NOVARTIS

Clinical Development

BGJ398

Protocol CBGJ398XUS04 / NCT02160041

Modular phase II study to link targeted therapy to patients with pathway activated tumors: Module 6 – BGJ398 for patients with tumors with FGFR genetic alterations

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List of abbreviations

ADME	Absorption Distribution Metabolism and Excretion
AE	Adverse Event
AKT	Protein Kinase B
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AML	Acute myelogenous leukemia
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
APL	Acute promyelcytic leukemia
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical Classification System
AUC0-24h	Area Under the Curve 0-24 h
BID	bis in diem/twice a day
BLRM	Bayesian Logistic Regression Model
BP	Blood pressure
BSC	Best supportive care
BUN	Blood Urea Nitrogen
Ca	Calcium
CA-125	Cancer Antigen-125
CABG	Coronary artery bypass graft
CBC	Complete blood count
CBR	Clinical Benefit Rate
cDNA	Circulating DNA
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence Interval
CL	Clearance
CLIA	Clinical Laboratory Improvement Amendments
CLL	Chronic lymphocytic leukemia
Cmax	Maximum Concentration
CML	Chronic Myeloid Leukemia
CMO&PS	Chief Medical Office and patient Safety
CNS	Central Nervous System
CR	Complete Response
CRC	Colorectal Cancer
CrCl	Creatinine clearance
CRO	Contract Research Organization
CSF	Clinical service form
CSR	Clinical study report

[redacted]

CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebrovascular accident
CYP	Cytochrome P
DLs	dose levels
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
DVT	Deep vein thrombosis
e.g.	for example
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EOT	End of Treatment
ERK/MAPK	Extracellular signal-regulated kinase/Mitogen-Activated Protein Kinase
ET	Essential thrombocythemia
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
FFPE	Formalin fixed paraffin embedded
FGFR	Fibroblast growth factor receptor
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	Gamma-glutamyltranspeptidase
GI	Gastrointestinal
GLP	Good laboratory practice
GM-CSF	Granulocyte macrophage colony-stimulating factor
GVHD	Graft-versus-host disease
HBV	Hepatitis B Virus
hCG	human chorionic gonadotropin
HCV	Hepatitis C Virus
HDL	High density lipoprotein
hERG	human Ether-à-go-go Related Gene
HFSR	Hand and Foot Skin Reaction
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
hr	hour
IB	Investigators Brochure

[redacted]

IC50	Half maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMWG	International Myeloma Working Group
IN	Investigator notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine system
IWG	International working group
KA	Keratoacanthoma
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LVEF	Left Ventricular Ejection Fraction
mCRC	Metastatic Colorectal Cancer
MDS	Myelodysplasia
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated ERK Kinase
MF	Myelofribrosis
mg	milligram
MI	Myocardial infarction
MM	Multiple Myeloma
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTOR	Mammalian target of rapamycin
MUGA	Multiple Gated acquisition scan
N	Sample size
NA	Not applicable
Na	Sodium
NCCN	National Comprehensive Cancer Network
NCI CTC	National Cancer Institute Common Terminology Criteria
nM	Nano molar
NSCLC	Non-small cell lung carcinoma
OC	Oral contraception
OR	Overall response
ORR	Overall Response Rate
OS	Overall survival
PD	Progressive disease
PD	Pharmacodynamics
PE	Pulmonary embolism
PET	Positron emission tomography

PFS	Progression-free survival
Ph	Philadelphia chromosome
PHI	Protected health information
Pi	Inorganic Phosphorus
PK	Pharmacokinetics
PLT	Platelets
PMT	Phosphaturic Mesenchymal Tumour
PR	Partial Response
PRBC	Packed Red Blood Cells
PSA	Prostate-specific antigen
PT	Prothrombin time
PTEN	Phosphatase and tensin homolog
PV	Polycythemia vera
QD	*quaque die*/once a day
QTc	QT corrected
QTcF	Q-T interval in the ECG (corrected according to the formula of Fridericia)
RAF	v-raf murine sarcoma viral oncogene
RAP	Report Analysis Plan
RAS	RAS oncogene (rat sarcoma viral oncogene homologue)
RBC	Red Blood Cells
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended phase two dose
RTK	Receptor tyrosine kinase
RU	Resource utilization
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SC	Steering Committee
SCC	Squamous cell carcinoma
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase/AST
SGPT	Serum glutamic pyruvic transaminase/ALT
SPEP	Serum protein electrophoresis
SUSAR	Suspected unexpected serious adverse reaction
TdP	Torsade de Pointes
TIA	Transient ischemic attack
TIO	Tumor-induced osteomalacia
Tmax	The time at which the maximum observed concentration (Cmax) occurs
TSH	Thyroid stimulating hormone
ULN	Upper Limit of Normal
UPEP	Urine protein electrophoresis
WBC	White Blood Cell

[redacted]

WHO	World Health Organization
WNL	Within normal limits

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days. For this protocol, a complete treatment cycle is defined as 28 days of once daily [3 weeks on 1 week off] treatment with BGJ398. The first dose of BGJ398 defines Day 1 of the treatment cycle and the last day of a complete treatment cycle is Day 28, unless extended due to adverse events.
Baseline	Pre-dose Cycle 1 day 1
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.BGJ398 is the investigational drug in this study.
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage. BGJ398 is the investigational treatment.
Patient Number (Patient No.)	A unique identifying number assigned to each patient who enrolls in the study
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Screening	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, completion of treatment, etc.
Stage in cancer	The extent of cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	BGJ398
Study treatment discontinuation	Point/time when patient permanently stops taking BGJ398, for any reason.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

[redacted]

Protocol summary

Protocol number	CBGJ398XUS04
Title	Modular phase II study to link targeted therapy to patients with pathway activated tumors: Module - 6 BGJ398 for patients FGFR altered tumors
Brief title	BGJ398 for patients with FGFR altered tumors
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this signal seeking study is to determine whether treatment with BGJ398 demonstrates sufficient efficacy in FGFR pathway-regulated solid tumors and/or hematologic malignancies to warrant further study.
Primary Objective(s) and Key Secondary Objective	**Primary objectives:** To assess clinical benefit associated with BGJ398 treatment based on local investigator assessment. For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR or PR or SD ≥ 16 weeks. For hematologic tumors, other appropriate hematological response criteria will apply and are included in the appendices. For patients with TIO diagnosis without measureable/evaluable disease, the following criteria will be the assessment at 16 weeks: • the tumor associated changes of metabolic parameters: plasma level of FGF23 < or =180 RU/mL; and inorganic phosphorous, calcium, and 1-25-dihydroxy vitamin D greater than the LLN (- 20%); and • without requirement of supplementation therapy for at least the preceding cycle of the 16 week assessment. **Key Secondary objective:** To assess Overall Response (OR) of Partial Response (PR) or greater based on local investigator assessment. For patients with solid tumors, the assessment criteria will be RECIST 1.1 and will include responses of CR and/or PR. For hematologic tumors, other appropriate hematological response criteria will apply and are included in the appendices.
Secondary Objectives	To assess: Progression-Free Survival (PFS) based on local investigator assessment per RECIST 1.1 or other appropriate hematological response criteria Overall Survival (OS) Duration of Response (DOR) based on local investigator assessment per RECIST 1.1 or other appropriate hematological response criteria Safety and tolerability
[redacted]	[redacted]

[redacted]

Study design	This is a phase II, open label study to determine the efficacy and safety of treatment with BGJ398 in patients with a diagnosis of solid tumors or hematological malignancies that have been pre-identified (prior to study consent) to have any FGFR genetic alterations [such as mutation, amplification, fusion, translocation of FGF receptors 1 – 4] and whose disease has progressed on or after standard treatment. Genomic profiling is becoming more accessible to patients and their physicians. As such, more patients have been identified with potentially-actionable mutations or pathway-activations but do not have access to targeted drug treatment. This is a signal-seeking study to match patients with tumors containing FGFR genetic alterations to treatment with the FGFR inhibitor BGJ398. Pre-identification of FGFR genetic alteration status will be performed locally at a CLIA certified laboratory prior to participation on the trial. Laboratory results must be 'unambiguous' or 'unequivocal'. Results that state 'ambiguous' or 'equivocal' imply low probability that genetic deregulation is truly present and an important driver of patient's tumor. Once the patient has been identified, treating physicians who are qualified investigators may contact Novartis to consider enrollment in this study. For the purpose of this study, genomic profiling is not considered part of screening. Informed consent must be signed before any screening activities take place. Once eligibility (screening criteria met) has been confirmed by Novartis, the patient will initiate therapy with BGJ398 single-agent. The patient may not receive any additional anti-cancer therapy during treatment with BGJ398. Patients will continue to receive study treatment until disease progression (assessed by investigator per RECIST 1.1 or appropriate hematologic response criteria or for patients with TIO diagnosis the recurrence or progression of disease or recurrence of abnormal metabolic parameters), unacceptable toxicity, death or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, start of a new anti-neoplastic therapy or at the discretion of the investigator), otherwise known as End of Treatment. Patients with TIO diagnosis that progress per RECIST but per investigator's assessment are receiving clinical benefit from treatment may remain on study upon approval from Novartis. All patients who discontinue from study treatment due to disease progression must have their progression clearly documented. Disease assessment (per RECIST 1.1 or appropriate hematological response criteria) will be performed every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle), until disease progression or end of treatment, whichever occurs first. Upon implementation of amendment 2, the frequency of disease assessment will be reduced and evaluations should be every 16 weeks after the first 16 weeks on treatment. Scans will be assessed locally by the investigator. After discontinuation of treatment, patients, regardless of reason for treatment discontinuation, will be followed for safety for 30 days after the last dose. Survival information will be collected every 3 months until 2 years after the last patient has enrolled in the study regardless of treatment discontinuation reason (except if consent is withdrawn). If the study primary efficacy endpoint is not met, Novartis may decide not to conduct survival follow up for the study.

[redacted]

Population	The study population consists of approximately 70-120 adult patients with a diagnosis of a solid tumor or hematological malignancy that have been pre-identified as having FGFR genetic alteration. Patients must have received at least one prior treatment for their recurrent, metastatic and/or locally advanced disease and have no remaining standard therapy options anticipated to result in a durable response. Patients must have progressive and measurable disease (per RECIST 1.1 or appropriate hematological response criteria) and be in need of treatment. This is a signal seeking study, attempting to identify additional patient populations who may benefit from treatment with single agent BGJ398. Patients must not have central nervous system (CNS) metastasis, leptomeningeal carcinomatosis, symptomatic cardiac disease, or impairment of GI function. Patients must have archival tissue available for submission to allow for molecular testing related to genetic alterations. If tissue is not available or not of sufficient quantity the patient must be willing to undergo a fresh tumor biopsy to allow for these analyses. Enrollment is meant to encompass solid tumors and hematologic malignancies as having FGFR genetic alterations that may be inhibited by BGJ398 who otherwise meet all the inclusion and none of the exclusion criteria. Though common for phase I studies, tissue-agnostic enrollment is unusual for phase II studies, which typically limit enrollment to one or a few well-defined tumor types. We expect that the study will enroll patients whose tumors have already been pre-identified to harbor FGFR genetic alterations The total number of patients to be enrolled per tumor type will be based on an adaptive design. The adaptive design will be patient-sparing and allow the early closure of non-responding arms or arms where early success can be declared.
Inclusion criteria	Patient has a confirmed diagnosis of a solid tumor (Urothelial cell carcinoma, Cholangiocarcinoma, and Glioblastoma multiforme with FGFR 1-4 genetic alterations are included,) Patient has been evaluated and pre-identified as having a tumor with a FGFR genetic alteration. The qualifying alteration must be assessed and reported by a CLIA-certified laboratory. NOTE: Patient must have received at least one prior treatment for recurrent, metastatic and /or locally advanced disease and for whom no standard therapy options are anticipated to result in a durable remission. Patient must have progressive and measurable disease per RECIST 1.1. or other appropriate hematological response criteria. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 See Section 5.2 for complete Inclusion criteria

[redacted]

Exclusion criteria	Patient has received prior treatment with BGJ398 Patients with Central Nervous System (CNS) metastasis or leptomeningeal carcinomatosis Patient has received chemotherapy or other anticancer therapy ≤ 4 weeks (6 weeks for nitrosourea, antibodies or mitomycin-C) prior to starting study drug. Patients with acute or chronic pancreatitis Patients with impaired cardiac function or clinically significant cardiac diseases History and/or current evidence of extensive tissue calcification Current evidence of corneal or retinal disorder/keratopathy History and/or current evidence of renal or endocrine alterations of calcium/phosphate homeostasis. NOTE: Not applicable for TIO diagnosis Patients with another primary malignancy within 3 years prior to starting study treatment, with the exception of adequately treated basal cell carcinoma, squamous cell carcinoma or other non-melanomatous skin cancer, or in-situ carcinoma of the uterine cervix See Section 5.3 for complete Exclusion criteria
Investigational and reference therapy	BGJ398 will be dosed at 125 mg once daily, 3 weeks on 1 week off. A complete treatment cycle is defined as 28 days.
Efficacy assessments	All screening evaluations must be performed as closely as possible to the beginning of treatment and never more than 28 days prior to starting study drug dose of BGJ398 to confirm patient's eligibility. During treatment phase, disease assessments must be performed every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle), until disease progression or end of treatment, whichever occurs first. Upon implementation of amendment 2, the frequency of disease assessment will be reduced and evaluations should be every 16 weeks after the first 16 weeks on treatment. Patients will continue to receive study treatment until disease progression (assessed by investigator per RECIST 1.1 or appropriate hematologic response criteria or for patients with TIO diagnosis the recurrence or progression of disease or recurrence of abnormal metabolic parameters, unacceptable toxicity, death or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, start of a new anti-neoplastic therapy or at the discretion of the investigator). Patients with TIO diagnosis that progress per RECIST but per investigator's assessment are receiving clinical benefit from treatment may remain on study upon approval from Novartis. Survival information will be collected every 3 months until 2 years after the last patient has enrolled in the study regardless of treatment discontinuation reason (except if consent is withdrawn). If the study primary efficacy endpoint is not met, Novartis may decide not to conduct survival follow up for the study.

[redacted]

Safety assessments	Adverse events. Physical examination including vital signs and weight. Performance status evaluation Cardiac monitoring (cardiac enzymes, ECGs, and assessment of LVEF) Laboratory evaluations (hematology, biochemistries, pregnancy tests and urinalysis) Ophthalmology examinations
Data analysis	The Full Analysis Set (FAS) will include all patients who have received at least one dose of study drug. FAS will be the primary population for the analysis of efficacy endpoints.
Key words	Solid tumor malignancy, hematologic malignancy, mutation, translocations, amplifications, fusions, signature, FGFR, ligand, BGJ398, breast cancer, stomach cancer, endometrial cancer, esophageal cancer, Squamous head & neck cancer, tumor induced osteomalacia, TIO

[redacted]

Amendment 3 (30-Jan-2017)

Amendment rationale

The clinical benefit rate set forth in Section 10.4 does not capture Patients who achieve a complete response (CR) or partial response (PR) prior to 16 weeks from start of treatment if they cannot get a confirmatory response assessment completed by week 16.

By achieving at least a CR or PR, the patient is receiving a clinical benef it with BGJ398, regardless of confirmatory response. In order to address patients who achieved unconfirmed CR or PR, further exploration of all responses and analysis of all response versus the clinical benefit rate as defined per protocol Section 10.4 is warranted.

This study observed 6 unconfirmed and 5 confirmed responses among the following tumor types: HNSCC, Ovarian, Bladder, NSCLC Squamous, Glioblastoma and Cholangiocarcinoma. Among the six unconfirmed responses, three unconfirmed responses would fit the criteria mentioned above. Therefore, in conjunction with showing clinical benefit rate, treatment with BGJ398 could represent a significant improvement in the medical management for the aforementioned six tumor types.

The main objectives of this amendment are:

- Re-open the enrollment for patients with six tumor types, HNSCC, Ovarian, Bladder (urothelial cell carcinoma), NSCLC Squamous, Glioblastoma multiforme and Cholangiocarcinoma
- To align with the BGJ398 Clinical Development program
- clarifications, operational aspects, administrative changes and corrections

The amendment contains changes to: re-open enrollments for patients that have the six tumor types which are, HNSCC, Ovarian, Bladder, NSCLC Squamous, Glioblastoma and Cholangiocarcinoma. Enrollment of each tumor cohort will remain open until each tumor types successfully enrolls 10 patients per cohort evaluable for futility analysis.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Protocol Summary Section updated to match the body of the protocol.

The following changes were implemented throughout the protocol:

Section 1.2.1.2.1

- Updated with more current information

Section 2.1

- Added rationale for reopening the study with 6 tumor types, HNSCC, Ovarian, Bladder, NSCLC Squamous, Glioblastoma and Cholangiocarcinoma
- Removed reference for FGF ligand alteration

[redacted]

Table 3-1

- Clarification added for endpoint.

Section 5.1, Section 5.2

- Revised the language regarding excluding FGFR alteration patients and inclusion of 6 tumor types for the reopening of the protocol. Removed corrected for serum albumin.

Section 7.1.4.3

- Revised language to allow survival follow up for six tumor types only

Section 7.2.1.1.3, Section 7.2.1.2, Section 7.2.1.3, Section 7.2.1.4

- Notify the exclusion of the tumor types from the protocol

Section 7.2.4.2.1, Section 8.1.1, Section 10.5.1

- Revised to notify the exclusion of hematologic malignancies references.

Section 8.2.2, Section 8.4.1,

- DS&E changed to CMO&PS

Section 10

- Updated the tumor types that are allowed in the protocol

Section 10.4

- Revised Primary objective to remove hematologic tumors

Section 10.4.1

- Added at week 16

Minor inconsistencies, edits, and typographical errors that were identified after the finalization of the protocol have been corrected with this amendment.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

Amendment 2

Amendment rationale

The main objectives of this amendment are:

- To include patients with a diagnosis of tumor-induced osteomalacia (TIO)
- [redacted]
- To modify the assessment schedule for those patients that are on treatment longer than 16 weeks
- To align with BGJ398 program
- Other (clarifications, operational aspects, administrative changes and corrections)

The amendment contains changes to: Include patients with a diagnosis of tumor-induced osteomalacia with FGF23-associated hypophosphatemia without good treatment options other than phosphate and activated vitamin D (calcitriol) supplementation, which is largely unsuccessful in preventing bone loss, fractures and muscle weakness. We propose that treatment with BGJ398 could represent a significant improvement in the medical management of this disease by directly addressing its molecular mechanism , especially in patients whose tumor is found to have an FGFR genetic alteration.

[redacted]

Upon implementation of this amendment, the frequency of disease assessment will be reduced and evaluations should be every 16 weeks after the first 16 weeks on treatment. This change will bring the disease assessment close to standard of care after the primary endpoint.

To align with the BGJ398 program, hyperphosphatemia management guidelines were updated to provide more detail regarding the prophylaxis of hyperphosphatemia and how to modify BGJ398 dose administration in response to elevated serum phosphorous levels.

Additional changes include the possible discontinuation of survival follow-up if the primary endpoint of the study is not met, a revised definition for “End of Study” to clarify when data will be reported.

Appendix R, the Bayesian adaptive design for the Modular phase II studies to link targeted therapy to patients with pathway activated tumors has been revised. In a single arm trial without a control arm, the quality of the inferences depend strongly on historical data used to create a credible estimate of the baseline control rate. This required an estimate of the patient population that would be enrolled. A control estimate was initially formed for each group based on that population estimate. As enrollment progressed, a different patient population was enrolled in terms of previous line of therapy exposure (heavily pretreated). In order to

[redacted]

produce the best inferences for future development decisions, it is important to change the assumed baseline control rates to match the population enrolled in the modular studies, rather than relying on the pre-trial assumptions. Previously this section was tailored to each of the specific study, The revised appendix will be used for all the Modular studies. The purpose of this section is to show how Bayesian adaptive design will be used for the analysis of the primary efficacy endpoint. Each study will be analyzed acco rding to the tumor cohorts that will be formed during the course of the study.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Protocol Summary Section updated to match the body of the protocol.

List of abbreviations updated to add the terms for CBR, cDNA, PMT, and TIO.

The following changes were implemented throughout the protocol:

Section 1.2.1.2.1 and Section 1.2.1.2.2

- Updated with more current information

Section 2.1

- Added rationale for including patients with Tumor-induced osteomalacia (TIO)

Section 2.1, Section 4.1, and Section 7.1.1

- Added language regarding the need for laboratory results to be ‘unambiguous’ or ‘unequivocal’.

Section 2.1, Section 7.1.1, Section 7.1.1.3, Section 7.1.2, Section 7.1.3.1, Section 7.2.4.3, Section 10.6, Table 7-1, and Table 7-3

- [redacted]

Table 3-1 and Section 10.4

- Updated primary objective and related primary endpoint to capture assessment of patients with TIO

Section 4.1.1, Section 6.1.2, and Section 6.1.3

- Updated to include disease progression assessment criteria for patients with TIO
- Updated to clarify that for patients with TIO that progress per RECIST but per investigator’s assessment are receiving clinical benefit from treatment may remain on study upon approval from Novartis

Section 4.1.1, Section 7.1.2, Section 7.2.1.1.4, Section 7.2.1.2.3, and Table 7-1

- Modified the frequency of efficacy assessments after the scheduled tumor assessment for primary endpoint, in order to align with the standard of care. The frequency of the efficacy assessments will be reduced allowing changes in the interval from every 8 weeks to every 16 weeks after 16 weeks of treatment.

[redacted]

Section 4.1.2, Section 7.1.4.3, and Section 10.5.2

- Updated to clarify that survival follow up may be discontinued if the primary endpoint of the study is not met.

Section 4.2

- Revised to include updated end of study definition and information regarding the analysis of study data and the CSR.

Section 5.1

- Updated to include TIO patient population

Section 5.2

- Added inclusion for patients with tumor-induced osteomalacia
- Clarified which inclusion criteria are not applicable for patient with tumor-induced osteomalacia
- Added, Leukemia patients must have peripheral blast counts < 50,000 blasts/mm
- Added inclusion "Proteinuria ≤Grade 2 (dipstick or 24hrs urine analysis) (Not applicable for Urothelial cell carcinoma patients)

Section 5.3

- Added exclusion of drugs known to be strong inhibitors or inducers of isoenzyme CYP3A, or substrates of CYP3A4 whose treatment cannot be discontinued or switched to a different medication prior to starting study drug
- Clarified that patients with neuropathy ≥ CTCAE grade 2 unrelated to prior cancer therapy, or > grade 2 neuropathy for any other reason will be excluded
- Added timeframe on history of cardiac events
- Updated screening to QTcF >470 msec for both male and female
- Added that in case of use of oral contraception women should have been stable on the same oral contraception for a minimum of 3 months before taking study treatment
- Clarified which exclusion criteria are not applicable for patient with tumor-induced osteomalacia

Section 6.1.1.1

- Updated to clarify administration of BGJ398

Section 6.3.2 and Table 6-2

- Added assessment criteria for a third dose reduction for TIO patients without measureable/evaluable disease

Table 6-2

- Added for patients with TIO diagnosis additional dose reductions may be allowed upon Novartis approval

Table 6-3

- Updated the lipase/amylase elevation information, hyperphosphatemia management and creatinine clearance information

[redacted]

Section 6.3.4

- Removed Table 6-4 as the information was duplicative and the information can be found in Table 6-3

Section 6.4.1

- Added permitted supplementation for patients with TIO.

