥ 3), MCL international prognostic index (low, intermediate, high), Ki-67, and blastoid histology (yes vs. no). Within group values (rates or means/medians) will be presented in forest plots.

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10.2.7 Biomarker Data

Tumor biomarker analysis includes but not limited to IGVH and TP53. Correlation between biomarkers and clinical outcome will be explored.

10.3 Safety Analysis

Safety will be assessed by monitoring and recording of all AEs graded by NCI CTCAE v4.03 (NCI, 2010). Laboratory values (hematology, clinical chemistry, coagulation, and urinalysis), vital signs, and physical examination and ECG findings will also be used in safety analysis. Descriptive statistics will be used to analyze all safety data in the Safety Population.

10.3.1 Extent of Exposure

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

The number (percentage) of subjects requiring dose reductions, dose interruption, dose delay, and drug discontinuation due to AEs will be summarized. The cycle in which the first dose reduction/interruption occurred will be summarized using descriptive statistics. Frequency of reductions and dose interruptions will be summarized by categories.

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10.3.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using MedDRA®. Adverse events will be coded to MedDRA (Version 18.1 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the date of first dose of study drug up to 30 days following study drug discontinuation (Safety Follow-up visit) or initiation of new anticancer therapy, whichever comes first. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once by the highest severity grade according to NCI CTCAE v4.03 (NCI, 2010) within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be possibly or probably related to study drug or with missing assessment of the causal relationship. Serious adverse events, deaths, TEAE with Grade 3 or above, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

10.3.3 Laboratory Analysis

Clinical laboratory (ie, hematology, serum chemistry, and qualitative urinalysis) values will be evaluated for each laboratory parameter by subject. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this protocol. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst post-baseline visit.

Laboratory parameters that are graded in NCI CTCAE v4.03 (NCI, 2010) will be summarized by CTCAE grade. In the summary of laboratory parameters by NCI CTCAE grade, parameters with NCI CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

10.3.4 Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure [BP], heart rate, respiratory rate, temperature, weight) and changes from baseline will be presented by visit for all visits. Vital signs will be listed by subject and visit.

10.3.5 Electrocardiogram

Electrocardiogram assessments will be performed at the Screening visit and at EOT and, for subjects CCI [redacted]. Descriptive statistics for baseline ECG parameters will be presented.

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11 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

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 basic principles of "GCP."

Investigators and all sub-investigators must provide documentation of their financial interest or arrangements with BeiGene, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify BeiGene of any change reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date that the last subject 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) current version of the Declaration of Helsinki.

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

If the protocol, the informed consent form, or any other information that the IEC/IRB has approved for presentation to potential subjects 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 informed consent form including obtaining IEC/IRB approval of the amended form before new subjects consent to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended informed consent form/other information and the approved amended informed consent form/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 consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent.

Informed consent will be obtained before the subject 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 9.1, 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

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, and an identification code (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 subjects screened and for all subjects enrolled in the trial.

The investigator agrees that all information received from BeiGene, including but not limited to the IB, this protocol, CRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of BeiGene during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from BeiGene. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11.2.6 Case Report Forms

For each subject enrolled, a CRF must be completed and signed by the principal investigator or sub-investigator within a reasonable time period after data collection. This also applies to records for those subjects who fail to complete the study (even during a pre-randomization screening period if a CRF was initiated). If a subject withdraws from the study, the reason must be noted on the CRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

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 product (quantity and condition), subject dispensing records and returned or destroyed study product. Dispensing records will document quantities received from BeiGene and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction 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 site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet BeiGene's requirements for disposal, arrangements will be made between the site 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 trial 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 ascertain 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 subjects, may be made only by BeiGene. All protocol modifications must be submitted to the IRB/IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

11.3.2 Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3) (ICH, 1996). Note that an abbreviated report may be prepared in certain cases.

For multi-center studies, the first publication or disclosure of study results shall be a complete, joint multi-center publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s).

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11.8 Joint Investigator/Sponsor Responsibilities

11.8.1 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 CRFs for consistency.

The monitor is responsible for routine review of the CRFs 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 subject records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

11.8.2 Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits of the 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 Signature of Investigator

PROTOCOL TITLE: A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Efficacy and Safety of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Subjects with Relapsed or Refractory Mantle Cell Lymphoma (MCL)

PROTOCOL NO: BGB-3111-206

Date and Version of Protocol: 6 September 2018, Version 4.0

This protocol is a confidential communication of BeiGene (Beijing) Co., Ltd. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work in accordance with ethical principles that have their origin in the Declaration of Helsinki and good clinical practice and applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior approval from BeiGene (Beijing) Co., Ltd.