Section 6.4.1.3

- Removed reference to Table 6-4
- Added that for patients with TIO diagnosis no prophylactic phosphate lowering therapy should be implemented

Section 6.4.2.5 and Section 6.4.3.5

- Revised for medications affecting QT/QTc interval

Section 6.4.3.6

- Added section on anticoagulants

Table 7-1

- Updated frequency of cardiac imaging
- Added frequency of laboratory assessments FGF23 plasma levels and 1-25-dihydroxy vitamin D for patients with TIO

Section 7.1.2, Section 7.2.2.6, and Section 7.2.2.6.7

- Added laboratory assessments for patients with TIO

Section 7.1.4.3

- Added clarification that survival information will be collected for every patient regardless of treatment discontinuation reason (except if consent is withdrawn).

Section 7.2.2.6.5

- Removed language on screening analysis results and subsequent requirements

Section 7.2.3

- Removed reference to BYL719

Section 7.2.3.1

- Added details on pharmacokinetic blood sampling and collection

Section 7.2.4.1

Added that an archival or fresh tumor sample may not be required if the patient has had their genomic profiling performed at the same laboratory that will be used for confirmatory analysis, and the patient consents to allow Novartis to use that data as their baseline molecular analysis results

References

- Updated to include TIO publications referenced

[redacted]

Appendix P and Appendix Q

- Revised to align with the BGJ398 program

Appendix R and Appendix V

- Removed Appendix R and Appendix V as the revised appendices P and Q contain the information included in appendices R-V previously.

Minor inconsistencies, edits, and typographical errors that were identified after the finalization of the original protocol have been corrected with this amendment. IRB/IEC Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 1

Amendment rationale

The main purpose of this protocol amendment is to include endometrial tumors with FGFR 1-4 genetic alterations and FGF ligand amplifications that were previously excluded. Additionally, Urothelial cell carcinoma, Cholangiocarcinoma, and Glioblastoma multiforme with FGF Ligand amplifications are also allowed.

Also, to better understand the safety picture of BGJ398, Pharmacokinetic (PK) testing of BGJ398 and its metabolites has been added to the study. Collection of unscheduled blood (Plasma) PK samples will be collected in the event of an adverse event at the investigators discretion.

Changes to the inclusion/exclusion criteria:

Patients with endometrial tumors will be included. Urothelial cell carcinoma, Cholangiocarcinoma, and Glioblastoma multiforme with FGF ligand amplifications are allowed. Although Urothelial cell carcinoma, Cholangiocarcinoma, and Glioblastoma multiforme with FGFR 1-4 genetic alterations are excluded, these tumors may be considered on a case by case basis upon prior approval by Novartis.

Patients with molecular analysis performed at the confirmatory laboratory will not require additional tumor submission at time of study entry if subject has consented to allow transfer of information from pre-existing analysis to Sponsor.

Clarification of hematological requirements applicable for leukemia patients to be included due to compromised bone marrow system of this patient population. Patients with Leukemia will be included with peripheral blast counts < 50,000 blasts/mm ^{3} to align with current standards.

Patients with clinical evidence of CNS leukemia will be excluded.

Patients who have received allogeneic stem cell transplant and/or have active graft -versus-host disease (GVHD) will be excluded.

Patients who have received autologous stem cell transplant within last 4 weeks will be excluded.

Exclusion #5 revised to add ‘significant’ to the history and/or current evidence of tissue calcification. It will read ‘History and/or current evidence of **significant** tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, myocardium and lung with the exception of calcified lymph nodes and asymptomatic coronary calcification.’

Exclusion # 31 was revised to indicate ‘Patients with previous or concurrent primary malignancy within 3 years prior to starting study treatment, with the exception of adequately treated basal cell carcinoma, squamous cell carcinoma or other non-melanomatous skin cancer, or in-situ carcinoma of the uterine cervix treated curatively and without evidence of recurrence’.

[redacted]

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following changes were implemented throughout the protocol:

Protocol summary “Purpose and rationale”, “Study design”, “Population”, Section 2.1 “Study rationale and purpose”, Section 2.2 “Rationale for the study design”, Section 4.1 “Description of study design”, Section 5.1 “Patient population”, Section 5.2 and Inclusion criteria number 3 removed the word “select”.

Section 2.1 and Section 5.1 were updated to clarify that Urothelial cell carcinoma, Cholangiocarcinoma, and Glioblastoma multiforme with FGFR 1-4 genetic alterations will be excluded, however these tumors may be included on a case by case basis upon prior approval by Novartis. Urothelial cell carcinoma, Cholangiocarcinoma, and Glioblastoma multiforme with FGF Ligand amplifications are allowed.

Section 7.2.3 ‘Pharmacokinetics’ was updated to allow for PK sample collection for BGJ398 and its metabolites.

[redacted]

Section 8.2.2 “Reporting” was update to provide guidance on SAE follow-up.

Section 5.1, Section 5.2, Section 7.1.1, and Section 7.2.4 were updated to include a Note indicating an archival or fresh tumor sample may not be required if the patient has had their genomic profiling performed at a laboratory selected by Novartis and the patient has agreed to allow Novartis to use baseline molecular analysis results.

Table 3-1 Primary endpoint was updated to indicate that, for hematologic tumors, other appropriate hematological response criteria will apply and are included in the appendices.

Section 7.1.4.3 was revised to indicate that the survival follow up may be done at the discretion of Novartis.

Section 7.2.1.1 was revised to add ‘For solid tumors, an assessment of PR or greater must be confirmed at least 4 weeks after initial observation using RECIST 1.1.’

Section 7.2.1.4 Leukemia was updated to add ‘For MF and PV, the Myeloproliferative Neoplasm (MPN) Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) will be completed as is indicated in Table 7-1.’

[redacted]

Table 6-4 Follow-up for toxicity was updated with a revised language for the management of hyperphosphatemia.

Table 7-1 was updated to separately list the visit schedules of Myelofibrosis and Polycythemia vera.

Table 7-1 was updated to add additional cardiac imaging at once a month for the first 4 cycles, if clinically indicated for subsequent cycles, and at EOT.

[redacted]

[redacted]

Section 8.2.2 Reporting was revised to remove 'The follow up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.'

Section 9.4 Database management and quality control was revised to replace 'violations' with 'deviations' in the statement 'At the conclusion of the study, the occurrence of any protocol deviations will be determined.'

Section 10 "Statistical methods and data analysis" updated section to be consistent with Appendix M. Added clarification on safety set. Clarified primary objective. Clarified handling of missing values. Clarified adverse event analysis. Clarified interim analysis and sample size calculation for consistency with Appendix M.

IRB/IEC Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Cancer epidemiological and molecular studies have reported a variety of genetic alterations including gene amplifications, chromosomal translocations and mutations, as well as aberrant protein expression of FGFs/FGFRs (Fibroblast growth factor/ fibroblast growth factor receptors; Turner et al 2010). Several lines of evidence indicate that these lead to constitutive receptor activation and, thus, upregulation of the coupled signaling pathways. Gene amplifications and protein overexpression are associated with ligand independent receptor dimerization. Gene mutations affecting the extracellular ligand-binding domain can result in either receptor dimerization or stabilization of the active conformation of the receptor irrespective of ligand binding. Alternatively, intracellular point mutations in the tyrosine kinase domain can result in constitutively active forms of the receptor that signal in the absence of ligand binding or receptor dimerization.

FGFR1 gene amplification, correlating with protein overexpression, has been described in about 8.5 % breast cancer by means of chromosome in situ hybridization (CISH) analysis. Survival analysis suggests that FGFR1 amplification may be an independent prognostic factor predicting poor outcome (Elbauomy Elsheikh et al 2007). Molecular epidemiology studies indicate that also FGFR2 is amplified in 4% triple negative breast cancers (Turner et al 2010). Independent efforts have identified FGFR2 amplification also in primary gastric cancers (3 - 10%) (Mor 1993; Yoshida 1993; Hara 1998) The 11q13 amplicon, which encompasses FGF3, FGF4, and FGF19 has been found amplified in several cancer types including breast carcinomas (Haverty et al 2008). Interestingly, FGF3 and FGF4 are two of the most commonly activated oncogenes upon mouse mammary tumor virus (MMTV) insertion in the mouse genome, leading to mammary tumors. Other tumor types in which this amplicon is altered include ovarian tumors, oral squamous cell carcinomas and hepatocellular carcinomas. In the latter, FGF3 is significantly associated with metastasis and recurrence (Hu et al 2007).

More recently, it has been shown that as much as 22% of lung squamous cell car cinoma strongly associated with smoking carry an amplification of FGFR1 (Weis 2010; Dutt 2011).

Somatic activating mutations in FGFR3 have been identified in solid tumors, being particularly high in bladder carcinomas (Cappellen et al 1999), where FGFR3 overexpression is also reported (Tomlinson et al 2007). Activating point mutations of FGFR2 are known in gastric carcinomas (Jang et al 2001) and more recently discovered in endometrial carcinomas (Dutt et al 2008).

Translocation and fusion of FGFR1 to other genes resulting in constitutive activation of its kinase by oligomerization is responsible for 8p11 myeloproliferative disorder (Cross and Reiter 2008). Similar translocations and fusions for FGFR3 are associated with peripheral T-cell lymphoma while in multiple myeloma (Maeda et al 2004), recurrent chromosomal translocations of 14q32 into the immunoglobulin heavy chain switch region result in deregulated over-expression of FGFR3 (Chesi et al 1997). FGFR1, FGFR2, and FGFR3 gene fusions have been identified in diverse cancer types including cholangiocarcinoma, breast

[redacted]

cancer, prostate cancer, thyroid cancer, lung SCC, bladder cancer, oral cancer, head and neck SCC, and glioblastoma at low frequency (Wu et al 2013). Additionally, there is evidence that some of the activating mutations in FGFRs still remain ligand dependent to a certain extent so co-expression of ligand either in an FGFR amplified setting or even in a setting of activating mutation the ligand may play a role (Dienstmann et al 2013).

On the basis of the activity of BGJ398 in a variety of cancer models bearing FGFR genetic alterations (Guagnano et al 2012), BGJ398 can be exploited for therapeutic gain to treat human cancers, both solid and hematologic malignancies.

1.1.1 BGJ398 target pathway

The FGFRs are Class IV transmembrane tyrosine kinase receptors. There are four FGFR genes in mammals: 1, 2, 3, and 4, encoding several splice variants. To date, 22 different FGF ligands have been identified which elicit a broad spectrum of biological activities, including cell growth, differentiation, morphogenesis and patterning, wound healing, and angiogenesis. Recently, a subfamily of FGF ligands, FGF19, FGF21 and FGF23, have been found to act as endocrine hormones and to be involved in various metabolic processes (Itoh 2007).

The Figure below illustrates the key components of FGFR signaling pathways. Ligand binding promotes receptor dimerization and tyrosine kinase activation (Eswarakumar et al 2005). Receptor auto-phosphorylation, in turn, induces and sustains the activation of several downstream signaling pathways. FRS2 (FGFR substrate 2), a membrane-anchored docking protein, is an essential component of FGFR signaling and links the activated FGFRs to the Ras-MAPK pathway (Kouhara et al 1997).

Please refer to the [Investigator's Brochure] for additional information on BGJ398.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of BGJ398

BGJ398 is an orally bio-available, selective and ATP competitive pan-fibroblast growth factor receptor (FGFR) kinase inhibitor which has demonstrated anti-tumor activity in preclinical, *in vitro* and *in-vivo* tumor models harboring FGFR genetic alterations. BGJ398 belongs to the pyrimidinyl aryl urea chemical class and its chem ical name is 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-{6-[4-(4-ethyl-1-piperazin-1-yl)phenylamino]-pyrimidinyl-4-yl}-1-methylurea phosphate(1:1).

Please refer to the [Investigator's Brochure] for additional information on BGJ398.

1.2.1.1 Non-clinical experience

At the cellular level, BGJ398 selectively inhibits the kinase activity of FGFR1, FGFR2, FGFR3, and FGFR4, as measured by inhibition of receptor autophosphorylation with IC50 values of 3 - 7 nM for FGFR1, FGFR2 and FGFR3, and 168 nM for FGFR4. In cellular kinase selectivity assays using a panel of BaF3 cell lines rendered IL -3 independent by various tyrosine kinases, the most potently inhibited kinase, in addition to the FGFRs were VEGFR2 and FLT1 with IC50s of 1510 nM and 1591 nM, respectively.

[redacted]

Consistent with inhibition of FGFR autophosphorylation, BGJ398 inhibits FGFR downstream signaling and proliferation of human cancer cell lines harboring genetic alterations of the FGFRs. These include, among others, lung and breast cancer cell lines with FGFR1 gene amplification, gastric cancer with FGFR2 gene amplification, endometrial cancer with FGFR2 mutations and bladder cancer with FGFR3 mutations or FGFR3 translocations (Wesche 2011). In line with its cellular activity, BGJ398 shows anti-tumor activity in multiple models bearing FGFR genetic alterations (Guagnano 2012; Konecny 2013).

1.2.1.1.1 Non-clinical pharmacodynamics

In all species tested, BGJ398 exhibited a high plasma CL (clearance) and a large Vss (Volume of distribution at steady state). The compound is highly bound to plasma proteins (~ 98%) but does not preferentially distribute to red blood cells. BGJ398 is widely distributed to tissues in the rat and has a high affinity to melanin containing tissues. *In vitro* hepatic systems metabolize BGJ398 predominantly to 2 pharmacologically active metabolites: BHS697 and BQR917. Biotransformation of BGJ398 to both metabolites was observed in human hepatocyte cultures. The compound is a P-gp and BCRP substrate and also inhibits BCRP-mediated transport with an IC50 value of 0.21µM. In addition, *in vitro* data indicate that BGJ398 is primarily a CYP3A4 substrate.

BGJ398 is a potent reversible inhibitor of CYP3A4 (Ki 0.26µM). The compound also reversibly inhibits CYP2C9 and CYP2C19 with Ki of 6.09µM and 4.1µM, respectively and CYP2C8 with IC50 of 12µM. BGJ398 is also a time dependent inhibitor of CYP3A4 with a KI = 37.3 µM and Kinact = 0.0547 min -1. In addition, CQM157, a recently identified metabolite in circulating plasma from patients, is also shown to be an inhibitor of CYP2C8, CYP2C9 and CYP3A4 (IC50 less than 10 µM) and CYP2C19 (IC50 12 µM). CQM157 is also an inhibitor of transporters P-gp, BCRP, OATP1B1 and OATP1B3 (IC50 less than 5 µM).

1.2.1.1.2 Safety pharmacology and toxicology

BGJ398 showed no evidence of *in vitro* genotoxicity in Ames and chromosome aberration tests and no evidence of phototoxicity in a 3T3 photo-cytotoxicity test. *In vitro* safety pharmacology assessment of BGJ398 revealed a decrease in human Ether -à-go-go-related gene (hERG) channel activity with an IC50 of 2.0 µM (1121ng/ml).

In vivo safety pharmacology studies in rats and dogs did not reveal an y effects on central nervous or respiratory systems and on hemodynamic or electrocardiographic parameters, respectively.

In repeated dose (oral gavage; up to 4-weeks) toxicity studies, BGJ398 did lead to increases in serum FGF23 and serum phosphorous associated with partially reversible ectopic mineralization (kidney, lung, vascular and digestive systems) along with largely reversible changes in renal function parameters and bone growth plate thickening / retention of the primary spongiosa in rats (≥ 10 mg/kg/day) and dogs (≥ 10 mg/kg/day). These effects were deemed to be on-target effects mediated by pharmacological inhibition of FGFR.

In rats, corneal changes were found upon 4 weeks of BGJ398 treatment consisting of irreversible, slight bilateral opacity with dose-dependent incidence, as assessed by in vivo ophthalmology. The clinical/ophthalmoscopic finding was associated with reversible, diffuse

[redacted]

epithelial keratopathy at the highest dose of 10 mg/kg. In the 2 -week rat toxicity study, doses of 20 mg/kg/day did lead to vasculopathy associated with moribundity after 6 administrations.

In dog toxicity study, minimal, fully reversible retention of the primary spongiosa and minimal increase in mineralization in lung and kidney without observed functional impairment were observed.

1.2.1.1.3 Genotoxicity study

BGJ398 was not mutagenic in the Ames S. typhimurium test and did not produce DNA damage in an *in vitro* leukocyte Comet test. In the Comet assay using L5178Y mouse lymphoma cells, BGJ398 induced DNA damage in L5178Y cells after a 3-hour incubation.

However, the elevated tail moment was observed at highly cytotoxic concentrations and it was therefore concluded that this effect was a consequence of excessive cytotoxicity rather than direct DNA interaction. BGJ398 was not clastogenic to human lymphocytes *in vitro*. BGJ398 is judged to be non-genotoxic.

1.2.1.2 Clinical experience

1.2.1.2.1 Clinical safety

As of data cut-off date September 6, 2016, 207 patients have received at least one dose of BGJ398 in phase I study BGJ398X2101. Forty-three patients were enrolled to dose escalation cohorts and 164 patients to dose expansion arms.

Enrollment to the dose escalation cohorts was as follows: 5mg [N=3], 10mg [N=3], 20mg [N=4], 40mg [N=6], 60mg [N=3], 100mg [N=6], 50 mg bid [N=4], 125mg [N=8], and 150mg [N=6]. MTD was identified to be 125 mg qd on a continuous dosing schedule.

Dose expansion consists of 4 arms enrolling different patient populations on two different dosing schedules at 125 mg (daily or 3 weeks on/1 week off in 28-day cycles). Arm 1 [N=28] is enrolling FGFR1-amplified advanced or metastatic squamous NSCLC with FGFR1 amplification on the continuous dosing schedule. Arm 2 [N=21], which is now closed, enrolled advanced solid malignancies with any FGFR mutation or amplification dosed continuously. Arm 3 [N=49] is enrolling advanced solid malignancies with any FGFR genetic alteration, mutation, or amplification on the 3 weeks on/1 week off dosing schedule. Arm 4 [N=66] is enrolling advanced or metastatic urothelial cell carcinoma (UCC) with FGFR3 mutation or gene fusion on the 3 weeks on/1 week off dosing schedule.

The 3 weeks on/1 week off schedule was implemented based on observations of the timing and duration of drug interruptions during Cycle 1 necessitated by episodes of hyperphosphatemia. The data indicated that the median time to drug interruption was 22 days and the median duration of the interruption was 7 days.

At the time of data cutoff, 21 patients were still receiving study medication. Of the 186 patients who have discontinued from the study, 135 discontinued treatment due to progression of disease, 28 discontinued due to adverse events, 6 died while on study, 15 discontinued due to withdrawal of consent, 1 due to administrative problems, and 1 due to protocol deviation.

[redacted]

The treatment emergent adverse events as of the cutoff date of September 6, 2016, regardless of BGJ398 relationship, that occurred in 20% or more of patients are: increases in phosphorus levels (covered by the preferred terms of hyperphosphatemia, 57.5%, and blood phosphorus increased, 9.2%), constipation (39.6%), decreased appetite (36.2%), fatigue (34.3%), stomatitis (33.3%), nausea (31.4%), blood creatinine increased (28.5%), diarrhea (27.5%), alopecia (26.1%), dry mouth (23.7%), vomiting (20.8%), and anemia, 20.3%. Approximately 58 percent of patients (120/207) experienced at least one grade 3 or 4 event regardles s of the relationship to BGJ398. Grade 3 or 4 events that occurred in at least 5% of patients were lipase increased (6.8%) and alanine minotransferase increased (5.3%). Overall, most adverse events reported have been mild to moderate in severity,reversible, and unrelated to BGJ398.

Hyperphosphatemia has been seen in the majority of patients treated at doses of 100 mg qd and higher and is a pharmacodynamic (PD) marker of on-target FGFR pathway inhibition. Renal tubular phosphate secretion and reabsorption are controlled through the FGFR1 pathway. Inhibition of this pathway leads to inability to secrete phosphate and secondary elevations in FGF23. The hyperphosphatemia has been managed in the Phase 1 study by dietary phosphate restrictions, phosphate lowering therapy, and drug interruptions and dose reductions, which led to the introduction of the alternate 3 weeks on/1 week off drug schedule. Preliminary safety data with this schedule suggest improved tolerability and compliance with drug administration (e.g. fewer dose interruptions during cycle 1), though dose reductions in later cycles of therapy are not uncommon. As of a March 15, 2014 data cut off, seventeen of 25 patients (68%) who received BGJ398 on the 3 week on/1 week off schedule experienced elevated phosphorous and only 4 patients (16%) required cycle 1 interruptions or reductions. In contrast, 41 of 47 patients (87%) on the continuous dosing cycle experienced serum phosphorous elevations. Twenty patients (43%) required cycle l dose interruptions and 13 patients (28%) required dose reductions during cycle l.

Preliminary analysis does not show any effect of BGJ398 on QTc prolongation. Please refer to the BGJ398X Investigator Brochure for additional information.

1.2.1.2.2 Clinical efficacy

Preliminary antitumor efficacy has been detected in patients treated at doses of ≥ 100 mg of BGJ398 with the following tumor types: FGFR1-amplified squamous NSCLC, FGFR1-amplified squamous cell carcinoma of the head and neck, FGFR3 -mutated/gene fusion bladder cancer, and advanced cholangiocarcinoma with FGFR2 gene fusion. Clinical activity with monotherapy BGJ398 has been shown to be minimal in breast cancer patients with FGFR genetic alterations, including amplification, with best response achieved of stable disease. While all patients who responded had exposures associated with increases in blood phosphorus levels, not all patients who experienced increases in blood phosphorus levels responded to treatment with BGJ398.

Please refer to the BGJ398X Investigator Brochure for additional information.

Preliminary data obtained from the CBGJ398X2101 first in human trial indicate that the main safety findings in patients treated with BGJ398 were predicted from preclinical studies. The on-target effects on calcium-phosphate homeostasis result in the observed increases in calcium, phosphorus, and creatinine, and not associated with clinical symptoms. In general,

[redacted]

the increases have been mild to moderate in severity and manageable and reversible upon interruption or discontinuation of BGJ398 administration.

Ocular adverse events are frequent, but generally mild to moderate in severity and reversible. Corneal or retinal adverse events are recognized on ophthalmologic evaluations.

No effect of BGJ398 on ECG intervals, including QTc has been noted. Asymptomatic, reversible decreases in LVEF have been noted in patients enrolled on study as measured by serial TTE or MUGA scans.

The preliminary efficacy signals observed in patients enrolled to the trial, combined with the emerging safety profile of BGJ398, warrant continued development of this compound for the treatment of solid tumors with genetic alterations of the FGFR pathway.

1.2.1.2.3 Clinical pharmacokinetics

The pharmacokinetics (PK) of BGJ398 and active metabolites have been evaluated following single and repeat daily doses in the ongoing phase 1 study ([CBGJ398X2101]).

At 5 and 10 mg/day, plasma concentrations were low and frequently below the lower limit of quantification. Plasma concentrations were consistently quantifiable starting at 20 mg/day.

Following a single dose, median Tmax was approximately 2-3 hours. The mean AUC0-24 on Day 1 increased approximately 9 fold from 20 to 150 mg. A mean terminal elimination half-life on Day 1(T1/2) was 3-7 hr. Despite the relatively short half-life on Day 1, accumulation was observed with daily dosing at doses ≥ 60 mg, likely due to auto-inhibition of CYP3A4 mediated clearance pathways. Mean accumulation ratio (Racc) ranged from 3 to 8 on Days 15 and 28. Since dose interruptions occurred frequently following continuous daily dosing of BGJ398, PK parameters on Day 28 should be viewed with caution. The inter-patient variability was high for BGJ398. When dosed at 125 mg with a schedule of 3 weeks on, 1 week off, the mean Cmax and AUC0-24 were 230 ng/mL (n=12) and 3492.9 ng*hr/mL, (n=10), respectively at day 15. The coefficient of variation for Cmax and AUC0 -24 ranged from approximately 50 – 75% and higher variability was observed while estimating secondary pharmacokinetic parameters like clearance and volume of distribution.

Concentration data from active metabolites BHS697 (desethyl metabolite) and BQR917 (N-oxide) was available across all cohorts. CQM157 (aniline metabolite) was analyzed in a few patients following Amendment 6 of the BGJ398X2101 clinical protocol. In most patients, BHS697 and BQR917 were measurable at levels of ~5-50%, and <15% of parent exposure, respectively. Mean exposures on Day 1 (N=8) for CQM157 relative to BGJ398 varied across patients (3% -300%). CQM157 (N=4) did not appear to accumulate on daily dosing, whereas accumulation was observed for BGJ398 and metabolites BHS697 and BQR917.

Please refer to the [Investigator's Brochure] for additional information on BGJ398.

[redacted]

2 Rationale

2.1 Study rationale and purpose

Genomic profiling is becoming more accessible to patients and their physicians. As such, more patients have been identified with potentially actionable mutations or pathway-regulations but do not have access to targeted drug treatment. Additionally, there is evidence that some of the activating mutations in FGFRs still remain ligand dependent to a certain extent so co-expression of ligand either in an FGFR amplified setting or even in a setting of activating mutation the ligand may play a role. This is a signal seeking study to match patients with FGFR genetic alterations to treatment with the pan-FGFR inhibitor BGJ398. Pre-identification of FGFR genetic alteration or FGF ligand amplification status will be performed locally at a CLIA certified laboratory prior to participation on the trial . Laboratory results must be 'unambiguous' or 'unequivocal'. Results that state 'ambiguous' or 'equivocal' imply low probability that genetic deregulation is truly present and an important driver of patient's tumor.

The purpose of this signal seeking study is to determine whether treatment with BGJ398 demonstrates sufficient efficacy in pathway-activated solid tumors and/or hematologic malignancies to warrant further study.

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome in which patients present with bone pain, fractures, and muscle weakness (Chong 2011). The cause is high blood levels of phosphate and vitamin D-regulating hormone, fibroblast growth factor 23 (FGF23).

FGF23 exerts its action through the binding of the receptor FGFR4 or the IIIc isoforms of FGFR1 and FGFR3 and its co-receptor Klotho at the renal proximal tubule. Excess levels of FGF23 downregulates the sodium-phosphate co-transporters NaPi-2a and NaPi-2c and, thereby, enhances renal excretion of phosphate leading to h ypophosphatemia with significant osteomalacia and increased fracture risk. FGF23 also reduces the levels of 1,25(OH)2D3 in the serum by increasing its metabolism and inhibiting its synthesis. (Shimada 2004). TIO is generally indolent and infrequently metastasizes. Thus, chemotherapy and radiation are ineffective, leaving surgical resection as the primary treatment. However, tumor location and surgical candidacy may preclude resection in some cases. These patients are left without good treatment options other than phosphate and activated vitamin D (calcitriol) supplementation, which is largely unsuccessful in preventing bone malformation and leaves patients significantly debilitated.

In a preclinical study, effect of BGJ398 was examined using two different mouse models of FGF23-mediated hypophosphatemic rickets, Hyp and Dmp1-null mice, models of the human diseases X-linked hypophosphatemic rickets (XLH) and autosomal recessive hypophosphatemic rickets (ARHR), respectively. A single dose of BGJ398 led to significant increases in serum calcium, phosphorus, and 1,25(OH)2D levels in these mouse models (Wöhrle et al 2013). Correspondingly, it was noted that the long-term FGFR inhibition in Hyp mice lead to the normalization of bone mineralization and a striking reorganization of the disturbed growth plate structure. Elevated serum parathyroid hormone (PTH) was also normalized after long-term treatment with BGJ398. These results show that aberrant FGF23

[redacted]

signaling could be suppressed by pharmacological inhibition of FGFRs, which efficiently alleviates the hypophosphatemia and hypocalcemia. Thus, this pharmacological approach might prove useful for the treatment of patients with hypophosphatemic disorders such as TIO caused by elevated FGF23 levels (Guagnano et al 2012). More importantly, in phase I study of BGJ398 in patients with FGFR mutated or overexpressed solid tumors, hyperphosphatemia was the most common adverse event. Phosphate elevations are a biomarker of on-target FGFR pathway inhibition which mediates renal tubular phosphate secretion and reabsorption. As serum phosphate increase is a desired outcome for patients with TIO, this provides sound rationale for evaluating the effect of BGJ398 in this patient population.

Recently, Lee JC et al (Lee et al 2015) identified a novel FN1–FGFR1 fusion gene in nine out of 11 Phosphaturic Mesenchymal Tumour (PMT) (60%) by next-generation RNA sequencing and Fluorescence in situ hybridization analysis. The fusion transcripts and proteins were subsequently confirmed with RT-PCR and western blotting. These findings may have therapeutic implications, as emerging FGFR1 antagonists such as BGJ398 have shown some anti-tumor efficacy in clinical trials, and might thus have a role in treating malignant and/or inoperable patients with TIO diagnosis.

Additional tumor types may be excluded during the course of the study at the discretion of Novartis.

Additionally, increased understanding of the genomic changes in tumors allows the selection of patients more likely to benefit from treatment. In most cases patients who respond well initially to treatment soon develop resistance to the new treatments; also, many patients have disease that does not respond. The biological complexity of cancers and lack of knowledge of the mechanisms responsible for resistance in patients pose challenges, therefore a successful development of treatments that provide sustained disease control or cure requires improving the understanding of the mechanisms responsible for drug resistance. [redacted] Details of the study design are provided in Section 4.

2.2 Rationale for the study design

This is a phase II, open label study to determine the efficacy and safety of treatment with BGJ398 in patients with a diagnosis of solid tumors or hematological malignancies that have been pre-identified (prior to study consent) to have FGFR genetic alterations and whose disease has progressed on or after standard treatment.

2.3 Rationale for dose and regimen selection

Patients enrolled in this study will receive 125 mg qd of BGJ398 on a 3 week on (21 day) /1 week off (7 day) schedule. This dose level and regimen is based on experiences from the [CBGJ398X2101] trial.

The MTD/RP2D from the CBGJ398X2101 study was identified as 125 mg administered once daily (qd) in continuous 28-day cycles. While dose levels of 100 mg qd and higher were tolerated by patients, the majority of the patients experienced reversible hyperphosphatemia, [redacted]

which lead to study drug interruptions. An evaluation of the drug administration records for patients prior to receiving prophylactic phosphate-lowering therapy, indicated that the median time until first dose interruption was approximately 23 days and the median duration of interruption was 7 days. This observation led to the introduction of an expansion arm in the ongoing CBGJ398X2101 study to evaluate the administration of 125 mg qd on a 3 weeks on (21 days) / 1 week off (7 days) schedule in 28 -day cycles. To date, the majority of patients enrolled in this arm have completed their first cycle of therapy without hyperphosphatemia - induced dose interruptions, while maintaining anti-tumor activity.

The selection of the starting dose follows the ICH S9 guidelines for choosing a starting dose for a first-in-human trial conducted in patients with cancer, and is shown in Table 6-2. It will be dosed on a flat scale and not adjusted by weight or body surface area.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary:		

• To assess clinical benefit associated with BGJ398 treatment based on local investigator assessment.
• For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR or PR or SD. For hematologic tumors other appropriate hematological response criteria will apply and are included in the appendices
• For patients with TIO diagnosis without measureable/evaluable disease, the assessment criteria will be the tumor associated changes of metabolic parameters (plasma level of FGF23 < or =180 RU/mL; and inorganic phosphorous, calcium, and 1-25-dihydroxy vitamin D greater than the LLN (- 20%); and without requirement of supplementation therapy for at least the preceding cycle of the 16 week assessment.)
	• Clinical benefit rate (e.g. defined as CR or PR or SD ≥ 16 weeks for solid tumors) at week 16. For hematologic tumors, other appropriate hematological response criteria will apply and are included in the appendices.
	• For patients with TIO diagnosis without measureable/evaluable disease, the following criteria will be the assessment at 16 weeks:
	  • the tumor associated changes of metabolic parameters: plasma level of FGF23 < or =180 RU/mL; and inorganic phosphorous, calcium, and 1-25-dihydroxy vitamin D greater than the LLN (- 20%); and
	  • without requirement of supplementation therapy for at least the preceding cycle of the 16 week assessment.
		Refer to Section 10.4.

Key secondary:		
• To assess Overall Response (OR) of Partial Response (PR) or greater based on local investigator assessment. • For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR and/or PR. For hematologic tumors other appropriate hematological response criteria will apply and are included in the appendices.	• Overall response rate (PR or greater)	Refer to Section 10.5.1.

[redacted]

Objective	Endpoint	Analysis
Other secondary:		
• To assess Progression-Free Survival (PFS) based on local investigator assessment per RECIST 1.1 or other appropriate hematological response criteria	• Time from the date of first dose to the date of first documented disease progression or relapse or death due to any cause	Refer to Section 10.5.2.
• To assess Overall Survival (OS)	• Time from the date of first dose to the date of death due to any cause	Refer to Section 10.5.2.
• To assess Duration of Response (DOR) based on local investigator assessment per RECIST 1.1 or other appropriate hematological response criteria	• Time from the first documented response to the date first documented disease progression or relapse or death due to any cause	Refer to Section 10.5.2.
• To assess safety and tolerability	• Incidence of adverse events (AEs), serious adverse events (SAEs), changes from baseline in vital signs, laboratory test results(hematology, biochemistry), ECG, and cardiac imaging will be assessed by the Common Terminology Criteria for Adverse Events (CTCAE), v4.03	Refer to Section 10.5.3.

[redacted]

[redacted]

4 Study design

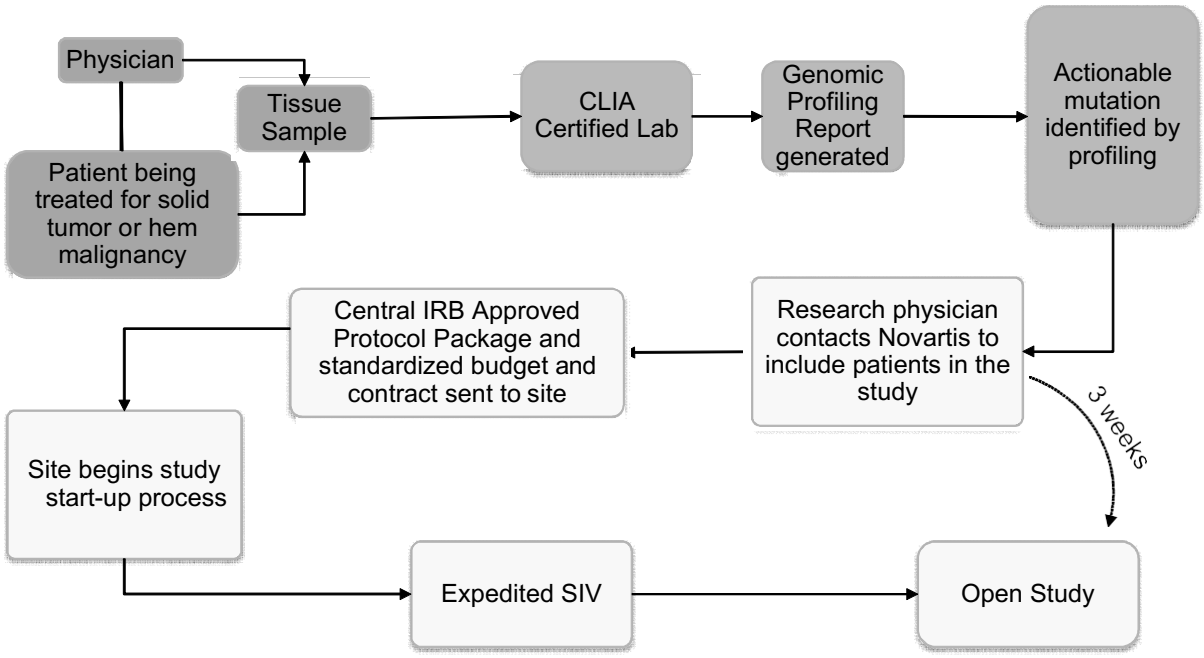
4.1 Description of study design

This is a phase II, open label study to determine the efficacy and safety of treatment with BGJ398 in patients with a diagnosis of solid tumors or hematological malignancies that have been pre-identified (prior to study consent) to have FGFR genetic alterations nd whose disease has progressed on or after standard treatment.

This study is intended for patients who have already had genomic profiling of their tumors in a CLIA certified laboratory and have already been pre-identified to have a tumor with a FGFR genetic alteration. Eligibility is based on FGFR genetic alteration status as assessed in the local, CLIA certified laboratory. The results of this testing must be known prior to signing the ICF and before formal screening begins. Laboratory results must be 'unambiguous' or 'unequivocal'. Results that state 'ambiguous' or 'equivocal' imply low probability that genetic deregulation is truly present and an important driver of patient's tumor. Once the patient has been identified, treating physicians who are qualified investigators may contact Novartis to consider enrollment in this study. For the purpose of this study, genomic profiling is not considered part of screening. Informed consent must be signed before any screening activities take place. Once eligibility criteria are met, the patient will initiate therapy with BGJ398 single-agent. The patient may not receive any additional anti-cancer therapy during treatment with BGJ398.

A schematic representation of the study start-up design is shown in Figure 4-1.

Figure 4-1 Study start-up design



[redacted]

4.1.1 Treatment phase

Patients will continue to receive study treatment until disease progression (assessed by investigator per RECIST 1.1 or appropriate hematologic response criteria or for patients with TIO diagnosis the recurrence or progression of disease or recurrence of abnormal metabolic parameters), unacceptable toxicity, death or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, start of a new anti-neoplastic therapy or at the discretion of the investigator), otherwise known as End of Treatment. Patients with TIO diagnosis that progress per RECIST but per investigator's assessment are receiving clinical benefit from treatment may remain on study upon approval from Novartis. Patients with TIO diagnosis that do not receive metabolic benefit by week 16 should discontinue unless approval from Novartis. All patients who discontinue from study treatment due to disease progression must have their progression clearly documented.

Disease assessments (per RECIST 1.1 or appropriate hematological response criteria) will be performed every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle), until disease progression or end of treatment, whichever occurs first. Upon implementation of this amendment, the frequency of disease assessment will be reduced and evaluations should be every 16 weeks after the first 16 weeks on treatment. Scans will be assessed locally by the investigator.

4.1.2 Follow-up phase

After discontinuation of treatment, patients, regardless of reason for treatment discontinuation, will be followed for safety for 30 days after the last dose.

All patients will be followed for survival status every 3 months for 2 years after the last patient has enrolled in the study, regardless of treatment discontinuation reason (except if consent is withdrawn or patient is lost to follow-up). If the primary efficacy endpoint is not met, Novartis may discontinue survival follow-up for this study.

[redacted]

For details on required assessments, please refer to Table 7-1.

4.2 Definition of end of the study

End of study is defined as the time when the last patient completes survival follow-up as described in Section 7.1.4.3, or when the last patient on study has died, been lost to follow up or withdraws consent, or when the study is terminated early, whichever occurs first.

The analysis of study data will be based on all patients' data up to the time when all patients have had the opportunity to complete at least 4 cycles (or 16 weeks) of treatment or discontinued the study. This will be the cut-off point for the primary clinical study report (CSR). Additional data for patients continuing to receive study treatment past the data cutoff

[redacted]

date for the primary CSR will be reported once all patients have discontinued treatment or been lost to follow-up. It will be reported in an addendum to the CSR, as appropriate.

At the time of CSR data cut-off, if patients are ongoing after 16 weeks on treatment and benefitting, they will continue to receive treatment, every effort will be made to continue provision of study treatment outside this study through an alternative setting to patients who in the opinion of the investigator are still deriving clinical benefit and the Novartis therapy is not commercially available and reimbursable.

4.3 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible for an end of treatment (EOT) visit and the assessments for EOT should be performed as described in Section 7 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board (IRB) and/or Ethics Committee (EC) of the early termination of the trial.

5 Population

5.1 Patient population

The study population will consist of 70- 120 adult patients with a diagnosis of a solid tumor or hematological malignancy that has been pre-identified as having FGFR genetic alterations. Patients with history/current evidence of tumor-induced osteomalacia (TIO) and FGF23-mediated hypophosphatemia with or without identification of an FGFR genetic alteration in the tumor will be allowed. Patients must have received at least one prior treatment for their recurrent, metastatic and/or locally advanced disease and have no remaining standard therapy options anticipated to result in a durable response. Patients must have progressive and measurable disease (per RECIST 1.1 or other appropriate hematological response assessment criteria) and be in need of treatment. For patients with TIO diagnosis, the presence of measurable or evaluable disease is not required provided there is evidence of FGF23-mediated hypophosphatemia (TIO patients will not be included in protocol amendment 3). This is a signal seeking study, attempting to identify additional patient populations who may benefit from treatment with single agent BGJ398.

Additional tumor types may be excluded during the course of the study at the discretion of Novartis. With Amendment 3, the study is re-opening for enrollment for the following six tumor types only: Head and Neck Squamous Cell Carcinoma, Bladder Cancer, Ovarian Cancer, Non-small cell lung carcinoma – Squamous, Glioblastoma with multiforme with FGFR 1-4 genetic alterations and Cholangiocarcinoma.

Patients must not have central nervous system (CNS) metastasis, leptomeningeal carcinomatosis, symptomatic cardiac disease, or impairment of gastrointestinal (GI) function. Patients must have archival tissue available for submission to allow for molecular testing related to pathway regulation. If tissue is not available or not of sufficient quantity the patient must be willing to undergo a fresh tumor biopsy to allow for this analysis. [redacted]

[redacted]

[redacted]

Note: An archival or fresh tumor sample may not be required if the patient has had their genomic profiling performed at a laboratory selected by Novartis and the patient has agreed to allow Novartis to use baseline molecular analysis results.

Enrollment is meant to encompass solid tumors and hematologic malignancies as having FGFR genetic alterations that may be inhibited by BGJ398 who otherwise meet all of the inclusion and none of the exclusion criteria. Amendment 3: no longer allows for patients with FGF ligand amplification or TIO diagnosis to be included. Though common for phase I studies, tissue-agnostic enrollment is unusual for phase II studies, which typically limit enrollment to one or a few well-defined tumors types. We expect that the study will enroll patients whose tumors have already been pre-identified to harbor FGFR genetic alterations such as Breast, Gastric, Esophageal, Colorectal, and Squamous Head and Neck cancers (the amendment 3 limits the tumor types from Head and Neck Squamous Cell Carcinoma, Bladder Cancer, Ovarian Cancer, Non-small cell lung carcinoma – Squamous, Glioblastoma with multiforme with FGFR 1-4 genetic alterations and Cholangiocarcinoma.). The total number of patients to be enrolled per tumor type will be based on an adaptive design. The adaptive design will be patient-sparing and allow the early closure of non-responding arms or arms where early success can be declared.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Patient has provided a signed study Informed Consent Form prior to any screening procedure
2. Patient is ≥ 18 years of age on the day of consenting to the study.
3. Patient must have:
   a. Confirmed diagnosis of (Head and Neck Squamous Cell Carcinoma, Bladder Cancer (Urothelial cell Carcinoma), Ovarian Cancer, Non-small cell lung carcinoma – Squamous, Glioblastoma multiforme and Cholangiocarcinoma are the only tumor types allowed) and is in need of treatment because of radiologic progression or relapse. Additional tumor types may be excluded during the course of the study at the discretion of Novartis. Note: Urothelial cell carcinoma, Cholangiocarcinoma, and Glioblastoma multiforme with FGFR 1-4 genetic alterations are allowed without any prior approval.
   b. [Note: as of Amendment 3, TIO patients will not be enrolled in the study]
   Clinical evidence of tumor-induced osteomalacia (TIO) associated with FGF23-mediated hypophosphatemia with or without identification of an FGFR genetic alteration, with:
      - Advanced or inoperable malignancy
      - or tumors with contraindication to surgical resection (an elevated FGF23 level at baseline must be demonstrated)
      - or tumors not amenable to cure by surgical excision (documented by investigator)

[redacted]

- or tumor-induced osteomalacia diagnosis without the presence of measurable or evaluable disease

NOTE: Patients with a diagnosis of TIO without a pre-identified tumor genetic alteration may be included on a case by case basis upon prior approval by Novartis

4. Patient is in need of treatment because of progression or relapse defined as:
   - radiological progression for solid tumor and lymphoma
   - for hematologic malignancies, measureable progression or relapse by appropriate criteria (see appendices)
5. Patient must have been pre-identified as having a tumor with any FGFR genetic alteration [such as mutation, amplification, fusion, translocation of FGF receptors 1 – 4]. The qualifying genetic alteration must be assessed and reported by a CLIA-certified laboratory. (The FGF alteration must be in combination with a mutation or fusion in FGFR.)
6. Patient must have archival tissue available for submission to allow for molecular testing related to pathway regulation. If the tissue is not available or is insufficient, the patient must be willing to undergo a fresh tumor biopsy to allow for this analysis. The sample must be submitted prior to first study dose unless agreed upon between Novartis and the investigator. See Section 7.2.4.2.1.