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

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

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_____

Appendix 2 Medications Which Are Known to Prolong the QT Interval and/or Induce Torsades de Pointes to be Avoided

Antiarrhythmics
amiodarone
disopyramide
dofetilide
flecainide
ibutilide
procainamide
quinidine
sotalol
Anticancer
arsenic trioxide
vavdetanib
Antihistamines
astemizole
terfenadine
Antibiotics
azithromycin
clarithromycin
erythromycin
moxifloxacin
sparfloxacin
Antianginal
bepridil
Antimalarial
chloroquine
halofantrine
Antipsychotics
chlorpromazine
haloperidol
mesoridazine
pimozide
thioridazine
Antinausea
domperidone
droperidol
dolasetron (intravenous and oral)
Anti-infective
pentamidine
Antilipemic
probucol

Antidpressants citalopram
Opiate agonists levomethadyl methadone
GI stimulant cisapride

Arizona Center for Education and Research on Therapeutics (CERT) “Drugs That Prolong the QT Interval and/or Induce Torsades de Pointes.” Available at: https://www.crediblemeds.org. Accessed 21 April 2017.

Appendix 3 Non-Hodgkin's Lymphoma LUGANO Response Criteria

For assessment of Non-Hodgkin's lymphoma LUGANO response criteria, positron emission tomography [PET] should be performed in cooperation with diagnostic contrast computed tomography [CT] simultaneously or in different procedures. The PET-CT should be used for response assessment in fluorodeoxyglucose (FDG)-avid histologies (using the 5-point scale provided in the footnote of the table below); CT is preferred for low or variable FDG avidity, in accordance with 2014 modification of the International Working Group on Non-Hodgkin's Lymphoma Criteria (Cheson, 2014).

Response	Site	PET-CT (Metabolic Response)	CT (Radiologic Response)[d]
Complete Response	Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass[b,c] on 5-point scale (5-PS)	All of the following: target nodes/nodal masses must regress to ≤ 1.5 cm in LDi, no extralymphatic sites of disease
	Nonmeasured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial Response	Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and no new or progressive lesion At interim, these findings suggest disease response At end of treatment, these findings indicate residual disease	All of the following: ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
	Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
	New lesions	None	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with biopsy or an interval scan	Not applicable

Response	Site	PET-CT (Metabolic Response)	CT (Radiologic Response)[d]
No response or stable disease	Target nodes/nodal masses, extranodal lesions	Score 4 or 5[b] with no significant change in FDG uptake from baseline at interim or end of treatment, no new or progressive lesion	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Unmeasurable lesion	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable
Disease Progression	Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5[b] with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	One of the following in PPD progression: An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and an increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline If not prior splenomegaly, must increase by at least 2 cm from baseline
	Unmeasurable lesion	None	New or clear progression of preexisting unmeasurable lesions

Response	Site	PET-CT (Metabolic Response)	CT (Radiologic Response)[d]
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extra nodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

a A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan.
b Refer to PET 5-point scale (5-PS).
c It is generally accepted that in Waldeyer's ring or high physiological uptake or spleen/bone marrow activated (eg, by chemotherapy or myeloid colony stimulating factor) extranodal sites, uptakes may be greater than normal mediastinum and/or liver. In this situation, if uptake of initial involvement site is no greater than surrounding normal tissues, even if the tissue has high physiologic uptake, complete molecular remission (CMR) can also be concluded.
d False positive result of PET scan related to infection or inflammation may be observed. Biopsy for involvement site is still the gold standard for new or persistent pathological changes.

PET 5-point scale:
1. no uptake above background
2. uptake ≤ mediastinum
3. uptake > mediastinum, but < liver
4. uptake moderately > liver
5. uptake markedly higher than liver and/or new lesions

X new areas of uptake unlikely to be related to lymphoma

Abbreviations: CMR, complete molecular remission; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transvers diameter of a lesion; PET, positron emission tomography; PPD, cross product of the longest transvers diameter of a lesion and perpendicular diameter; 5-PS, 5-point scale; SDi, shortest axis perpendicular to the longest transvers diameter of a lesion; SPD, sum of the product of the perpendicular diameters for multiple lesions.

Appendix 4 Strong CYP3A Inhibitors and Inducers

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, elvitegravir, conivaptan, mibefradil, nefazodone
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Strong CYP3A Inducers
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort (hypericum perforatum)

Abbreviation: CYP3A, cytochrome P450, family 3, subfamily A.
Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for CYP3A inhibition or induction risks or contact the Medical Monitor of the protocol.

Food and Drug Administration Center for Drug Evaluation Research (CDER). FDA Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations. 2012.

Appendix 5 Medications to be Used with Caution (Sensitive CYP2C8, CYP2C9, and CYP2C19 Sensitive Substrates or CYP2C8, CYP2C9, and CYP2C19 Substrates With a Narrow Therapeutic Index)

CYP2C8 Substrates	CYP2C9 Substrates	CYPC19 Substrates
repaglinide[1]	celecoxib	**Anti-epileptics:**
paclitaxel	phenytoin[2]	S-mephenytoin[1,2]
	warafarin[2]	
		Proton Pump Inhibitors
		lansoprazole[1]
		omeprazole[1]

[1] Sensitive substrates: Drugs that exhibit an area under plasma concentration-time curve (AUC) ratio (with and without inhibitor - AUCi/AUC) of 5-fold or more when co-administered with a known strong inhibitor.

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

Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for drug interaction information or contact the Medical Monitor of the protocol.

Food and Drug Administration Center for Drug Evaluation Research (CDER). FDA Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations. 2012.

Appendix 6 ECOG Performance Status

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

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

Appendix 7 New York Heart Association Classification

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

Abbreviations: NYHA, New York Heart Association.