   Note: An archival or fresh tumor sample may not be required if the patient has had their genomic profiling performed at a laboratory selected by Novartis and the patient has agreed to allow Novartis to use baseline molecular analysis results. ()
7. Patient must have received at least one prior treatment for recurrent, metastatic and /or locally advanced disease and for whom no standard therapy options are anticipated to result in a durable remission.
8. Recovery from adverse events of previous systemic anti-cancer therapies to baseline or grade 1, except for:
   a. Alopecia
   b. Stable neuropathy of ≤ grade 2 due to prior cancer therapy
9. [Note: as of Amendment 3 **Diffuse large B cell lymphoma** patients will not be enrolled in the study] **Diffuse large B cell lymphoma only:** Patient has received or is ineligible for autologous or allogeneic stem cell transplant. This does not apply to patients with Mantle cell lymphoma or follicular lymphoma
10. Patients must have measurable disease as per appropriate guidelines:[as of Amendment 3 **Lymphoma, Symptomatic Multiple Myeloma, Leukemia and TIO** patients will not be enrolled in the study]
    a. **Solid Tumors:** by RECIST 1.1 (Appendix A)
    b. **Lymphoma:** Patient has at least one measurable nodal lesion (≥2 cm) according to Cheson criteria (Cheson 2007). In case where the patient has no measurable nodal lesions ≥ 2 cm in the long axis at screening, then the patient must have at least one measurable extra-nodal lesion (Appendix B)
    c. **Symptomatic Multiple Myeloma:** by International Myeloma Working Group (IMWG)
       - Serum M-component of ≥1 gm/dL
       - Urine M-component of ≥200 mg/24 h

[redacted]

- Patients with plasmacytoma must have a definite increase in the size; a definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion

d. **Leukemia only:** Relapsed/refractory leukemia for which no standard therapy options are anticipated to result in a durable remission:
   - Acute myelogenous leukemia (AML) by World Health Organization (WHO) classification or acute lymphoblastic leukemia (ALL) relapsed or refractory to standard chemotherapy; unsuitable for standard chemotherapy or unwilling to undergo standard chemotherapy. Philadelphia chromosome (Ph) positive ALL eligible if failed prior tyrosine-kinase inhibitor therapy.
   - Age > 60 years with AML not candidates for or have refused standard chemotherapy, excluding patients with acute promyelocytic leukemia (APL) or with favorable cytogenetic abnormalities [inv16, t(8;21)].
   - For patients with Chronic Myeloid Leukemia (CML) only accelerated and blast phase CML will be allowed.

e. **TIO diagnosis:** refer to inclusion 3b

11. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 (Appendix N).
12. Patient has a life expectancy of at least 16 weeks
13. All patients must have adequate bone marrow as described below:
    a. Absolute Neutrophil Count (ANC) ≥ 1.0 x 10^9/L (not applicable for leukemia patients)
    b. Platelets (PLT) ≥ 75 x 10^9/L (no platelet transfusion within past 14 days) (not applicable for leukemia patients)
    c. Hemoglobin (Hgb) ≥ 9 g/dl (not applicable for leukemia patients)
    d. For Leukemia patients, peripheral blast counts < 50,000 blasts/mm^3
    e. International Normalized Ratio (INR) ≤ 1.5
    f. For Leukemia patients, peripheral blast counts < 50,000 blasts/mm^3
14. All patients must have adequate organ function defined as described below:
    a. Potassium, calcium inorganic phosphorous and magnesium within normal limits (WNL). Supplementation is allowed to meet eligibility requirements
    b. Serum creatinine ≤ 1.5 x ULN
    c. Alanine aminotransferase (AST) and/or aspartate aminotransferase (ALT) ≤ 2.5 x upper limit of normal range (ULN) or ≤ 5 x ULN if liver metastases are present
    d. Total serum bilirubin within normal range (or ≤ 1.5 x ULN)
    e. Serum amylase and lipase ≤ upper limit of normal (ULN)
    f. Proteinuria ≤ Grade 2 (dipstick or 24hrs urine analysis) (Not applicable for Urothelial cell carcinoma patients)

5.3 Exclusion criteria

Patients eligible for this study must not meet any of the following criteria:

1. Patients who have received prior treatment with BGJ398

[redacted]

2. Patients with a known hypersensitivity to BGJ398 or to its excipients
3. Patients with metastatic CNS tumors are excluded, unless the patient meets criteria a-e:
   a. 4 weeks from prior therapy completion (including radiation and/or surgery)
   b. Clinically stable with respect to the CNS tumor at the time of study entry
   c. Not receiving steroid therapy
   d. Not receiving anti-convulsive medications (that were started for brain metastases)
   e. Patient with no leptomeningeal involvement
4. Current evidence of corneal or retinal disorder/ keratopathy including, but not limited to, bullous/band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjunctivits, confirmed by ophthalmologic examination
5. History and/or current evidence of significant tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, myocardium and lung with the exception of calcified lymph nodes and asymptomatic coronary calcification
6. History and/or current evidence of endocrine alterations of calcium/phosphate homeostasis, e.g. parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis etc.
7. Use of medications that increase serum levels of phosphorus and/or calcium. NOTE: Not applicable for TIO diagnosis
8. Consumption of grapefruit, grapefruit juice, pomegranates, star fruits, Seville oranges or products within 7 days prior to first dose
9. Use of medications that are known to prolong the QT interval and/or are associated with a risk of Torsades de Pointes (TdP) 7 days prior to first dose
10. Use of amiodarone within 90 days prior to first dose
11. Current use of therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulants. Heparin and/or low molecular weight heparins are allowed.
12. Patients who are currently treated with drugs known to be strong inhibitors or inducers of isoenzyme CYP3A, or substrates of CYP3A4 whose treatment cannot be discontinued or switched to a different medication prior to starting study drug.
13. Patients with diarrhea ≥ CTCAE grade 2
14. Patients with neuropathy ≥ CTCAE grade 2 unrelated to prior cancer therapy, or > grade 2 neuropathy for any other reason
15. Patients with acute or chronic pancreatitis.
16. Patients with external biliary drains.
17. Patients with impaired cardiac function or clinically significant cardiac diseases, including any of the following:
    a. History (<6 months) or presence of serious uncontrolled ventricular arrhythmias or atrial fibrillation
    b. Clinically significant resting bradycardia
    c. LVEF < 50% as determined by MUGA scan or ECHO
    d. Any of the following within 6 months prior to starting study drug: myocardial infarction (MI), severe/unstable angina, coronary artery bypass graft (CABG),

[redacted]

congestive heart failure (CHF) requiring treatment, cerebrovascular accident (CVA), transient ischemic Attack (TIA), deep vein thrombosis, or pulmonary embolism

e. Uncontrolled hypertension defined by a SBP ≥ 160 mm Hg and/or DBP ≥ 100 mm Hg, with or without anti-hypertensive medication(s). Initiation or adjustment of antihypertensive medication(s) is allowed prior to study entry.
f. QTcF >470 msec (for male and female) on screening ECGs

18. Patients with uncontrolled diabetes mellitus.
19. Patients with clinical evidence of active CNS leukemia
20. Patients who have received allogeneic stem cell transplant and/or have active graft-versus-host disease (GVHD)
21. Patients who have received autologous stem cell transplant within last 4 weeks
22. Impairment of GI function or GI disease that may significantly alter the absorption of BGJ398 (e.g. severe ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
23. Any other condition that would, in the Investigator's judgment, contraindicate patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g. infection/inflammation, intestinal obstruction, unable to swallow oral medication, social/psychological complications
24. Patients who have been treated with any hematopoietic colony-stimulating growth factors (e.g., G-CSF, GM-CSF) ≤ 2 weeks prior to starting study drug. Erythropoietin or darbepoetin therapy, if initiated at least 2 weeks prior to enrollment, may be continued. Restriction is not applicable for patients with Leukemia
25. Patient has received chemotherapy or anticancer therapy ≤ 4 weeks (6 weeks for nitrosourea, monoclonal antibodies or mitomycin-C) prior to starting study drug or who have not recovered to a grade 1 from side effects of such therapy (except for alopecia and neuropathy). Patients with leukemia may receive therapy with hydroxyurea and/or steroids for the purpose of cytoreduction but must discontinue use prior to first dose of study drug.
26. Patients who have received the last administration of an anticancer targeted small molecule therapy (e.g. sunitinib, pazopanib, everolimus) ≤ 2 weeks prior to starting study drug, or who have not recovered from the side effects of such therapy.
27. Patients not able to discontinue their current anti-cancer therapy prior to first dose of study drug.
28. Patients who have received radiotherapy ≤ 4 weeks prior to starting the study drug or who have not recovered from radiotherapy-related toxicities (note: palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting study drug is allowed)
29. Patients who have undergone major surgery (e.g., intra-thoracic, intra-abdominal, intra-pelvic) ≤ 2 weeks prior to starting study treatment or who have not recovered from side effects of such surgery.
30. Patients with previous or concurrent primary malignancy within 3 years prior to starting study treatment, with the exception of adequately treated basal cell carcinoma, squamous cell carcinoma or other non-melanomatous skin cancer, or in-situ carcinoma of the uterine cervix treated curatively and without evidence of recurrence.

[redacted]

31. Cirrhosis of the liver or known hepatitis B or C infection that is either acute or is considered chronic because the virus did not become undetectable:
    a. Hepatitis C Virus (HCV) infection: acute or chronic infection as depicted by a positive HCV RNA testing (note: in a patient with known anti-HCV but with a negative test for HCV RNA, re-testing for HCV RNA 4-6 months later is requested to confirm the resolution of HCV infection).
    b. Hepatitis B Virus (HBV) infection: acute infection (HBsAg+ with or without HBeAg+ or detectable serum HBV DNA), HBV carriers as evidence by ongoing presence of HBsAg and detectable serum HBV DNA levels.
32. Patients who have received investigational agents within $\leq 5t_{1/2}$ of the agent (or ≤ 4 weeks when half-life is unknown) prior to starting study drug.
33. Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory).
34. Patient has a history of non-compliance to medical regimen
35. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
36. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 months following the discontinuation of study treatment.
    Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    - Combination of the following (a+b or a+c, or b+c):
        a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception women should have been stable on the same oral contraception for a minimum of 3 months before taking study treatment.

Oral contraceptives (OC), injected or implanted hormonal methods are not allowed as the sole method of contraception because BGJ398 has not been characterized with respect to the potential to interfere with PK and/or the effectiveness of OCs.

[redacted]

Post-menopausal women are allowed to participate in this study. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment, then she will be considered not of child bearing potential.

37. Sexually active males unless they use a condom during intercourse while taking drug and for 3 months after the last dose of the study drug and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

6 Treatment

6.1 Study treatment

The investigational or study drug to be used in the course of this trial is BGJ398 oral formulation.

Novartis Drug Supply Management or its designee will provide BGJ398 as 100-mg and 25-mg hard gelatin capsules as individual patient supply, packaged in bottles or blisters. BGJ398 will be dosed on a flat scale and not be adjusted to body weight or body surface area.

6.1.1 Dosing regimen

BGJ398 will be dosed on a flat scale of 125 mg (e.g., 1 x 100 mg and 1 x 25 mg capsules) once daily for the first 21 days of the 28-day cycle (3 weeks on, 1 week off in a cycle). A complete treatment cycle is defined as 28 days (refer to Table 6-1).

The patient must continue to meet all eligibility criteria on C1D1, as they did during the screening period. Refer to Section 7.1 for more details.

Table 6-1 Dose and treatment schedule

Study treatment	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
BGJ398	Capsule(s) for oral use	125 mg (administered as one 100 mg capsule and one 25 mg capsule)	Daily (3 weeks on, 1 week off schedule in 28-day cycles)

6.1.1.1 BGJ398 administration

The following general guidelines should be followed for administration.

- Patients should be instructed to take their daily dose of BGJ398 in the morning, at approximately the same time each day (24 ± 2 hour interval).
- BGJ398 should be administered in the fasted state, at least 1 hour before or 2 hours after a meal

[redacted]

- Phosphate binders should be given with meal (low phosphate diet), every day on days BGJ398 is given. No treatment with phosphate binders is needed during the BGJ398 off week in a cycle, unless the lab results indicate higher serum phosphorus levels that require continuous treatment with phosphate binders.
- BGJ398 should be taken with a large glass of water (~250 mL) and consumed over as short time as possible. Patients should be instructed to swallow the capsules whole and not to chew or crush them.
- If the patient forgets to take the scheduled dose in the morning, he/she should not take the dose more than 2 hours after the usual time and should continue treatment the next day. Any doses that are missed should be skipped altogether and should not be replaced or made up at the next scheduled dosing.
- Patients must avoid consumption of grapefruit, grapefruit juice, grapefruit hybrids, pomelos, pomegranates, star fruits, Seville oranges or juice within 7 days prior to the first dose of study medications, through the end of study participation. This is due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.
- BGJ398 is characterized by pH-dependent solubility, and therefore, medicinal products that alter the pH of the upper gastro-intestinal tract may alter the solubility of both compounds, and limit bioavailability. These agents include, but are not limited to, proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids. Therefore, BGJ398 should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting and/or diarrhea (or increased stool frequency) must be noted in the AEs section of the eCRF.
- At each visit, responsible site personnel will ensure that the appropriate dose of each study drug is administered and will provide the patient with the correct amount of study drug(s) for subsequent dosing. Patients will be instructed to return unused study drugs to the site at the end of each cycle.
- The investigator (or his/her designee) must instruct the patient to take BGJ398 exactly as prescribed. The patient should be instructed to contact the investigator (or his/her designee) if he/she is unable for any reason to take BGJ398 as prescribed. All dosages prescribed and dispensed to the patient, and all dose changes during the study, must be recorded on the Dosage Administration Record eCRF. Patients must be advised to bring their unused BGJ398 capsules/tablets to the investigative site at each visit.

6.1.2 Guidelines for continuation of treatment

Patients will be treated until disease progression (as assessed by investigator per RECIST 1.1 or appropriate hematologic response criteria or for patients with TIO diagnosis the recurrence or progression of disease or recurrence of abnormal metabolic parameters) or unacceptable toxicity death or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, start of a new anti-neoplastic therapy or at the discretion of the investigator). Patients with TIO diagnosis that progress per RECIST but per investigator's assessment are receiving clinical benefit from treatment may remain on study upon approval from Novartis.

[redacted]

Guidance for continuation of study treatment in case of toxicity (e.g. dose delay and/or modification) is provided in Section 6.3.

6.1.3 Treatment duration

Patients may continue treatment with the study drug until the patient experiences unacceptable toxicity that precludes further treatment, disease progression as assessed by the investigator (per RECIST 1.1 or appropriate hematological response assessment criteria or for patients with TIO diagnosis the recurrence or progression of disease or recurrence of abnormal metabolic parameters), death and/or treatment is discontinued due to any other reason. Patients with TIO diagnosis that progress per RECIST but per investigator's assessment are receiving clinical benefit from treatment may remain on study upon approval from Novartis. The reason for end of treatment (EOT) will be recorded in the corresponding eCRF.

6.2 Dose escalation guidelines

Not applicable.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. Any changes in BGJ398 administration must be recorded on the Dosage Administration Record eCRF.

BGJ398 dose modification guidelines are described in Section 6.3.2. Any planned variance from these guidelines in the view of the patient safety must be previously discussed with the sponsor unless there is an urgent need for action.

All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria for adverse events (NCI-CTCAE version 4.03). Once a dose has been reduced during a treatment cycle, re-escalation will not be permitted during any subsequent cycle.

If the administration of BGJ398 is interrupted for reasons other than toxicity, then treatment with the study drug may be resumed at the same dose. The same applies if the patient experienced an unacceptable toxicity not specifically described in Table 6-3 or Section 6.3.4, provided this toxicity resolved to ≤ CTCAE grade 1, unless otherwise specified.

6.3.2 Permitted study treatment adjustments for BGJ398

For patients who are unable to tolerate the protocol-specified dosing schedule, dose reductions or interruptions are permitted to manage drug-related toxicities. For patients with TIO diagnosis additional dose reductions may be allowed upon Novartis approval.

- When dose reduction is necessary, the dose of BGJ398 may be reduced to 100 mg, QD.
- If an additional dose reduction is required, BGJ398 may be reduced to 75 mg, QD.
- Once the BGJ398 dose is reduced it cannot be re-escalated.
- All dose reductions should be based on the worst preceding toxicity.

[redacted]

- Patients are allowed only 2 dose reductions (to 100 mg and 75 mg) as specified in (Table 6-2).

Table 6-2 BGJ398 dose modifications

BGJ398 Dose Level	BGJ398 Dose
Starting dose level (0)	125 mg po QD (3 weeks on, 1 week off in a 28 day cycle)
Dose level – 1	100 mg po QD (3 weeks on, 1 week off in a 28 day cycle)
Dose level – 2	75 mg po QD (3 weeks on, 1 week off in a 28 day cycle)

- A third or subsequent reduction (to 50 mg, QD) in dose may be allowed if the patient is clearly benefiting from study treatment (i.e., stable disease, partial response, or complete response) but is experiencing adverse events that prevent continued treatment at the already reduced dose. For patients with TIO diagnosis without measureable/evaluable disease, the assessment criteria for additional dose reduction will be the tumor associated improvement of metabolic parameters. A third reduction or subsequent dose reduction requires approval from Novartis.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event including abnormal laboratory values must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. The maximum time allowed for treatment interruption due to toxicity is 14 days (2 weeks) from the intended dosing day. If interruption is > 14 days, the patient must be discontinued from the study treatment. However, the patient will continue to be followed for toxicity. Dose interruptions should be reported on the appropriate Dosage Administration eCRF.

6.3.3 Criteria for interruption and re-initiation of BGJ398 treatment

If the administration of BGJ398 must be interrupted because of an unacceptable toxicity, BGJ398 dosing will be interrupted or modified according to rules described in Table 6-3.

A patient who requires a dose interruption (regardless of the reason for the interruption) lasting >14 days (counting from the first day when a dose was missed) should discontinue the study treatment unless clearly demonstrating clinical benefit.

[redacted]

Table 6-3 BGJ398 related toxicity management guidelines

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Cardiac disorders	
Cardiac - Prolonged QTcF interval	
Grade 1 and 2 : QTcF ≥ 481msec and ≤ 500 msec (asymptomatic)	Maintain dose level of BGJ398 ECG (Electrocardiogram) assessments should be performed for 2 additional cycles at the same frequency as in cycle 1, or as clinically indicated • If ECG assessments show no QTcF ≥ 481 msec, for subsequent cycles ECG monitoring will be performed as per visit schedule. • If ECG assessments are still abnormal (QTcF ≥ 481 msec and ≤500 msec), then ECG monitoring must continue at the same frequency as in cycle 1 for all subsequent cycles.

Grade 3 : QTcF > 500msec as identified on the ECG by the investigator	• Hold BGJ398.
	• Monitor patient with hourly ECGs until the QTcF has returned to baseline.
	• Perform further monitoring as clinically indicated.
	• Exclude other causes of QTcF prolongation such as hypokalemia, hypomagnesaemia and decreased blood oxygenation.
	• Patients should receive appropriate electrolyte replacement and should not receive further BGJ398 until electrolytes are documented to be within normal limits.
	• Once the QTcF prolongation has resolved and if the QTcF prolongation was confirmed by the central reader, patients may be re-treated at one lower dose level at the investigator's discretion
	• ECG assessments should be performed for 2 additional cycles at the same frequency as in cycle 1 or as clinically indicated
	  • If ECG assessments show no QTcF ≥ 481 msec, for subsequent cycles ECG monitoring will be performed as per visit schedule.
	  • If ECG assessments are still abnormal (QTcF ≥ 481 msec and ≤500 msec),

[redacted]

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
	then ECG monitoring must continue at the same frequency as in cycle 1 or as clinically indicated, for all subsequent cycles • Patients who experience recurrent QTcF ≥ 500msec after one dose reduction will be discontinued from study. NB: If ventricular arrhythmia or Torsades de Pointes is observed in a patient, he/she will be discontinued from the study. Whenever QTcF > 500msec is observed, a plasma sample for determination of BGJ398 concentration should be obtained with the time of sample collection noted.
Cardiac disorders - others Grade ≥ 3, or congestive heart failure ≥ 2	Discontinue patient from study treatment.
Investigations-Hematology	
ANC decreased (Neutropenia) Grade 3 (ANC < 1.0 - 0.5 x 10^9/L)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1or baseline (repeat parameter at least twice a week and as indicated), then • If resolved within ≤ 7 days, maintain dose level of BGJ398 • If resolved within > 7 days, ↓ 1 dose level of BGJ398.
Grade 4 (ANC < 0.5 x 10^9/L)	Hold dose until resolved to CTCAE Grade ≤ 1 or baseline (repeat parameter at least twice a week and as indicated), then: • If resolved by ≤ 7 days after suspending BGJ398, maintain dose level. • If resolved by > 7 days after suspending BGJ398, ↓ 1 dose level.
Febrile neutropenia Grade 3 (ANC < 1.0 x 10^9/L, single temperature of > 38.3°C or a sustained temperature of ≥ 38.0°C)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1, then • If resolved within ≤ 7 days, ↓ 1 dose level of BGJ398. • If not resolved within 7 days discontinue patient from study drug treatment.
Grade 4	Discontinue patient from study treatment.

[redacted]

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Hemoglobin	
Grade 3 (<8.0 mg/dL – 6.5 mg/dL)	Hold dose of BGJ398 until resolved or corrected to CTCAE Grade ≤ 1 or baseline, then maintain dose level
Grade 4 (< 6.5 mg/dL)	Hold dose of BGJ398 until resolved or corrected to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level
Platelet count decreased (Thrombocytopenia)	
Grade 3 (PLT < 50 - 25 x 10^9/L) without bleeding	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline (repeat parameter at least twice a week and as indicated), then: • If resolved within ≤ 7 days, maintain dose level of BGJ398. • If resolved within > 7 days, ↓ 1 dose level of BGJ398
Grade 3 (PLT < 50 - 25 x 10^9/L) with bleeding orGrade 4 (PLT < 25 x 10^9/L)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline (repeat parameter at least twice a week and as indicated), then ↓ 1 dose level
Investigations – Renal	
Serum creatinine	
Grade 1	Maintain dose level
Grade 2	Omit dose until resolved to CTCAE Grade ≤ 1 or baseline, then: • If resolved by ≤ 7 days after suspending BGJ398, maintain dose level. • If resolved by > 7 days after suspending BGJ398, ↓ 1 dose level.
Grade ≥ 3 or 4	Omit dose and discontinue patient from study. If serum creatinine **Grade ≥ 2** has been demonstrated **in conjunction with hyperphosphatemia**, serum creatinine levels must be repeated at least weekly until resolution, and 24-hour urine collection should be obtained as clinically indicated for total phosphate, calcium, protein, and creatinine clearance. Ultrasound examination of the kidneys should be performed as clinically indicated to evaluate *de-novo* calcifications until resolution or stabilization of creatinine.

[redacted]

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Investigations – Hepatic	
Blood bilirubin (patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only)	
Grade 2 for > 7 consecutive days	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline (repeat parameter at least twice a week and as indicated), then: • If resolved within ≤ 7 days, maintain dose level of BGJ398. • If resolved within > 7 days, ↓ 1 dose level of BGJ398.
Grade ≥ 3	Omit dose until resolved to CTCAE Grade ≤ 1or baseline (repeat parameter at least twice a week and as indicated), then ↓ 1 dose level.
Grade 4	Discontinue patient from study treatment. Patients with total bilirubin ≥ Grade 1 (any duration) should have fractionation of bilirubin into total/direct or indirect/direct components and any additional work-up as clinically indicated by these results. Follow-up of hyperbilirubinemia should proceed as per the guidelines mentioned above, irrespective of the results of fractionation.
AST or ALT	
Grade 3	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline (repeat parameter at least twice a week and as indicated), then: • If resolved within ≤ 7 days, maintain dose level of BGJ398. • If resolved within > 7 days, ↓ 1 dose level of BGJ398.
Grade 4	Discontinue patient from study treatment.
AST or ALT and Bilirubin	
AST or ALT > 3.0 – 5.0 x ULN and total bilirubin > 2.0 x ULN without liver metastasis or evidence of disease progression in the liver	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 • If resolved within ≤ 7 days, ↓ 1 dose level of BGJ398. • If resolved within > 7 days, discontinue patient from study treatment.
AST or ALT > 5.0 x ULN and total bilirubin > 2.0 x ULN	Discontinue patient from study treatment.

[redacted]

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Laboratory / Metabolic disorders	
Asymptomatic amylase and/or lipase elevation	
Grade 3 (> 2.0 - 5.0 x ULN)	• Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 2. • ↓ 1 dose level of BGJ398 For recurrent grade 3 asymptomatic lipase or amylase elevation despite dose reduction, drug should be held and continuation of therapy should be discussed with the medical monitor following resolution to ≤ grade 2.
Grade 4 (>5.0 x ULN)	For any grade 4 asymptomatic lipase or amylase elevation, drug should be held and continuation of therapy should be discussed with the medical monitor following resolution to ≤ grade 2. Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder should be performed as clinically indicated within 1 week of the first occurrence of any CTCAE ≥ Grade 3 amylase and/or lipase.
Grade 4 (> 5.0 x ULN)	Discontinue patient from study treatment
Hyperphosphatemia Serum phosphorus > 7.0 mg/dL for more than 7 days despite maximal phosphate lowering therapy (Sevelamer), **Or**, Single serum phosphorus > 9.0 mg/dL regardless of duration or dose of phosphate lowering therapy (Sevelamer). (Start phosphate lowering therapy from **Cycle 1 Day 1**. Optimize/maximize dose and schedule of phosphate lowering therapy in accordance with package insert, country or institutional guidelines.)	Hold BGJ398 dose until resolved to serum phosphorus ≤ 5.5 mg/dL: Restart BGJ398 at the same dose level with maximal phosphate binder dosing if the patient did not receive maximal phosphate binder dosing for serum phosphorus > 7.0 mg/dL for > 7 days. Reduce one dose level of BGJ398 if the patient had received maximal phosphate lowering therapy for serum phosphorus > 7.0 mg/dL for > 7 days **Or** if patient had a one-time serum phosphorus of > 9.0 mg/dL. Restart BGJ398 with maximal phosphate binder dosing. It is recommended that phosphate binder dosing continues during BGJ398 dose interruptions for hyperphosphatemia and that serum phosphorus values be monitored frequently, e.g. every 2-3 days. Phosphate binder dosing should be held during the week off BGJ398 therapy each cycle (Days 22-28) for “3 weeks on / 1 week off” dosing regimen and during BGJ398 dose interruptions for non-hyperphosphatemia adverse events.

[redacted]

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Hypercalcemia	
Serum calcium grade 2	Hold BGJ398 dose until resolved to grade 1 or baseline: • if resolved within ≤ 7 days after suspending BGJ398, maintain dose level • if resolved within > 7 days after suspending BGJ398, ↓ 1 dose level
Serum calcium ≥ grade 3	Discontinue patient from the study
Nervous system disorders	
Neurotoxicity	
Grade 2	Omit dose of BGJ398 until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of BGJ398
Grade ≥ 3	Discontinue patient from study drug treatment
GI disorders	
Pancreatitis	
Grade ≥ 2	Discontinue patient from study drug treatment
Diarrhea	
Grade 1	Maintain dose level of BGJ398,initiate anti-diarrheal treatment
Grade 2	• Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 • Optimize anti-diarrheal treatment, maintain dose level of BGJ398. • For reoccurrence of diarrhea CTCAE Grade 2, hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1, ↓ BGJ398 by 1 dose level
Grade 3	• Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 • Optimize anti-diarrheal treatment • ↓ BGJ398 by 1 dose level • For reoccurrence of diarrhea CTCAE Grade 3, despite optimal anti-diarrheal treatment, discontinue patient from study treatment.

[redacted]

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended Dose Modifications any time during a cycle of therapy**
Grade 4	Discontinue patient from study treatment. Note: Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea
Vomiting	
Grade 2 not controlled by optimal anti-emetic therapy	Hold BGJ398 doses until ≤ grade 1, ↓ 1 dose level
Grade 3 not controlled by optimal anti-emetic therapy or Grade 4	Discontinue patient from study
Eye Disorders (confirmed by ophthalmologic examination)	
Retinal and Corneal disorders	
Grade 2 CSR and CSR-like events, Grade 2 Corneal disorder	Hold BGJ398 until resolved to ≤ grade 1 and continue ophthalmologic evaluation • If resolved within ≤ 14 days, ↓ BGJ398 by 1 dose level • If resolved within > 14 days, discontinue BGJ398
Grade 3 CSR and CSR-like events and any other grade 3 eye disorders	Hold BGJ398 until resolved to grade ≤ 1. • If resolved within ≤ 14 days, ↓ BGJ398 by 1 dose level • If resolved within > 14 days, discontinue BGJ398
≥ grade 1 retinal vein occlusion, grade 4 CSR and CSR-like events, and grade 4 other eye disorders	Discontinue BGJ398
Other ocular/visual toxicity	
≥ grade 3	Hold BGJ398 until resolution to ≤ grade 1 If resolution within ≤14 days, ↓ 1 dose level, otherwise discontinue BGJ398
General disorders	
Fatigue	
Grade 3	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 • If resolved within ≤ 7 days, maintain dose level of BGJ398. • If resolved within > 7 days, discontinue patient from study treatment.

[redacted]

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended Dose Modifications any time during a cycle of therapy**
Other clinically significant AEs	
Grade 3	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of BGJ398.
Grade 4	Discontinue patient from study treatment.
All dose modifications should be based on the worst preceding toxicity. Once a dose reduction has occurred, no dose increases can be subsequently implemented. Patients who require more than two dose reductions of BGJ398 will be generally discontinued from study drug treatment.	

[redacted]

6.3.4 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.

Clinical experts or specialists, such as ophthalmologist, endocrinologist, should be consulted as deemed necessary. All patients must be followed up for adverse events and serious adverse events for 30 days following the last doses of BGJ398.

6.3.5 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria as well as specific dose modification are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., hyperphosphatemia, renal toxicities are provided in Section 6.3.3. Refer to preclinical toxicity and or clinical data found in the [Investigator's Brochure].

6.4 Concomitant medications

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted (see Section 6.4.1 and Section 6.4.2), except as specifically prohibited (see Section 6.4.3).

The patient must be told to notify the investigational site about any new medications he/she takes after the start of study treatment. All medications and non-drug therapies (including physical therapy, oxygen, and blood transfusions) administered to the patient within 30 days prior to the first dose of study drug, during the course of the study, and until 30 days after the last dose of study drug, must be reported on the appropriate eCRFs.

Patients must be instructed to not take additional medications (including over-the-counter products and herbal/alternative medications) during the study without prior consultation with the investigator.

Patients taking chronic medications should be maintained on the same dose and schedule throughout the study period, if medically feasible.

6.4.1 Permitted concomitant therapy

In addition to receiving the study treatment, all patients should receive best supportive care (BSC), as per standard local practice for the treatment of pre-existing medical conditions or adverse events that may arise during the study. BSC is defined as drug or non-drug therapies, nutritional support, physical therapy, or any other treatment alternative that the investigator believes to be in the patient's best interest, but excluding other antineoplastic treatments.

Pain medication to allow the patient to be as comfortable as possible, nutritional support or appetite stimulants (e.g., megestrol), and oxygen therapy and blood products or transfusions will be allowed unless otherwise prohibited in Section 6.4.3.

[redacted]

For ongoing patients only:

For patients with TIO diagnosis phosphate supplementation is allowed, and may be titrated until discontinuation as clinically indicated throughout BGJ398 administration. Other permitted supplementation for patients with TIO diagnosis includes calcitriol and cinacalcet supplementation.

6.4.1.1 Hematopoietic growth factors

Hematopoietic growth factors (e.g. erythropoietin, G-colony stimulating factor (CSF) and GM-CSF) are not to be administered prophylactically or to be used to meet eligibility criteria. However, these drugs may be administered as per the label of these agents or as dictated by local practice or guidelines established by the American Society of Clinical Oncology (ASCO).

6.4.1.2 Hormone replacement therapies

Hormone replacement therapies such as thyroid and growth hormones are allowed, as well as estrogen replacement hormone treatment.

6.4.1.3 Phosphate-lowering therapy

Phosphate-lowering treatment, including low phosphate diet and phosphate binding therapy, such as sevelamer hydrochloride, should be implemented prophylactically at study drug initiation and modified as clinically indicated throughout BGJ398 administration.

For patients with TIO diagnosis no prophylactic phosphate lowering therapy should be implemented.

6.4.2 Permitted concomitant therapy requiring caution and/or action

6.4.2.1 Drugs that alter the pH of the GI tract

BGJ398 is characterized by pH-dependent solubility, and therefore, medicinal products that alter the pH of the upper gastro-intestinal tract may alter the solubility of BGJ398, and limit bioavailability.

6.4.2.2 CYP substrates and inhibitors

BGJ398 was shown to inhibit the CYP3A4 in in-vitro assays, thus, suggesting an increased risk of drug interactions with concomitant medications that are metabolized by CYP3A4.

BGJ398 is a substrate of CYP3A4. Therefore moderate inhibitors and inducers should be used with caution if no other alternative is available. See Appendix P.

6.4.2.3 Transporter substrates

In vitro data show that BGJ398 is an inhibitor of BCRP. Medications which are BCRP substrates must be monitored for potential toxicity and may require dose titration or reduction of the medication.

6.4.2.4 Anti-emetics

Anti-emetics are allowed for the treatment of nausea or vomiting. It is recommended to avoid using drugs that are known to cause QT prolongation. Note that some anti-emetics have a known risk for Torsade de Pointes, and therefore need to be used with caution (Appendix C). Aprepitant is both a sensitive substrate and a moderate CYP3A4 inhibitor and should be used with caution if an alternative is not available.

6.4.2.5 Medications with a possible or conditional risk of QT/QTc interval prolongation or Torsade de Pointes

Preliminary data have shown that BGJ398 has no effect on cardiac conduction or ECG intervals (see current version of the BGJ398 Investigator Brochure). However, medications that have the potential to prolong the QT/QTc interval or induce Torsade de Pointes are allowed with caution. Investigators at their discretion may co-administer such medications, but patients should be carefully monitored. See Appendix P for list of drugs that need to be used with caution. Please note that the list might not be comprehensive.

6.4.3 Prohibited concomitant therapy

6.4.3.1 Other investigational and anti-neoplastic therapies

Concurrent use of other investigational drugs is not permitted.

Anticancer therapy (chemotherapy, biologic or radiation therapy (that includes > 30% of the bone marrow reserve and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the study.

6.4.3.2 CYP inhibitors

Strong inhibitors of CYP3A4 are prohibited because BGJ398 is a likely substrate of this isoenzyme. See Appendix Q.

6.4.3.3 CYP inducers

Strong inducers of CYP3A4 are prohibited because their usage may decrease the exposure of BGJ398. Please note that the list may not be exhaustive. See Appendix Q.

6.4.3.4 Phosphorus and calcium

Medications that increase the serum levels of phosphorus and/or calcium are prohibited.

6.4.3.5 Known risk of QT/QTc interval prolongation or Torsade de Pointes medications

Preliminary data have shown that BGJ398 has no effect on cardiac conduction or ECG intervals (See current version of the BGJ398 [Investigator's Brochure]). However, medications that are known to prolong the QT/QTc interval or induce Torsade de Pointes (Risk of TdP/QT prolongation) are prohibited.

[redacted]

Please refer to Appendix Q for the list of prohibited medications. Please note that the list might not be comprehensive.

6.4.3.6 Anticoagulants

Warfarin or any other coumadin-derivative anticoagulants are not permitted. Heparin and/or low molecular weight heparins are allowed

6.5 Patient numbering, treatment assignment and enrollment

6.5.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first screened and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each Patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No. available at the site.

6.5.2 Treatment assignment and randomization

Not applicable.

6.5.3 Treatment blinding

This is an open-label study.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Patients will be provided with an adequate supply of study drug for self-administration at home, including instructions for administration, until at least their next scheduled study visit. Patients will receive BGJ398 on an outpatient basis. The investigator shall provide the patient with instructions for BGJ398 administration according to the protocol.

6.6.1 Study drug packaging and labeling

BGJ398 will be supplied as 100 mg and 25 mg capsules (refer to Table 6-4). BGJ398 capsules are packaged in HDPE bottles with child resistant closures.

Medication labels will comply with US legal requirements and are printed in the local language. The label contains BGJ398 identifying information (e.g., formulation, batch number, and expiration date), the patient number (to be entered by the investigator or designee) and storage conditions.

Table 6-4 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
BGJ398 (BGJ398)	Capsules (25 mg and 100 mg) in bottles	Labeled as BGJ398 Dosing frequency: once-a-day, 21 days on, 7 days off in a cycle of 28 days

6.6.2 Drug supply and storage

Each site will be supplied by Novartis with oral BGJ398. Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access.

Upon receipt, BGJ398 should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure]. These instructions should also be made clear to the patient for storage and self-administration of BGJ398 at home.

Site staff will be responsible for managing adequate re-supplies for BGJ398.

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

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

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to Novartis or designee.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

[redacted]

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column). Every effort must be made to follow the schedule of assessments within the ±4 days.

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Reference to assessment	Screening phase	Treatment Phase								Post treatment follow-up phase	Survival phase
			Screening	C1				C2		Subsequent cycles	EOT	Safety follow up	Survival FU
Visit Number			1	2	3	4	5	6	7	8	777	501	701
Cycle days[1]			-28 to -1	1	8	15	21	1	15	1		EOT + 30 (±4) days	EOT + every 3 months[2]
ALL PATIENTS INFORMED CONSENT													
Tumor sample (archival or fresh) for pathway activation	D	7.1.1 & 7.2.4.2.	X								X[13]		
Informed consent	D	7.1.1.	X										
[redacted]													
PATIENT HISTORY													
Demography	D	7.1.1.3.	X										
Inclusion/exclusion criteria	S	5.2 & 5.3.	X										
Eligibility checklist	S	7.1.1.1.	X										
End of phase disposition	D	7.1.3.1.									X		
Relevant medical history/ current medical conditions	D	7.1.1.3.	X										
Diagnosis and Extent of cancer	D	7.1.1.3.	X										
Prior anti-neoplastic therapy	D	7.1.1.3.	X										
PHYSICAL EXAMINATION													
Physical examination	S	7.2.2.1.	X	X[4]				X		X	X		

[redacted]

	Category	Reference to assessment	Screening phase	Treatment Phase								Post treatment follow-up phase	Survival phase
			Screening	C1				C2		Subsequent cycles	EOT	Safety follow up	Survival FU
Visit Number			1	2	3	4	5	6	7	8	777	501	701
Cycle days[1]			-28 to -1	1	8	15	21	1	15	1		EOT + 30 (±4) days	EOT + every 3 months[2]
Vital signs	D	7.2.2.2.	X	X[4]				X		X	X		
Height	D	7.2.2.3.	X										
Weight	D	7.2.2.3.	X	X[4]				X		X	X		
Ophthalmic examination	D	7.2.2.4.	X			X		X		1st day of every subsequent cycle	X		
ECOG performance status	D	7.2.2.5.	X	X[4]				X		X	X		
IMAGING AND OTHER ASSESSMENTS													
Cardiac imaging (MUGA/ECHO)	D	7.2.2.8.2.	X	Monthly for the first 4 cycles. For subsequent cycles, If clinically indicated							X		
ECG	D	7.2.2.8.1.	X	X[4]		X		X	X	X	X		
LABORATORY ASSESSMENTS													
Hematology	D	7.2.2.6.1.	X	X[4]	X	X	X	X	X	X	X		
Biochemistry (including liver function tests)	D	7.2.2.6.2.	X	X[4]	X	X	X	X	X	X	X		
FGF23 plasma level[16]	D	7.2.2.6.7.	X	X[4]		X		X		X	X		
1-25-dihydroxy vitamin D[16]	D	7.2.2.6.7.	X	X[4]		X		X		X	X		
Thyroid Function	D	7.2.2.6.3.	X	X[4]						every 3 cycles starting from C3D1 or If clinically indicated	X		
Cardiac enzymes	D	7.2.2.8.3.	X	If clinically indicated									
Coagulation	D	7.2.2.6.4.	X	X[4]	If clinically indicated								

[redacted]

	Category	Reference to assessment	Screening phase	Treatment Phase								Post treatment follow-up phase	Survival phase
			Screening	C1				C2		Subsequent cycles	EOT	Safety follow up	Survival FU
Visit Number			1	2	3	4	5	6	7	8	777	501	701
Cycle days[1]			-28 to -1	1	8	15	21	1	15	1		EOT + 30 (±4) days	EOT + every 3 months[2]
Urinalysis	D	7.2.2.6.5.	X	X[4]				X		X	X		
Pregnancy test[6]	D	7.2.2.6.6.	X	X[4]				X		X	X		
SAFETY													
Prior and concomitant medications	D	6.4.	X	Continuous								X	
Surgical and medical procedures	D	6.4.	X	Continuous								X	
Adverse events	D	8.1.	X	Continuous								X	
DRUG ADMINISTRATION AND OTHERS													
BGJ398 administration	D	6.1.1.		Daily [3 weeks on, 1 week off every cycle]									
Prophylactic phosphate-lowering therapy[10,15]	D	6.4.1.3.		Daily with meal (low-phosphate diet) on days BGJ398 is given[10]									
Survival	D	7.1.4.3.											X
ADDITIONAL EFFICACY ASSESSMENTS													
SOLID TUMOR													
Physical examination for measurement of superficial disease (only if present)[9]	D	7.2.1.1.1.	X	Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) for the first 16 weeks of treatment and every 16 weeks (±4 days) thereafter							X		
Radiological tumor assessment/ response assessment (MRI/CT Scans[3,5,7,8])	D	7.2.1.1.4.	X	Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) for the first 16 weeks of treatment and every 16 weeks (±4 days) thereafter							X		

[redacted]

	Category	Reference to assessment	Screening phase	Treatment Phase								Post treatment follow-up phase	Survival phase
			Screening	C1				C2		Subsequent cycles	EOT	Safety follow up	Survival FU
Visit Number			1	2	3	4	5	6	7	8	777	501	701
Cycle days[1]			-28 to -1	1	8	15	21	1	15	1		EOT + 30 (±4) days	EOT + every 3 months[2]
Cancer Antigen-125 (for ovarian cancer only)	D	7.2.1.1.2.	X	Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) for the first 16 weeks of treatment and every 16 weeks (±4 days) thereafter							X		
Prostate-specific antigen (PSA) (for prostate cancer only)	D	7.2.1.1.3.	X	Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) for the first 16 weeks of treatment and every 16 weeks (±4 days) thereafter							X		
LYMPHOMA													
Examination for enlarged spleen or liver	D	7.2.1.2.1.	X	To confirm response of CR							X		
Physical examination for measurement of superficial disease and B symptoms[9]	D	7.2.1.2.2.	X	Day 1 of every cycle (±4 days) after first dose of study drug							X		
Radiological tumor assessment/ response assessment (MRI/CT Scans[3,5,7,8])	D	7.2.1.2.3.	X	Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) for the first 16 weeks of treatment and every 16 weeks (±4 days) thereafter							X		
Bone Marrow Biopsy or aspirate	D	7.2.1.2.4.		To confirm response of CR[11]									
Serum protein electrophoresis (SPEP)	D	7.2.1.2.5.	X	Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) for the first 16 weeks of treatment and every 16 weeks (±4 days) thereafter only if abnormal M-protein detected at baseline							X		
PET Scan	D	7.2.1.2.6.		To confirm response of CR (can be part of CT/PET)									

[redacted]

	Category	Reference to assessment	Screening phase	Treatment Phase								Post treatment follow-up phase	Survival phase
			Screening	C1				C2		Subsequent cycles	EOT	Safety follow up	Survival FU
Visit Number			1	2	3	4	5	6	7	8	777	501	701
Cycle days[1]			-28 to -1	1	8	15	21	1	15	1		EOT + 30 (±4) days	EOT + every 3 months[2]
SYMPTOMATIC MULTIPLE MYELOMA													
Skeletal Survey	D	7.2.1.3.1.	X	If clinically indicated									
Urine protein electrophoresis (UPEP)[7]	D	7.2.1.3.2.	X	Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) for the first 16 weeks of treatment and every 16 weeks (±4 days) thereafter							X		
Free light chain[7]	D	7.2.1.3.3.	X	Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) for the first 16 weeks of treatment and every 16 weeks (±4 days) thereafter							X		
Serum protein electrophoresis (SPEP)[7]	D	7.2.1.3.4.	X	Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) for the first 16 weeks of treatment and every 16 weeks (±4 days) thereafter							X		
MRI/CT Scans (For plasmacytoma Only)	D	7.2.1.3.5.	X	Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) for the first 16 weeks of treatment and every 16 weeks (±4 days) thereafter									
Bone Marrow Biopsy or aspirate	D	7.2.1.3.6.	X	To confirm response of CR									
CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)													
Examination for enlarged spleen or liver	D	7.2.1.2.1.	X	To confirm response of CR									
Physical examination for measurement of superficial disease and B symptoms[9]	D	7.2.1.2.2.	X	Day 1 of every cycle (±4 days) after first dose of study drug							X		

[redacted]

	Category	Reference to assessment	Screening phase	Treatment Phase								Post treatment follow-up phase	Survival phase
			Screening	C1				C2		Subsequent cycles	EOT	Safety follow up	Survival FU
Visit Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**777**	**501**	**701**
Cycle days[1]			**-28 to -1**	**1**	**8**	**15**	**21**	**1**	**15**	**1**		**EOT + 30 (±4) days**	**EOT + every 3 months[2]**
Radiological tumor assessment/ response assessment (MRI/CT Scans[3,5,7,8])	D	7.2.1.2.3.	X	Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) for the first 16 weeks of treatment and every 16 weeks (±4 days) thereafter							X		
Bone Marrow Biopsy or aspirate	D	7.2.1.2.4.		To confirm response of CR									
Peripheral Blood for CBC differential and blast count	D	7.2.1.4.1.	X	X		X		X	X	X	X		
Physical examination for assessment of Extramedullary disease or Organomegaly (if present)	D	7.2.1.4.3.	X	X		X		X	X	X	X		
LEUKEMIA, MDS, and ET													
Peripheral Blood for CBC differential and blast count	D	7.2.1.4.1.	X	X		X		X	X	X	X		
Physical examination for assessment of Extramedullary disease or Organomegaly (if present)	D	7.2.1.4.3.	X	X		X		X	X	X	X		
Bone Marrow Biopsy or aspirate	D	7.2.1.4.2.	X	To confirm response of CR or if clinically indicated									
Assessments of chromosomal abnormalities/Karyotype	S	7.2.1.4.4.	X[12]										
Evaluation of transfusion dependency	D	7.2.1.4.5.	X	X		X		X	X	X	X		
MF and PV													
Peripheral Blood for CBC differential and blast count	D	7.2.1.4.1.	X	X		X		X	X	X	X		

[redacted]

	Category	Reference to assessment	Screening phase	Treatment Phase								Post treatment follow-up phase	Survival phase
			Screening	C1				C2		Subsequent cycles	EOT	Safety follow up	Survival FU
Visit Number			1	2	3	4	5	6	7	8	777	501	701
Cycle days[1]			-28 to -1	1	8	15	21	1	15	1		EOT + 30 (±4) days	EOT + every 3 months[2]
Physical examination for assessment of Extramedullary disease or Organomegaly (if present)	D	7.2.1.4.3.	X	X		X		X	X	X	X		
Bone Marrow Biopsy or aspirate	D	7.2.1.4.2.	X	To confirm response of CR or if clinically indicated									
Assessments of chromosomal abnormalities/Karyotype	S	7.2.1.4.4.	X[12]										
Evaluation of transfusion dependency	D	7.2.1.4.5.	X	X		X		X	X	X	X		
Myeloproliferative Neoplasm (MPN) Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)	D	7.2.1.4.	X	X		X		X	X	X	X		

[1] A complete cycle is defined as 28 days

[2] Additional survival assessments may be performed outside the 3 months follow-up schedules if a survival update is required for an interim assessment to meet safety or regulatory needs.

[3] Tumor assessments at EOT are required for patients who discontinue study treatment before the first scheduled post-screening tumor assessment and for patients whose previous tumor assessment did not demonstrate PD and was done at least 8 weeks (± 4 days) prior to end of treatment visit.

[4] These assessments should be performed only if the screening assessment occurred > 4 days from Cycle 1 Day 1. The patient must continue to meet all eligibility criteria on C1D1, as they did during the screening period prior to first dose.

[5] Tumor assessments include CT/MRI of the chest abdomen and pelvis at all timepoints. Tumor assessments are described in Section 7.2.1.

[6] Women of childbearing potential must undergo a serum pregnancy test at screening and EOT. Women of child-bearing potential will undergo monthly urine pregnancy tests during the study.

[7] For patients who have a response of PR or greater, a confirmation assessment must be performed at least 4 weeks after the initial observation.

[8] Upon implementation of amendment 2, the frequency of disease assessment will be reduced and evaluations should be every 16 weeks after the first 16 weeks on treatment.

[9] Skin lesions should be documented using a digital camera (color photography) in clear focus showing the ruler or calipers and the corresponding measurement in such a way that the size of the lesion(s) can be determined from the photograph

[redacted]

	Category	Reference to assessment	Screening phase	Treatment Phase								Post treatment follow-up phase	Survival phase
			Screening	C1				C2		Subsequent cycles	EOT	Safety follow up	Survival FU
Visit Number			1	2	3	4	5	6	7	8	777	501	701
Cycle days[1]			-28 to -1	1	8	15	21	1	15	1		EOT + 30 (±4) days	EOT + every 3 months[2]

[10] Phosphate binders should be given with meal (low phosphate diet), every day on days BGJ398 is given. No treatment with phosphate binders is needed during the BGJ398 off week in a cycle, unless the lab results indicate higher serum phosphorus levels that require continuous treatment with phosphate binders. Calcium-containing phosphate binders are not recommended.

[11] Only to confirm complete responses in patients with bone marrow tumor involvement prior to study treatment

[12] Information on the patient's chromosomal abnormalities/karyotyping based on documented history prior to study entry must be present in his/her source documents. 12 Additional testing to confirm these response categories will not be required and should be done at the discretion of the attending physician.

[13] For patients with a best response of Stable disease or better who discontinue study treatment due to disease progression, an optional tumor sample should be obtained for genomic analysis. For details, refer to Section 7.2.4.

[redacted]

[15] For patients with TIO diagnosis no prophylactic phosphate lowering therapy should be implemented

[16] Only applicable for patient with TIO diagnosis. FGF23 plasma levels and 1-25-dihydroxy vitamin D should be measured: at screening, C1D1 (if screening assessment occurred > 4 days from Cycle 1 Day 1), C1D15, and on Day1 of each subsequent cycles up to and including Day 1 of Cycle 5. Thereafter, should be measured every 16 weeks and EOT. A +/-4 days window is allowed for each assessment

[redacted]

7.1.1 Screening

For the purpose of this study, genomic profiling is not considered part of screening. This study is intended for patients who have already had genomic profiling of their tumors in a CLIA certified laboratory and have already been pre-identified to have tumors with relevant pathway activation. Eligibility is based on the pathway-activation study as assessed in the local, CLIA certified laboratory. The results of this testing must be known prior to signing the ICF and before formal screening begins. Laboratory results must be 'unambiguous' or 'unequivocal'. Results that state 'ambiguous' or 'equivocal' imply low probability that genetic deregulation is truly present and an important driver of patient's tumor. Written informed consent must be obtained before any study specific assessments are performed, including screening. All screening evaluations must be performed as closely as possible to the beginning of treatment and never more than 28 days prior to starting study drug dose of BGJ398 to confirm patient's eligibility.

Upon signing the Informed Consent Form (ICF), a patient will be assigned a 7-digit patient number.

Patient must have archival tissue available for submission to allow for molecular testing related to pathway activation and other analyses. If the tissue is not available or not of sufficient quantity, the patient must be willing to undergo a fresh tumor biopsy to allow for this analysis. The tissue submitted will not be used to determine study eligibility. Eligibility is based on the local assessment. The tissue will be collected and may be analyzed at some future date for markers of pathway activation.

Note: An archival or fresh tumor sample may not be required if the patient has had their genomic profiling performed at a laboratory selected by Novartis and the patient has agreed to allow Novartis to use baseline molecular analysis results.

For the purposes of enrollment, the patient's pathway activation status is based on the presence of known FGFR genetic alterations or FGF ligand amplification as assessed in a CLIA-certified laboratory and primary documentation in the form of a test result from that laboratory.

Patients who fail to start on treatment may be re-screened.

Disease assessments (per RECIST 1.1 or appropriate hematologic response criteria) must be performed within 28 days prior to enrollment and will be assessed locally by the investigator.

When information from procedures (for example imaging assessments) that may have been previously performed as part of the patient's routine disease care (prior to enrolling in the trial) is allowed to be used to satisfy inclusion criteria, if it was performed within 28 days before the start of study treatment.

For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure.

[redacted]

For details of assessments, refer to Table 7-1 and Section 7.2.

7.1.1.1 Eligibility screening

Once all screening procedures are completed, patient's mutational status will be confirmed by Novartis or designee prior to the subject receiving the first dose of study drug.

7.1.1.2 Information to be collected on screening failures

Patients who sign the ICF, but are not enrolled for any reason will be considered a screen failure.

For screen failure patients, the reason for not proceeding with enrollment will be entered on the Screening Log eCRF. No waivers will be granted.

The following eCRFs must be completed for screening failure patients:

- Screening Log eCRF page (including reason for not being started on treatment)
- Informed Consent
- Demography
- Serious Adverse Event after signing the ICF - see Section 8 for SAE reporting details.

7.1.1.3 Patient demographics and other baseline characteristics

Patient information to be collected at screening will include:

- Pathway regulation inhibited by BGJ398 status
- Demographic data (age, gender, race)
- Diagnosis and Extent of Cancer
- Relevant Medical History (e.g., important medical, surgical, and allergic conditions from the patient's medical history, which could have an impact on the patient's evaluation) / Current Medical Conditions (e.g., all relevant current medical conditions which are present before the first dose of study drug is administered).
    - Cancer-related conditions and symptoms which are recorded on the Medical History eCRF should include the grade
- Prior Anti-neoplastic Medications
- Prior Anti-neoplastic Radiotherapy
- Prior Anti-neoplastic Surgery
- All other medications and non-drug therapies (including physical therapy, oxygen and blood transfusions) administered to the patient within 28 days prior to the first dose of study drug) must be reported on the appropriate eCRFs
- Furthermore the following assessments will be performed to assess the eligibility of the patient:
- Physical Examination (See Section 7.2.2.1)
- Vital signs (See Section 7.2.2.2)
- Height, weight (See Section 7.2.2.3)
- ECOG performance status (See Section 7.2.2.5)

[redacted]

- Ophthalmic examination (See Section 7.2.2.4)
- Laboratory evaluations (e.g., hematology, coagulation, biochemistry, urinalysis, liver function monitoring) (See Section 7.2.2.6)
- [redacted]
- Serum pregnancy (See Section 7.2.2.6.6)
- Cardiac assessment (See Section 7.2.2.8)
- Disease evaluations (See Section 7.2.1)
- Radiological assessments (e.g., CT scan) if clinically indicated (See Section 7.2.1)

7.1.2 Treatment period

Patients will be treated with BGJ398 (125 mg, orally, once-a-day,) until disease progression, unacceptable toxicity, death or discontinuation from the study treatment due to any other reason.

For details of safety and efficacy assessments, refer to Table 7-1 and Section 7.2.

- Visits and associated assessments that occur ± 4 days from the scheduled date (except for cycle 1 Day1 where no visit window is allowed) will not constitute protocol deviations.
- The cycle length is 28 days. Day 1 of subsequent cycles will be calculated from cycle 1, day 1.
- Disease Assessments (per RECIST or appropriate hematological response criteria) must be performed every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle), until disease progression or end of treatment, whichever occurs first. Upon implementation of this amendment, the frequency of disease assessment will be reduced and evaluations should be every 16 weeks after the first 16 weeks on treatment.
- Laboratory assessments performed as part of the screening evaluations and within 4 days of the first dose of study treatment, are not required to be repeated on the first dosing day.
- [redacted]
- For ongoing patients with TIO diagnosis FGF23 plasma assessment and 1-25-dihydroxy vitamin D will be collected, refer to Table 7-1 and Section 7.2.2.6.7.

7.1.3 End of treatment visit, including premature withdrawal and study discontinuation visit

7.1.3.1 End of treatment (EOT) visit

Patients who completely discontinue study treatment should be scheduled for an End of Treatment (EOT) visit within 14 days following the date study treatment is permanently discontinued, at which time all of the assessments listed for the EOT visit will be performed. For details of assessments, refer to Table 7-1. If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit.

[redacted]

An End of Treatment Phase Disposition eCRF page should be completed, giving the date and reason for stopping the study treatment. If a study withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment Phase Disposition eCRF page.

End of treatment/Premature withdrawal visit is not considered as the end of the study.

[redacted]

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

7.1.3.2 Criteria for premature patient withdrawal (EOT phase completion)

Patients **may** voluntarily withdraw from the study or be dropped from it at the discretion of the investigator or by the sponsor at any time.

Premature patient withdrawal refers to the point/time when the patient exits from the study treatment prior to the planned completion of all study treatment administration and/or assessments; at this time, all study drug treatment is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival.

Patients may be withdrawn from the study treatment if any of the following occur:

- Adverse Event
- Lost to follow-up
- Non-compliance with study treatment
- Physician decision
- Pregnancy
- Progressive Disease
- Protocol deviation
- Study terminated by sponsor
- Subject/guardian decision
- Death
- In addition to the general withdrawal criteria, the following **study specific criteria** will also require study treatment discontinuation:
  - Adjustments to study treatment that result in discontinuation. Please refer to Section 6.3.
  - Use of prohibited medication. Please refer to Section 6.4.3.

[redacted]

- Interruption of study treatment for > 14 days, regardless of reason, from the intended day of the next scheduled dose

7.1.4 Follow up period

7.1.4.1 Safety follow up

All patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations (i.e., assessment of AEs and/or SAEs, concomitant medications) for 30 days after the last dose of study treatment. Patients whose treatment is interrupted or permanently discontinued due to an adverse event, including abnormal laboratory value, must be followed at least once a week for 4 weeks and subsequently at 4-weeks intervals until resolution or stabilization of the event, whichever comes first.

If patients refuse to return for safety evaluation visits or are unable to do so, every effort should be made to contact them by telephone to determine their status. Attempts to contact the patient should be documented in the source documents (e.g., dates of telephone calls, registered letters, etc.).

7.1.4.2 Efficacy follow-up

Not applicable.

7.1.4.3 Survival follow-up

Survival information will be collected, only for six tumor types that are listed in the inclusion criteria,every 3 months until 2 years after the last patient has enrolled in the study regardless of treatment discontinuation reason (except if consent is withdrawn). If the study primary efficacy endpoint is not met, Novartis may decide not to conduct survival follow-up for the study. Additional survival assessments may be performed outside the 3 months follow-up schedules if a survival update is required for an interim assessment to meet safety or regulatory needs.

Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs.

7.1.4.4 Lost to follow-up

Patients lost to follow up should be recorded as such in the eCRFs. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7.1.5 End of post-treatment follow-up (Study phase completion)

Not applicable.

[redacted]

7.2 Assessment types

7.2.1 Efficacy assessments

The primary efficacy endpoint is clinical benefit rate as defined in Section 10.4. The key secondary efficacy endpoint is overall response rate of PR or greater as defined in Section 10.5. Other secondary endpoints are time from the date of first dose to the date of first documented disease progression or relapse or death due to any cause, time from the date of first dose to the date of death due to any cause, time from the first documented response to the date first documented disease progression or relapse or death due to any cause, AE rate, and other safety measurements as defined in Section 10. The local investigator's assessment will be used for the analysis and for treatment decision making.

Clinical suspicion of disease progression at any time will require assessment and confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment. In case of an unscheduled or delayed tumor assessment for any reason, subsequent disease assessments must be performed according to the originally planned schedule from baseline.

7.2.1.1 Solid tumors

Response will be evaluated, using modified Response Evaluation Criteria in Solid Tumors, based on RECIST 1.1. For complete details, refer to Appendix A.

Clinical evaluation and tumor assessments will be performed as is indicated in Table 7-1, based on physical examination and radiological evaluation. For solid tumors, an assessment of PR or greater must be confirmed at least 4 weeks after initial observation using RECIST 1.1.

Any lesion that has been previously treated with radiotherapy should be considered as a non-target lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a target lesion.

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Definitions for measurable and non-measurable lesions, and criteria for response, should be based on RECIST 1.1 (Appendix A).

7.2.1.1.1 Physical examination for superficial disease

Clinical assessment of any existing superficial lesions (skin nodules and palpable lymph nodes) at screening and at each subsequent tumor assessment must be performed on the same schedule as radiological tumor assessments (see Section 7.2.1.1.4).

Skin lesions should be documented using a digital camera (color photography) in clear focus showing the ruler or calipers and the corresponding measurement in such a way that the size of the lesion(s) can be determined from the photograph. Skin photographs should be continued at subsequent tumor assessments for any lesions that were photographed at screening.

[redacted]

7.2.1.1.2 Cancer Antigen-125 (CA-125)

Cancer Antigen-125 (CA-125) will be used in the assessment of ovarian cancer at screening. Subsequent tumor assessments must be performed on the same schedule as radiological tumor assessments (see Section 7.2.1.1.4).

7.2.1.1.3 Prostate Specific Antigen (PSA)

Prostate Specific Antigen (PSA) will be used in the assessment of prostate cancer at screening. Subsequent tumor assessments must be performed on the same schedule as radiological tumor assessments (see Section 7.2.1.1.4).

7.2.1.1.4 Radiological tumor assessment

At screening and at each subsequent tumor assessment (not applicable for patients with TIO diagnosis without measurable/evaluable disease), all patients must have a CT scan with contrast of the Chest/Abdomen and Pelvis. If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts) plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.

The same type of CT scan used at screening must be used for all subsequent assessments. MRI with contrast will be allowed only in those cases when CT scan cannot be performed and will be used at baseline and all subsequent assessments in these patients. No modality change will be allowed during the study when assessing overall tumor status. For subsequent scans in the same patient, the radiologist must account for all lesions that were present at screening and must use the same technique as used at screening. If possible, a single radiologist should perform all tumor response evaluations for an individual patient. Only in exceptional cases when during the study a patient develops intolerance to the CT scan contrast medium, a CT scan without contrast will be acceptable to avoid modality change. At screening, tumor assessments should preferably be performed ≤ 4 days prior to the first dose of BGJ398, however tumor assessments ≤ 28 days prior to first dose of study drug will be acceptable.

Tumor assessments will be performed at screening and every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle). Upon implementation of this amendment, the frequency of disease assessment will be reduced and evaluations should be every 16 weeks after the first 16 weeks on treatment.

7.2.1.2 Lymphoma

[Please note that these assessments are for ongoing patients only. There will not be additional Lymphoma patients enrolled for amendment 3]

Response will be evaluated, using modified criteria for malignant lymphoma Cheson (Appendix B) and Ann Arbor Staging Classification (Appendix C).

Clinical evaluation and tumor assessments will be performed periodically, as is indicated in Table 7-1, based on evaluation of spleen and liver, physical examination for superficial disease and B symptoms, radiological evaluation, Serum Protein electrophoresis (SPEP), core bone marrow biopsy (only to confirm complete responses in patients with bone marrow tumor

[redacted]

involvement prior to study treatment), and positron emission tomography (PET) (only to confirm complete responses in patients where PET was used for study entrance).

7.2.1.2.1 Enlarged spleen and liver

The presence of enlarged spleen or liver before start of treatment on the basis of CT scan (or MRI scan) should be recorded on the corresponding eCRF at baseline, and reassessed if the patient has a radiological CR.

A maximum four of the largest dominant measurable nodules representing all involved anatomic locations should be selected as splenic and hepatic index lesions to be measured.

All other splenic or hepatic nodules (both measurable and non-measurable) are considered as non-index lesions.

7.2.1.2.2 Physical examination for superficial disease and B symptoms

Tumor assessment by physical examination and 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) will be performed at screening and day 1 of every cycle (±4 days) after first dose of study drug. Refer to Appendix B for specifications and measurement.

Skin lesions should be documented using a digital camera (color photography) in clear focus showing the ruler or calipers and the corresponding measurement in such a way that the size of the lesion(s) can be determined from the photograph. Skin photographs should be continued at subsequent tumor assessments for any lesions that were photographed at screening.

7.2.1.2.3 Radiological tumor assessment

Tumor assessments will be performed at screening, and every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle), until disease progression or end of treatment, whichever occurs first. Upon implementation of this amendment, the frequency of disease assessment will be reduced and evaluations should be every 16 weeks after the first 16 weeks on treatment.

At screening and at each subsequent tumor assessment, all patients must have a CT scan with contrast of the Chest/Abdomen and Pelvis. If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts) plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.

MRI with contrast will be allowed only in those cases when CT scan cannot be performed and will be used at baseline and all subsequent assessments in these patients. No modality change would be allowed during the study. When assessing overall tumor status. For subsequent scans in the same patient, the radiologist must account for all lesions that were present at screening and must use the same technique as used at screening. If possible, a single radiologist should perform all tumor response evaluations for an individual patient. Only in exceptional cases when during the study a patient develops intolerance to the CT scan contrast

medium, a CT scan without contrast will be acceptable to avoid modality change. At screening, tumor assessments should preferably be performed ≤ 4 days prior to the first dose of BGJ398, however tumor assessments ≤ 28 days prior to first dose of study drug will be acceptable.

All patients should have at least one site of measurable nodal disease > 2.0 cm in the longest transverse diameter and clearly measurable in at least two perpendicular dimensions, as determined by CT scan (MRI is allowed only if CT scan cannot be performed). Complete guidance for selecting index lesions is provided in Appendix B. Index lesions will be measured and recorded at baseline and during the course of the study. They should be selected on the basis of their size and suitability for accurate repeat measurements. Skin lesions, if the area is ≥ 2 cm in at least one diameter, must be histologically confirmed for lymphoma involvement (the site must document the histological confirmation (yes or no) to the corresponding eCRF) and photographed (color photography using digital camera).

A sum of the product of diameters (SPD) for lesions measured prior to study treatment will be calculated and reported at cycle 1 day 1.

Conventional CT and MRI should be performed with contiguous cuts of 7.5 mm or less in slice thickness. Spiral CT should be performed using a 5 mm or less contiguous reconstruction algorithm (this specification applies to tumors of the chest, abdomen and pelvis).

If a very small lesion cannot be reliably measured because of its size, it is recommended to enter the minimum lesion size (i.e., 5 mm for spiral CT). In other cases where the lesion cannot be reliably measured for reasons other than its size (i.e., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

Any measurable extranodal lesions (organs other than lymph nodes) that resolves from baseline (disappear completely) must be assigned a size of 0 mm when documenting on the corresponding eCRFs. An extranodal lesion must be ≥ 1 cm x 1 cm to be considered measurable. Refer to Appendix B for complete reporting guidelines.

7.2.1.2.4 Bone marrow assessment

Information on the patient's bone marrow involvement based on documented history prior to study entry must be present in his/her source documents. Prior tumor bone marrow involvement should be entered on the corresponding eCRF.

Core bone marrow biopsy or aspirate will not be performed at screening but is required to confirm complete responses (at the first occurrence of radiological and clinical evidence of CR) in patients with bone marrow tumor involvement prior to study treatment who achieve Complete Response based on clinical and radiological evidence. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). Bone marrow biopsy or aspirate should be obtained no later than at the next visit immediately following clinical and radiological evidence of CR (i.e. < 28 days ± 7 days from the date of the radiological assessment, on which the CR is based on).

7.2.1.2.5 Serum protein electrophoresis (SPEP)

Serum protein electrophoresis (SPEP) will be performed by the local laboratory at screening and on the same schedule as radiological tumor assessments (see Section 7.2.1.2.3) only if abnormal M-protein is detected at screening.

7.2.1.2.6 Positron emission tomography (PET)

The use of Positron emission tomography (PET) is not standard in Novartis Oncology Lymphoma studies. PET evaluations that have been done as standard of care prior to enrollment will be recorded in the eCRF. Repeat PET will be required only for patients who have responses of CR for the purpose of this study and should be done within +/- 7 days of the CT or MRI to confirm CR. Refer to Appendix B for lesion measurements.

7.2.1.3 Symptomatic multiple myeloma

[Please note that these assessments are for ongoing patients and no new patients with symptomatic myeloma will be enrolled]

Response will be evaluated using the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma. For complete details, refer to Appendix O.

Clinical evaluation and disease assessments will be performed periodically, as is indicated in Table 7-1, based on a skeletal survey Urine protein electrophoresis (UPEP), Free light chain, Serum Protein electrophoresis (SPEP), bone marrow biopsy, and MRI/CT Scans (For plasmacytoma only).

7.2.1.3.1 Skeletal survey

Skeletal survey will be performed at screening and if clinically indicated as outlined in Table 7-1.

7.2.1.3.2 Urine protein electrophoresis (UPEP)

Urine protein electrophoresis (UPEP) will be performed by the local laboratory at screening, every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) and EOT.

7.2.1.3.3 Free Light Chain

Free Light Chain will be performed by the local laboratory at screening and on the same schedule as UPEP assessments (see Section 7.2.1.3.2).

7.2.1.3.4 Serum protein electrophoresis (SPEP)

Serum protein electrophoresis (SPEP) will be performed by the local laboratory at screening and on the same schedule as UPEP assessments (see Section 7.2.1.3.2).

7.2.1.3.5 MRI/CT scans (for plasmacytoma only)

For patients with plasmacytoma, a MRI/CT scan will be performed by the local laboratory at screening and on the same schedule as UPEP assessments (see Section 7.2.1.3.2).

[redacted]

7.2.1.3.6 Bone marrow assessment

Information on the patient bone marrow involvement prior to study entry must be present in his/her source documents. Prior tumor bone marrow involvement should be entered on the corresponding eCRF.

Core bone marrow biopsy is required to confirm Complete Responses (at the first occurrence of radiological and clinical evidence of CR) in patients with bone marrow tumor involvement prior to study treatment who achieve Complete Response based on clinical and radiological evidence. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). Bone marrow biopsy should be obtained no later than at the next visit immediately following clinical and radiological evidence of CR (i.e. < 28 days ± 7 days from the date of the radiological assessment, on which the CR is based on).

7.2.1.4 Leukemia

[Please note that these assessments are for ongoing patients and no new patient with Leukemia will be enrolled]

Response for AML will be evaluated using the revised recommendations of the International Working Group (IWG) as noted in Cheson (2003) (Appendix E). Response for ALL will be evaluated using guidelines adapted from NCCN Guidelines Version 1.2013 (Appendix F). CML will be evaluated using guidelines adapted from NCCN Guidelines Version 4. 2013 (Appendix G). The response for CLL will be evaluated using the revised recommendation of the IWG as noted in Hallek (2008) (Appendix H). The response for myelodysplasia (MDS) will be evaluated using the revised recommendation of the IWG as noted in Cheson (2006) (Appendix L). The response for polycythemia vera (PV) and essential thrombocythemia (ET) will be evaluated using the recommendation of IWG-MRT as noted in Barosi (2013) (Appendix J and Appendix K respectively). The response for myelofibrosis (MF) will be evaluated using IWG-MRT as noted in Tefferi (2013) (Appendix I).

Clinical evaluation and disease assessments for AML, ALL, CML, MDS, PV, ET, and MF will be performed periodically, as is indicated in Table 7-1, based on peripheral blood and bone marrow assessment as well as the presence or absence of extramedullary disease, and organomegaly, and evaluation of transfusion dependency. For MF and PV, the Myeloproliferative Neoplasm (MPN) Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) will be completed as is indicated in Table 7-1.

Clinical evaluations and disease assessments for CLL will be performed periodically as is indicated in Table 7-1, based on the lymphoma assessments schedule for evaluation of physical examination for superficial disease and B symptoms, radiological evaluation, core bone marrow biopsy (only to confirm complete responses in patients with bone marrow tumor involvement prior to study treatment) and Rai staging criteria (Appendix D). Peripheral blood, and the presence or absence of extramedullary disease and organomegaly will also be performed on the same schedule as other leukemia evaluations as indicated below.

To assess response, the time interval between bone marrow and blood assessments may not exceed 5 days. If the time interval is more than 5 days, response status cannot be assessed at that time point. Regular bone marrow assessments are not required after achieving a CR unless indicated by blood counts or clinical assessments or specified in the protocol

[redacted]

The response assessment date is defined as the last of all dates of measurements which are required to qualify for a response category within the period listed above. This rule applies also in case of multiple measurements of the same variable. In case of relapse, the first of all measurement dates associated with a disease assessment will be used as assessment date. The assessment date will be used for the derivation of the time-to-event endpoints.

7.2.1.4.1 Peripheral blood evaluation for CBC

Peripheral blood evaluations will be performed by the local laboratory at screening, Day 1 and Day 15 of Cycles 1 and 2, at Day 1 of each subsequent cycle, and at EOT.

Peripheral blood evaluation for CBC will be taken from the same sample and include evaluation of blast, neutrophil, and platelet cell count.

7.2.1.4.2 Bone marrow assessment

Bone marrow will be assessed for blast cell count at screening, to confirm response of CR or if clinically indicated.

Percent blast cell count will be determined by cytological examination. This assessment can be performed in terms of bone marrow aspirate and/or biopsy. Results from these tests are considered to be interchangeable to assess blasts counts. In case both aspirate and biopsy were done, both tests will be considered for response assessment:

In case of only one assessment with non-missing values: Data of the non-missing test result will be used.

In case of both assessments with differing, non-missing data: For blast counts, the highest value will be considered. For Auer rods, the positive finding will be considered, if applicable

7.2.1.4.3 Physical examination for extramedullary disease and/or organomegaly

Extramedullary involvement (CNS and/or soft tissue) is to be assessed at each visit for response assessment. Presence with specification of location or absence of extramedullary disease is to be captured in the eCRF. Extramedullary disease is to be assessed via clinical examination or relevant imaging techniques as clinically appropriate.

In case of extramedullary disease at baseline or (re-)appearance during the study, the lesions need to be confirmed cytologically if technically and/or clinically feasible. A clinical assessment will be made in case a cytological confirmation is not possible

The presence of organomegaly (hepatomegaly and/or splenomegaly) is to be assessed at baseline at visits as part of the response assessment. The modality used: scan or palpation is to be noted.

7.2.1.4.4 Assessments of chromosomal abnormalities

Information on the patient’s chromosomal abnormalities/karyotyping based on documented history prior to study entry must be present in his/her source documents. Additional testing to confirm these response categories will not be required and should be done at the discretion of the attending physician.

[redacted]

7.2.1.4.5 Evaluation of transfusion dependency

Transfusion dependency will be assessed at screening as well as during the course of the trial for all patients. Transfusion of blood products will be recorded in a separate module of the eCRF. The type and reason for transfusion, start and end date as well as the number of units will be captured at each visit with hematologic assessment.

A period of one week without any transfusion has been taken as a convention to define the status of transfusion independence to assess response. Any sample of peripheral blood which was taken within seven days after a transfusion will be considered as transfusion dependent.

For the definition of transfusion dependency, it does not matter which type of blood product was transfused. Moreover, the rules and time windows defined below apply not only to blood transfusions but also to erythropoietin, thrombopoietic agents and/or myeloid growth factors.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, vital signs, weight, performance status evaluation, ECG, cardiac imaging, ophthalmology examinations, laboratory evaluations as well as collecting all serious and non-serious Adverse Events (AE). For details on AE collection and reporting, please refer to Section 8.1.

Clinically significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent and meet the definition of an AE must be recorded on the Adverse Event page of the patient's eCRF.

7.2.2.1 Physical examination

A complete physical examination will be performed at screening at Day 1 of each cycle and at the EOT visit. Visit windows of ± 4 days are allowed (except at cycle 1 Day 1). As specified in Table 7-1, a screening physical examination performed prior to 4 days of first dosing does not need to be repeated at Cycle 1 Day 1.

The physical examination comprises a total body examination that should include: general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological review. If indicated, rectal, external genitalia, breast and pelvis exams will be performed. Information about the physical examination must be present in the source documentation at the study site.

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) will be monitored at screening, EOT, and before administration of BGJ398 at Day 1 of each cycle. Screening vital sign assessments performed within 4 days of first dosing do not need to be repeated at Cycle 1 Day 1. Vital signs will be measured according to normal medical practice.

7.2.2.3 Height and weight

Height and body weight will be measured. Weight will be measured at the screening visit, at Day 1 of each cycle, and at EOT. Screening weight assessment performed within 4 days of

[redacted]

first dosing does not need to be repeated at Cycle 1 Day 1. Height will be collected at screening only.

7.2.2.4 Ophthalmic examination

Ophthalmologic examination will be performed as indicated in Table 7-1 which includes: visual acuity testing, slit lamp examination of the anterior eye segment, IOP, and fundoscopy. Additional examination methods such as specular microscopy (that enables a magnified, direct view of the corneal epithelium), corneal pachymetry, and dilated fundoscopy will be performed as clinically indicated.

7.2.2.5 Eastern Cooperative Oncology Group (ECOG) Performance status

Eastern Cooperative Oncology Group (ECOG) Performance status

The performance status will be assessed according to the ECOG performance status scale (Oken 1982). ECOG performance status will be assessed at screening, at Day 1 of each cycle and at the EOT visit (Appendix N). ECOG performance assessment performed within 4 days of first dosing does not need to be repeated at Cycle 1 Day 1.

7.2.2.6 Laboratory evaluations

Clinical laboratory analyses (hematology, biochemistry, coagulation, lipase, urinalysis, pregnancy test) are to be performed by the local laboratory according to the Visit Schedule outlined in Table 7-1. Visit windows of ± 4 days are allowed (except at cycle 1 Day 1). As specified in Table 7-1, screening laboratory assessments performed prior to 4 days of first dosing do not need to be repeated at Cycle 1 Day 1. For patients with TIO diagnosis blood should be collected for FGF23 plasma assessment and 1-25-dihydroxy vitamin D. Novartis must be provided with a copy of the local laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the date of revalidation. Additionally, if at any time a patient has laboratory parameters obtained from a different (outside) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

More frequent laboratory examinations may be performed at the investigator's discretion if clinically indicated.

At any time during the study, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (*e.g.*, require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the Adverse Events eCRF page. Laboratory data will be summarized using the Common Terminology Criteria for Adverse events (CTCAE) version 4.0.3. Additional analyses are left to the discretion of the investigator.

[redacted]

7.2.2.6.1 Hematology

Hematology tests are to be performed by the local laboratory at screening, Days 1, 8, 15, 21 of Cycle 1 and Days 1and 15 of Cycles 2, at Day 1 of each subsequent cycle and at EOT according to the Visit Schedule outlined in Table 7-1. The hematology panel includes hemoglobin, hematocrit, platelet count, total red blood cells (RBC), total white blood cells (WBC) count, and a WBC differential including neutrophils, lymphocytes, monocytes, eosinophils and basophils.

7.2.2.6.2 Biochemistry

Biochemistry tests are to be performed by the local laboratory at screening, Days 1, 8, 15, 21 of Cycle 1 and Days 1and 15 of Cycles 2, at Day 1 of each subsequent cycle and at EOT according to the Visit Schedule outlined in Table 7-1. The full biochemistry panel includes blood urea nitrogen (BUN), creatinine, uric acid, sodium, magnesium, potassium, glucose, calcium, inorganic phosphate [Pi], LDH, total protein, albumin, bicarbonate, amylase, lipase, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides. Additionally liver function test including AST/SGOT, ALT/SGPT, GGT, alkaline phosphatase, total, direct and indirect bilirubin will be measured.

7.2.2.6.3 Thyroid function

Thyroid function tests parameters include: thyroid stimulating hormone (TSH), free T3, and free T4.

Thyroid function should be assessed at screening, Day 1 of Cycle 1, Day 1 of Cycle 3, every 3 cycles from C3D1 during the treatment phase (or if clinically indicated), and at EOT.

7.2.2.6.4 Coagulation

International normalized ratio (INR) and pro-thrombin time (PT), activated partial thromboplastin time and fibrinogen will be measured at screening, Day 1 of Cycle 1, and during the treatment phase if clinically indicated.

7.2.2.6.5 Urinalysis

Urinalysis includes dipstick analysis of pH, bilirubin, ketones, leukocytes, protein, glucose, blood, and specific gravity, and will be performed at screening, Day 1 of each cycle and at EOT.

If clinically indicated based on macroscopic urinalysis results, a microscopic evaluation examination will be performed and will include Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, and Epithelial cells.

7.2.2.6.6 Pregnancy and assessments of fertility

Women of childbearing potential must undergo a serum pregnancy test at screening to confirm eligibility in the trial (≤ 4 days before first dose of study drug), and at EOT. Women of child-bearing potential must additionally undergo a monthly urine pregnancy test during the treatment phase.

[redacted]

In case of pregnancy, the patient must permanently stop study treatment immediately, withdraw from the trial, and the pregnancy must be reported on the Clinical Trial Pregnancy Form.

7.2.2.6.7 FGF23 plasma and 1-25-dihydroxy vitamin D

For ongoing patients with TIO diagnosis FGF23 plasma levels and 1-25-dihydroxy vitamin D should be measured: at screening, C1D1 (if screening assessment occurred > 4 days from Cycle 1 Day 1), C1D15, and on Day1 of each subsequent cycles up to and including Day 1 of Cycle 4. Thereafter, should be measured every 16 weeks and EOT. A +/-4 days window is allowed for each assessment. Blood collection should be performed according to institutional guidelines.

7.2.2.7 Radiological examinations (for safety)

Not applicable.

7.2.2.8 Cardiac assessments

7.2.2.8.1 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed at screening, Day 1 and Day 15 of Cycles 1 and 2, at Day 1 of each subsequent cycle and at EOT according to the Visit Schedule outlined in Table 7-1.

The interpretation of the tracing must be made by a qualified physician and documented in the ECG section of the eCRF. Each ECG tracing should be labeled with the study number, patient initials (if permitted by local regulations), Patient Number, date, and kept in the source documents at the study site. Only clinically significant abnormalities should be reported in the Adverse Events eCRF. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with the Novartis Medical Monitor prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

7.2.2.8.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

MUGA (multiple gated acquisitions) scan or echocardiogram (ECHO) will be used to assess LVEF as indicated in Table 7-1 to assess signs or symptoms of cardiotoxicity. In case of clinically significant abnormalities, they should be reported on the Adverse Events eCRF.

In case a patient develops left ventricular systolic dysfunction while on study treatment dose adjustment guidelines described in Section 6.3 must be followed.

7.2.2.8.3 Cardiac enzymes

Cardiac enzymes (Cardiac troponin-I or troponin-T) will be measured at screening and during the treatment phase if clinically indicated, especially in case of LVEF decrease.

[redacted]

7.2.3 Pharmacokinetics

Unscheduled blood samples for BGJ398 plasma concentration measurements will be collected in the event of an adverse event at the investigators discretion. Residual plasma samples may also be used for exploratory analysis to further characterize the PK of BGJ398 and its metabolite(s). This analysis may include using leftover samples for protein binding analysis or metabolite profiling (e.g., other metabolites and markers for metabolic enzyme activity) if there is sufficient sample remaining. Study samples may be re-analyzed at other Novartis approved facilities for the determination of long term stability or cross-check between Novartis approved laboratories. These additional investigations are not considered part of this study and, as such, the results of any such analyses will not be included in the final report. Exact dates and actual PK blood draw time will be recorded on the appropriate eCRF and the time of dose administration prior to the sample collection will also be recorded. Any sampling problems must be noted in the comments section of the eCRF and on appropriate source documentation. Unscheduled PK samples will be assigned PK sample numbers beginning with 1001 (1002, 1003 etc in the event of additional samples taken).

Examples of rationale for the collection of unscheduled PK samples are provided below:

- If a patient treated with investigational drug experiences an AE that results in an unscheduled visit or fits the criteria of a SAE or DLT, as determined by the investigator.
- Whenever an ECG with a QTcF change from baseline > 60 ms or a new absolute QTcF ≥ 501ms result is known, two separate unscheduled blood samples should be collected concomitantly to assess concentrations of BGJ398. The exact time of sample collection should be noted in the eCRF

7.2.3.1 Pharmacokinetic blood sample collection and handling

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Blood should be collected in accordance with institutional guidelines. At the specified time points, 3 mL blood sample will be collected in tubes with a specific anticoagulant K_3-EDTA. Immediately after each tube of blood is drawn, it should be inverted gently several times to ensure the mixing of tube contents (e.g. anticoagulant). Avoid prolonged sample contact with the rubber stopper. Blood samples should be kept in an ice water bath at approximately until centrifugation. The tubes should be centrifuged as soon as possible but within no more than 30 minutes after collection at approximately 800 x g at 4ºC for 15 minutes to separate plasma. The plasma (approximately 1.5 mL) will be separated into 2 aliquots (at least 0,5 mL each) to be transferred to a polypropylene screw-cap tube, the tube capped, and then immediately placed in a freezer set at ≤ -60ºC until shipment to Novartis for analysis.

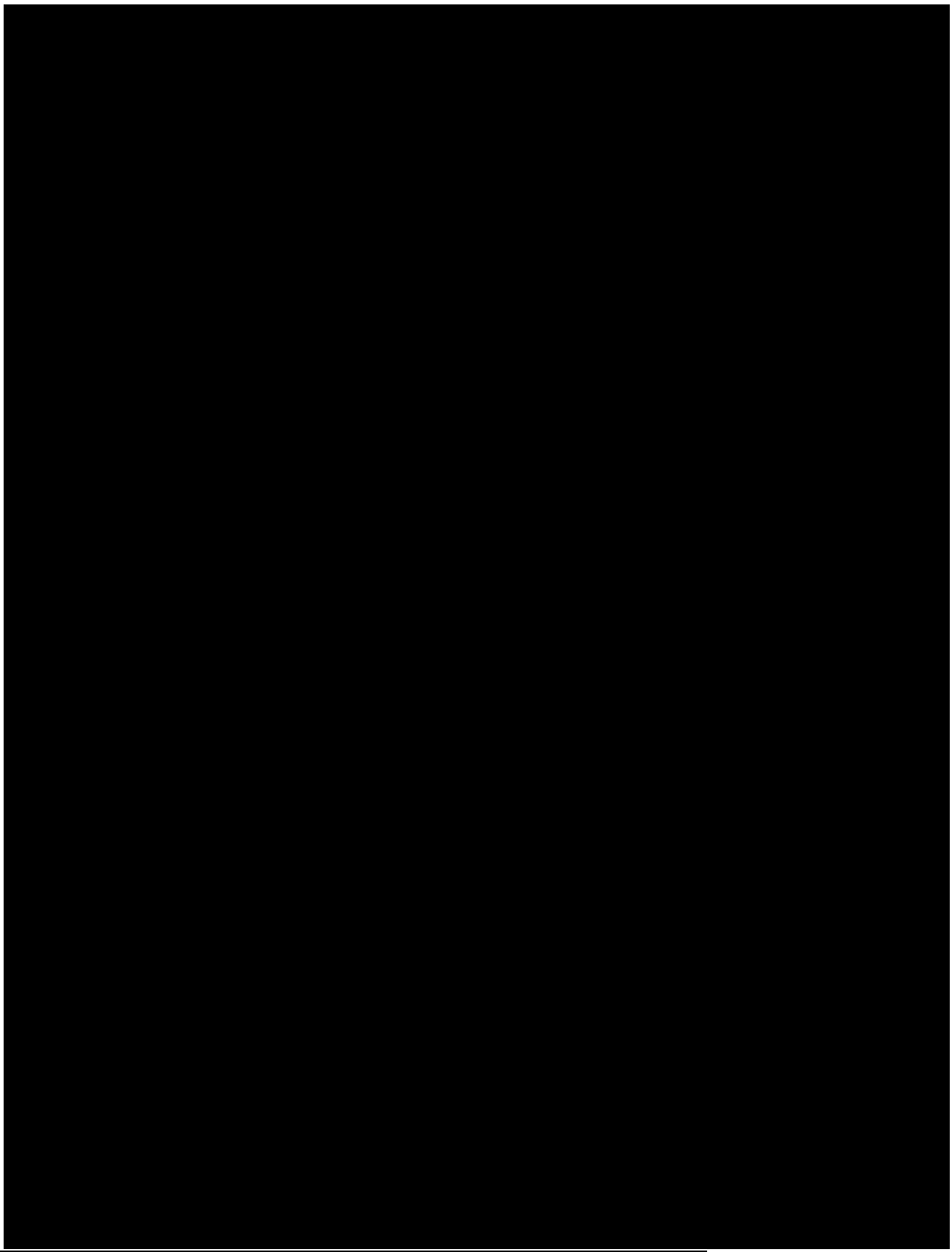
Refer to the [Laboratory Manual] for detailed instructions for the collection, handling and shipping of samples.

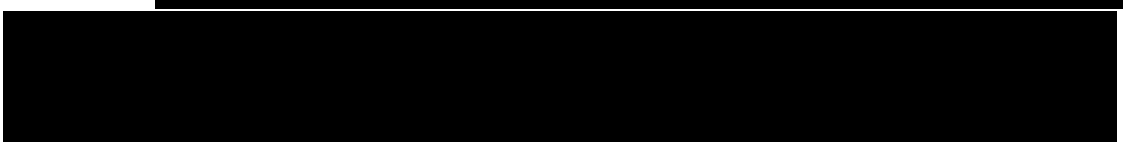
7.2.3.2 Analytical method

Plasma concentrations of BGJ398 and its active metabolites (BHS697 and CQM157) will be measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of approximately 1.0 ng/mL.

[redacted]

Concentrations below the LLOQ will be reported as 0 ng/mL and missing samples will be labeled accordingly.





[redacted]

[redacted]

7.2.5 Other assessments

No additional tests will be performed on patients entered into this study.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event (AE) is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

[redacted]

For patients who sign the ICF, all AEs will be captured in the AE eCRF from time of signature through 30 days after permanent study treatment discontinuation. For patients who fail the screening, only SAEs will be captured in the AE eCRF page.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History eCRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1-4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (as per RECIST 1.1 criteria for solid tumors), should not be reported as a serious adverse event or adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAEv4.03 does not automatically indicate an SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol and is still, by definition, an adverse event.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

[redacted]

- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

SAE collection starts at time of ICF signature whether the patients is a screen failure or not.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded on the Serious Adverse Event Report Form on a paper SAE Form. The investigator must assess and record the relationship of each SAE to the study treatment, and complete the SAE Report Form in English.

The SAEs recorded on the paper SAE form should be faxed to [redacted] **within 24 hours of awareness of the SAE** to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS). The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Note that any follow up information provided should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

Refer to Section 7.1.1.2 for additional details regarding the reporting of SAEs which occur during the screening period.

8.3 Emergency unblinding of treatment assignment

Not applicable

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination,

[redacted]

details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS)department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator's Brochure]. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

Not applicable.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

[redacted]

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the Investigator or designee will enter all required patient data into the eCRF within 72 hours (3 days) of the patient visit. The field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

This study will use Electronic Data Capture (EDC) and the designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Mutational analysis data will be generated by CLIA certified local labs. We anticipate that the data available in the report will vary from lab to lab. The PI will enter data directly onto the eCRF to verify that the patient meets the requirements of “pathway activation” as outlined in the inclusion criteria Section 5. Anonymized lab reports will be collected to gather information regarding pathway activations.

If a tumor sample is obtained at the time of disease progression (optional), data about the sample will be collected in the eCRF.

Laboratory assessments for hematology, biochemistry, coagulation, urinalysis, MUGA and ECGs will be collected locally and entered directly onto the eCRFs.

9.4 Database management and quality control

This study will be using eCRFs and the designated CRO will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA current version) terminology.

Data from the screening molecular analysis will be collected locally and entered directly onto the eCRF. Tissue samples for pathway activation confirmation will be analyzed centrally.

At the conclusion of the study, the occurrence of any protocol deviations will be determined. After this action has been completed and the data has been verified to be complete and accurate, the database will be declared locked and the data made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the US Oncology Medical Affairs Franchise Head and the US Oncology Medical Affairs Franchise Vice President.

After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

All data except the primary efficacy variable clinical benefit rate will be analyzed by a designated CRO in collaboration with Novartis. The analysis of the clinical benefit rate will be performed by a separate CRO using the Bayesian adaptive design approach described in details in Appendix R. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation. The data from all centers that participate in this study will be combined in the final safety and efficacy analysis.

This trial will enroll patients from at 6 histologic groups:

- NSCLC - Squamous
- Ovarian
- Glioblastoma Multiforme
- Squamous Head and Neck
- Bladder
- Cholangiocarcinoma

[redacted]

In addition, another group currently simply referred to as "Other" may be identified and enrolled throughout the study (e.g. "Other" will be a focused histologic group, but may not be explicitly identified until the trial is ongoing due to recruitment issues). We discuss the logistics in more detail below, but a decision will only be made for a group other than the 6 listed if 1) more than 3 patients are enrolled in the group, and 2) a reasonable estimate of the clinical benefit rate is available.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) will include all patients who have received at least one dose of the study drug.

FAS will be used for the analysis of all efficacy endpoints.

10.1.2 Safety Set

The Safety Set will include all patients who received at least one dose of study treatment and had at least one post-baseline safety assessment.

Please note: the statement that a patient had no adverse event (on the Adverse Event eCRF) constitutes a safety assessment.

The Safety Set will be used for the analysis of all safety endpoints.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be listed and summarized by patients groups formed by the type of cancer at study entry using the FAS (please see Table 4-1 of Appendix B for predicted target cancer population). Additional groups may be added based on enrollment (See Appendix R). Categorical data, such as gender, race, etc., will be presented by frequencies and percentages. Descriptive summary statistics (e.g., frequency, mean, median, range and standard deviation) will be used to present numeric data.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study medication

Duration of study treatment exposure, cumulative dose and dose intensity will be summarized by the patient groups as above using the Safety Set. The number of patients with dose changes/interruptions will be presented along with reasons for the dose change/interruption. The Safety Set will be used for the tables and listings.

10.3.2 Concomitant therapies

Concomitant medications and significant non-drug therapies taken concurrently with the study drugs will be listed and summarized for the FAS by Anatomical Therapeutic Chemical Classification System (ATC) term and preferred term by means of frequency counts and percentages. These summaries will include medications starting on or after the start of study

treatment (defined as cycle 1 day 1) or medications starting prior to the start of study treatment and continuing after the start of study treatment.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed. The Safety Set will be used for all above mentioned concomitant medication tables and listings.

10.4 Primary objective

The primary endpoint is clinical benefit rate (CBR) in each group, with clinical benefit being assessed at 16 weeks.

For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR or PR or SD ≥ 16 weeks. For hematologic tumors other appropriate hematological response criteria will apply and are included in the appendices.

For patients with TIO diagnosis without measureable/evaluable disease, the following criteria will be the assessment at 16 weeks:

- the tumor associated changes of metabolic parameters: plasma level of FGF23 < or =180 RU/mL; and inorganic phosphorous, calcium, and 1-25-dihydroxy vitamin D greater than the LLN (- 20%); and
- without requirement of supplementation therapy for at least the preceding cycle of the 16 week assessment.

For solid tumors, an assessment of CR or PR must be confirmed at least 4 weeks after initial observation, using RECIST 1.1. If the two assessments differ, the best response will be determined by Table 3-3 of Appendix A.

10.4.1 Variable

The primary efficacy variable is the clinical benefit rate (CBR) (e.g. defined as CR or PR or SD ≥ 16 weeks for solid tumors) at week 16.

10.4.2 Statistical hypothesis, model, and method of analysis

The study will enroll patients from at least 6 histologic groups. In addition, another group simply referred to as "Other" may be identified and enrolled throughout the study.

Let Y_i be the response indicator for the i^{th} subject, and let R_g be the assumed probability of response within a control population and $\pi_g = \Pr(Y_i = 1 \mid g_i = g)$ be the underlying probability of response for group g. We transform to the logit scale for modeling purposes. Let θ_g be the mean log odds treatment effect, i.e.:

$$\theta_g = \log\left(\frac{\pi_g}{1-\pi_g}\right) - \log\left(\frac{R_g}{1-R_g}\right) = \log\left(\frac{\pi_g}{1-\pi_g}\right) - \log\left(\frac{R_g}{1-R_g}\right)$$

Thus, θ_g is the group specific logistic regression coefficient for the treatment within group g. The primary analysis is a set of group specific tests that $\theta_g > 0$, meaning that the treatment is better than the assumed control rate within that group. Thus, we wish to test the set of hypotheses

[redacted]

$$H_{0g}: \theta_g \leq 0$$

$$H_{1g}: \theta_g > 0$$

We proceed in a Bayesian fashion, assigning a prior distribution (details in Appendix R) and computing the posterior probability of H_{1g} within each group g. If, at the final analysis,

$$\Pr(\theta_g > 0 \mid \text{data}) > 0.90$$

Then group g will be declared a success (thus, the final analysis produces a separate decision for each group). The trial also allows for early stopping of groups, described below.

The statistical design borrows information across subgroups with a hierarchical model. The hierarchical model allows dynamic borrowing of information between groups such that more borrowing occurs when the groups are consistent and less borrowing occurs when the groups differ. In this way, the model is a compromise between the two alternate extremes of either a completely pooled analysis or a separate analysis in each group. We additionally incorporate a clustering mechanism that allows borrowing within clusters but treats clusters separately. This minimizes borrowing across groups that are quite different in terms of CBR.

The purpose of such an analysis (discussed in more detail in the appendix) is to produce higher power or lower type I error in situations where we see some commonality (identical effects are not required) among the groups. The model will borrow more in situations where the groups appear similar than situations where the groups appear different.

Details of the hierarchical model are provided in Appendix R.

10.4.3 Evaluation of trial success and futility

The clinical benefit rate will be evaluated for futility and early success by comparing posterior quantities for the rate to pre-specified early stopping criteria. The evaluations are planned to occur after the first 30 patients have been dosed for at least 16 weeks or discontinued, then every 13 weeks thereafter.

Early futility

If there is less than 10% probability that the response rate in a group exceeds the historical rate R_g, then the group will stop enrollment early for futility. Formally, enrollment will stop early for futility if:

$$\Pr(\pi_g > R_g) < 0.10.$$

A group is only eligible for early stopping once a minimum of 10 patients has been evaluated for response in that group.

Early success

If there is at least 95% probability that the response rate in a group exceeds the historical rate, then the group will stop enrollment early for success. Formally, enrollment will stop early for success if:

$$\Pr(\pi_g > R_g) > 0.95.$$

[redacted]

A minimum of 15 subjects will need to be evaluated prior to declaring a group to be efficacious.

Final analysis

The final analysis will occur when both accrual and follow-up are complete for all subjects. If, at the completion of the trial, there is at least 90% probability that the response rate in a group exceeds the historical rate, then the group will be considered a success. Formally:

$$\Pr(\pi_g > R_g) > 0.90.$$

In addition, a group will be considered as "promising' if:

$$0.80 =< \Pr(\pi_g > R_g) < 0.90.$$

The control rates R_g are shown in Table 14-1 of Appendix R.

10.4.4 Handling of missing values/censoring/discontinuations

A patient who has not progressed or died at the date of the analysis cut-off would have his/her PFS and OS censored at the time of the last adequate assessment before the cut-off date. Any disease assessment indicating response status other than "unknown" or "not done" is considered an adequate response assessment.

No imputation of missing values will be performed on any of the efficacy endpoints.

10.4.5 Supportive analyses

Not applicable.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

The key secondary objective of this study is to assess Overall Response (OR) of Partial Response (PR) or greater based on local investigator assessment.

For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR and/or PR. For hematologic tumors other appropriate hematological response criteria will apply and are included in the appendices.

The overall response rate (PR or greater) and its 95% exact confidence interval will be provided for each patient group.

10.5.2 Other secondary efficacy objectives

The secondary efficacy objectives of the study:

- To assess progression free survival (PFS) based on local investigator assessment per RECIST 1.1 or other appropriate hematological response criteria
- To assess overall survival
- To assess duration of response (DOR) based on local investigator assessment per RECIST 1.1 or other appropriate hematological response criteria

[redacted]

The secondary efficacy variable progression free survival (PFS) is defined as the time from the date of first dose to the date of first documented disease progression or relapse or death due to any cause.

PFS will be summarized and graphed using the Kaplan-Meier product-limit method for each patient group. Patients who drop-out without progression will be censored at the time of last adequate assessment. The estimates of the 25th, median, 75th percentiles of the PFS and their 95% confidence intervals will be provided, if applicable.

Overall survival (OS) is defined as the time from the date of first dose to the date of death due to any cause. If a patient is not known to have died, survival time will be censored at the date of the last contact.

OS will be summarized and graphed using the product-limit method as above.

The duration of response (PR or greater) applies only to patients whose best response was PR or greater. For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR and/or PR. For hematologic tumors other appropriate hematological response criteria will apply and are included in the appendices. The duration of response is defined as the time from the first documented response to the date first documented disease progression or relapse or death due to any cause. The duration of response will be summarized descriptively for each patient group.

If the study primary efficacy endpoint is not met, Novartis may decide not to conduct some of the above secondary efficacy analyses but instead provide those endpoints in listings only.

10.5.3 Safety objectives

For all safety analyses, the Safety Set will be used. All listings and tables will be presented by patient groups.

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., electrocardiogram, vital signs) will be considered as appropriate. All safety data will be listed.

The safety summary tables will include only assessments collected no later than 30 days after study treatment discontinuation. Those collected later than 30 days after study treatment discontinuation will be flagged in listings.

10.5.3.1 Analysis set and grouping for the analyses

10.5.3.1.1 Adverse events (AEs)

All adverse events recorded during the study will be summarized. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by presenting the number and percentage of patients by system organ class and/or preferred term, maximum severity (based on CTCAE v4.03), type of adverse event, and relationship to the study treatment. In addition, adverse events of related nature may be analyzed by categories regrouping the relevant preferred terms, as appropriate. Adverse events that occurred on the same subject in the same system organ class and/or preferred term will be counted only once for the one with the highest severity.

[redacted]

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and patient group.

10.5.3.1.2 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade will be calculated using appropriate common terminology criteria (CTCAE v4.03).

A severity grade of 0 will be assigned when the value is within normal limits. For lab parameters for which severity grades are determined both through normal limits and absolute cut-offs, in the unlikely case when a local laboratory normal range overlaps into the higher (i.e. non-zero) CTCAE grade, the laboratory value will still be taken as within normal limits and assigned a CTCAE grade of zero.

A listing of laboratory values will be provided by laboratory parameter, patient, and visit. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities). Lab values collected later than 30 days after study treatment discontinuation will be flagged in the listings

The following by-group summaries will be generated separately for hematology, and biochemistry parameters:

- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

10.5.3.1.3 Other safety data

Summary statistics for data from other tests will be provided, notable values will be flagged, and any other information collected will be listed as appropriate.

Descriptive summary statistics will be provided for :

- Electrocardiograms: changes from baseline to last available ECG results
- Cardiac imaging: number and percentage of patients with notable LVEF values
- Vital signs: number and percentage of patients with at least one post-baseline vital sign abnormality
- ECOG performance status: shift table comparing baseline to worst post baseline ECOG performance status.
- All other safety related procedures as required
- Listings with flagged notable values and any other information collected will be provided as appropriate.

[redacted]

[redacted]

10.7 Interim analysis

Scheduled interim analysis will occur for the primary endpoint of clinical benefit rate only as required by the Bayesian Hierarchical design. The first interim analysis will be performed after the first 30 patients have been dosed for at least 16 weeks or discontinued, then every 13 weeks thereafter. Interim analyses may be performed more frequently dependent on enrollment rate to avoid over-enrollment in any of the disease cohorts. At each interim analysis, the groups will be evaluated for early futility and early success by comparing posterior quantities for the response rate to pre-specified early stopping criteria.

There is no plan for a formal interim analysis of safety or other secondary endpoints for this study. However, for publication or other purposes, interim data review of clean data will be performed as necessary. At these interim reviews, patient demographics/baseline characteristics, the primary and secondary endpoints as applicable and all important safety endpoints will be summarized. No formal report will be issued for these interim data reviews.

10.8 Sample size calculation

The sample size was chosen by the usual criteria of obtaining adequate power for the alternative hypothesis of interest as shown in Section 14.4.4.1 of Appendix R. This hypothesis corresponds to a generally effective treatment across groups and incorporates variation in treatment effects to reflect the realistic expectation that treatment effects may differ by group. In this setting, analytical power calculations are not possible, but the design was simulated to obtain the power of the study as shown in the appendix. The sample sizes shown (minimum of 10 for futility stopping, minimum of 15 for early success and maximum of 30 as a group cap) achieve adequate power for the alternative hypothesis. The simulations included the expected

[redacted]

variable accrual by simulating a Poisson process with expected accrual also shown in the Appendix R.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

Novartis will provide investigators in a separate document with a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH and GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential and fertile males should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. Women of child bearing potential must agree to adhere to contraception requirement until at least 4 weeks after the final dose of study treatment. Fertile males must agree to adhere to contraception requirement until at least 12

[redacted]

weeks after the final dose of study treatment. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.2.

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study eCRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. An audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

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Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who is directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the clinical study report (CSR).

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

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14 Appendices

14.1 Appendix A: Criteria for therapeutic response/outcome assessment of solid tumors and/or lymph nodes (based on RECIST 1.1)

Tumor assessments will be based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guidelines (Eisenhauer 2009).

1 Measurability of tumor lesions at baseline

All tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

1.1 Measurable

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

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

1.2 Non-measurable

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.2.1 Bone lesions

- B, PET and plain films are not adequate to measure bone lesions; they may be used to determine the presence or absence of a lesion.
- Lytic or lytic-blastic lesions with identifiable soft tissue component that can be measured by CT or MRI and meets size requirement can be considered measurable. Blastic bone lesions are non-measurable

1.2.2 Cystic lesions

- Cystic lesions that meet the criteria for simple cysts are not measurable

[redacted]

- Cystic lesions that are thought to be cystic metastatic disease can be considered measurable disease, however if non-cystic lesions are present in the same patient these are preferable to include as target lesions.

1.2.3 Lesions previously treated

- Lesions within radiotherapy ports or who have been subject to other loco-regional treatment are usually not considered to be measurable and will be allowed on this study only with approval of the sponsor.

2 Specification by methods of measurement

2.1 Measurement of lesions

All measurements should be taken and recorded in metric notation. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

2.1.1 Target lesions

All lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions. If the largest lesion does not lend itself to reproducible measurement, the next largest lesion which can be measured reproducibly should be selected.

Pathological lymph nodes which are measurable may be identified as target lesions if they have a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. Nodal size is normally reported as two dimensions in the plane in which the image is obtained. The smaller of these measures is the short axis. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

2.1.2 Non-target lesions

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”). Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

2.2 Response criteria

2.2.1 Evaluation of target lesions

This section provides the definitions of the criteria used to determine overall tumor response for target lesions as shown below in Table 2-1.

[redacted]

Table 2-1 Evaluation of target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.[1]
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (Note: the appearance of one or more new lesions is also considered progression)
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

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

2.2.2 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions as shown below in Table 2-2. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Table 2-2 Evaluation of non-target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis)
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.2.3 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded appropriately in the eCRF.

[redacted]

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion
- If new disease is observed in a region which **was not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment.
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥10 mm for the first time in the study plus 5 mm absolute increase.
  a. Negative FDG-PET at baseline, with a positive[1] FDG-PET at follow-up is a sign of PD based on a new lesion.
  b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD

2.2.4 Tumor markers

Tumors markers alone will not be used to assess overall response. If elevated at baseline, they must normalize for a patient to be considered as having a CR. For the purpose of this protocol, Cancer Antigen-125 (CA-125) will be used in the assessment of ovarian and Prostate Specific Antigen (PSA) will be used in the assessment of prostate.

3 Evaluation of best overall response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as indicated below in Table 3-1 and Table 3-2.

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence. The best overall response for CR and PR will be determined at 8 weeks as indicated below in Table 3-3.

[redacted]

Table 3-1 Time point response: patients with target (plus/minus non-target) disease

Target lesions	Non-target lesions	New lesions	Overall lesion response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 3-2 Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/non-PR[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PR
Any	Yes	SD

[a] 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

[redacted]

Table 3-3 Best overall response when confirmation of CR and PR required

Overall lesion response at first time point	Overall lesion response at subsequent time point	Best overall lesion response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD[b]
CR	PD	SD[b]
CR	NE	SD[c]
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD[b]
PR	NE	SD[c]
NE	NE	NE

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[b] Provided minimum criteria for SD duration met, otherwise, PD

[c] Provided minimum criteria for SD duration met, otherwise, NE

4 References (available upon request)

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[redacted]

14.2 Appendix B: Criteria for therapeutic response/outcome assessment in lymphoma studies (based on Cheson response criteria)

Disease assessments will be based on the International Working Group response criteria (Cheson 1999), and the International Harmonization Project revised response criteria (Cheson et al 2007b). Further clarification on these criteria has been published by (Cheson 2007a).

1 Definitions and criteria for normalization

a Definitions

i Nodal vs extranodal lesion

A lesion is categorized based on the location as:

- **Nodal lesion**,
- **Extranodal lesion**, if it is located in organs other than lymph node or nodal mass, but including spleen and liver.

2 Measurability of tumor lesions at baseline

All tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

a Measurable nodal and extranodal lesions

A lesion will be called **measurable** if it can be measured accurately in 2 perpendicular dimensions and:

- For nodal lesion, if the long axis is > 15 mm, regardless of the length of the short axis,
- For extranodal lesion, if the long and short axes are ≥ 10 mm.

Patients should have **at least one measurable nodal lesion greater than 20 mm** in the long axis.

In cases where the patient has no measurable nodal lesions greater than 20 mm in the long axis at Screening, then the patient must have at least one measurable extranodal lesion

b Classification of lymph nodes

Lymph nodes are classified according to their size and/or relationship to the disease:

- A lymph node meeting the measurability requirement above will constitute a **measurable nodal lesion**.
- A lymph node not meeting the measurability requirement but with long axis ≥15 mm (e.g. short axis cannot be measured accurately) will constitute a **non-measurable nodal lesion**.
- A lymph node not meeting the measurability criteria but with a size of 11 mm to 15 mm in the long axis and ≥ 10 mm in the short axis will be checked for relationship to disease:

[redacted]

- If it is thought to be disease related, it will constitute a **non-measurable nodal lesion**
- If it is not thought to be disease related, it will constitute an **abnormal lymph node** but not a lesion.

- All other lymph nodes will be considered normal and will not constitute nodal lesions.

c Criteria for normalization of lesions

The normalization of lesions is defined as follow:

- A measurable nodal lesion must become ≤ 15 mm in long axis to be considered normalized.
- A non-measurable nodal lesion must decrease to ≤ 10 mm in the short axis and be ≤ 15 mm in long axis to be considered normalized.
- An extranodal lesion must disappear completely (assigned a size of 0 mm x 0 mm) to be considered normalized.

3 Specification by methods of measurement

a Measurement of lesions

All radiological measurements should be taken in two perpendicular dimensions and recorded in metric notation, using a ruler or calipers.

i PET

Visual assessment currently is considered adequate for determining whether a PET scan is positive, and use of the standardized uptake value is not necessary.[1] In brief, a positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology, without a specific standardized uptake value cutoff.[1] Other causes of false-positive scans should be ruled out. Exceptions include mild and diffusely increased FDG uptake at the site of moderate- or large-sized masses with an intensity that is lower than or equal to the mediastinal blood pool, hepatic or splenic nodules 1.5 cm with FDG uptake lower than the surrounding liver/spleen

ii CT scan (or MRI)

For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at Screening and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If at Screening a patient is known to be allergic to CT contrast or develops allergy during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa,

[redacted]

regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in an "Unknown" overall radiological response assessment. However, another overall radiological response than the Novartis calculated "Unknown" response may be accepted from the investigator if a definitive overall radiological response can be justified to be based on the available information.

In order to calculate the sum of the product of the diameters (SPD) of all index lesions (or extranodal lesions), their size must be entered throughout the study.

Actual lesion measurements should be entered on the corresponding eCRFs. If, during the course of the study, either of the perpendicular diameters of a lesion cannot be reliably measured because of its small size, it is recommended to enter the minimum limit of detection as the diameter size (e.g. 5 mm for spiral CT). In other cases when, during the course of the study, the diameter cannot be reliably measured for reasons other than its size (i.e. borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

If lesions become confluent over time, it is recommended to measure them as one lesion, report the overall diameters to one of the lesions and assign 0 mm x 0 mm to each of the other previously measured lesions. If a lesion splits during the study, each sub-lesion should be measured separately for all subsequent assessments and all sub-lesions contribute to the SPD.

iii Bone marrow assessment

Documentation of status of bone marrow involvement by lymphoma based on prior bone marrow biopsy or aspirate findings is required at Screening for all patients.

If no such documentation is available then a bone marrow biopsy or aspirate should be performed at Screening.

If bone marrow involvement is assessed by biopsy, the biopsy sample should have a goal of > 20 mm unilateral core. If the biopsy sample is indeterminate by morphology (immunohistochemistry), then flow cytometry may be performed on bone marrow aspirate to confirm the findings.

iv Physical examination and assessment of B-symptoms

Skin lesions, if the size is ≥ 20 mm in at least one diameter, must be histologically confirmed for lymphoma involvement (the investigational site must document the histological confirmation (yes or no) on the corresponding eCRF) and photographed including a ruler (color photography using digital camera). Tumor assessment will be performed and results will be recorded on the corresponding eCRF at Screening and at Day 1 of every cycle (±4 days) after first dose of study drug.

B-symptoms are of importance in determining prognosis and should resolve completely in patients who have achieved complete response. B-symptoms in lymphoma patients are disease related clinical symptoms and are not caused by anticancer therapy (or drug toxicity).

B-symptoms are defined as follows:

[redacted]

- Significant unexplained fever (≥ 38°C),
- Unexplained, recurrent drenching night sweats
- Unexplained loss of > 10% body weight within the previous 6 months, as assessed and reported (present vs. absent) by the Investigator.

4 Evaluation of radiological response

For the sake of simplicity, complete remission and complete response will both be referred to as complete response.

Definitions of Response for Lymphoma patients are listed in Table 4-1. To evaluate disease response to treatment, all index and non-index lesions will be followed and assessed throughout the study. At each assessment, response is evaluated separately for the **index lesions** (Table 4-1) and **non-index lesions** (Table 4-2) identified at Screening, then a combined overall radiological response is determined (Table 4-3).

[redacted]

Table 4-1 Response definition for lymphoma

Response	Definition	Nodal Masses	Spleen. Liver	Bone Marrow
CR	Disappearance of all evidence of disease	a FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative b Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistoch emistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes a FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site b Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	a FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET b Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

a Evaluation of index lesions (nodal and extranodal)

i When index nodal lesions are not in complete response

The response for index lesions is evaluated by calculating the Sum of the Products of Diameters (SPD) of all index lesions (see Table 4-2), except when there is a Complete Response for index nodal lesions (i.e. complete normalization of all index nodal lesions) (see Section ii).

[redacted]

Table 4-2 Radiological status based on SPD calculation for all index lesions

Response Criteria[1]	Evaluation of index lesions
Complete Response (CR)	See Table 4-4 below (not based on SPD calculation for all index lesions)
Partial Response (PR)	At least 50% decrease from Screening in the SPD of all index lesions
Stable Disease (SD)	Failure to attain the criteria needed for CR or PR and failure to fulfill the criteria for PD
Progressive Disease (PD)	At least a 50% increase from nadir[2] in the SPD of all index lesions

[1] At each assessment (if the index nodal lesions are not in CR status), the response status based on SPD calculation will be first assessed for meeting PD status criteria, then PR status and SD status.

[2] Nadir is defined as the smallest sum of the product of the diameters of all index lesions recorded so far, at or after Screening.

ii When index nodal lesions are in complete response

When there is a Complete Response for index nodal lesions (i.e. complete normalization of all index nodal lesions as defined in Section v: all index lesion ≤ 15 mm in long axis), the SPD for these index nodal lesions may not be equal to zero and therefore a calculation of a SPD for all index lesions may be misleading. Therefore, by default, a specific response for extranodal index lesions needs to be evaluated, based on the SPD calculation restricted to all index extranodal lesions only (see Table 4-3).

Table 4-3 Radiological response criteria for index extranodal lesions in case of CR in index nodal lesions

Response Criteria[1]	Evaluation of index extranodal lesions
Complete Response (CR)	Complete disappearance of all index extranodal lesions
Partial Response (PR)	At least 50% decrease from Screening in the SPD restricted to all index extranodal lesions
Stable Disease (SD)	Failure to attain the criteria needed for CR or PR and failure to fulfill the criteria for PD
Progressive Disease (PD)	At least a 50% increase from nadir[2] in the SPD restricted to all index extranodal lesions

[1] At each assessment, response will be first assessed for meeting CR status. If CR status is not met, response will be assessed for PD status, then PR status and SD status.

[2] Nadir is defined as the smallest sum of the product of the diameters restricted to all index extranodal lesions recorded so far, at or after Screening.

The algorithm for evaluating the response integrating index extranodal lesions and the SPD calculated on all index lesions (where appropriate) provides an overall response for index lesions.

iii Evaluation of response for all index lesions

The evaluation of response for all index lesions is based on the combination of the response for index nodal lesions (CR or non-CR), the response for index extranodal and the status based on the SPD calculated on all index lesions (nodal and extranodal), as described in Table 4-4.

[redacted]

Table 4-4 Radiological response for index lesions

Response for index nodal lesions[1]	Response for index extranodal lesions[1]	Status based on SPD calculation for all index lesions	Response for index lesions
CR	CR	Not calculated	CR
CR	SD/ PR	Not calculated	PR
CR	PD	PD	PD
CR	PD	PR	PR
CR	PD	SD	SD
Non-CR	Not evaluated	PD	PD
Non-CR	Not evaluated	PR	PR
Non-CR	Not evaluated	SD	SD

[1] If no index nodal lesions are present at Screening, then index lesions response is equal to the index extranodal lesions response. A similar rule applied if no index extranodal lesions are present at Screening, then index lesions response is equal to the index nodal lesions response.

In case of missing measurements of any of the index lesions, the radiological response for index lesions at that assessment will be "Unknown (UNK)", unless progression was seen.

All lesions must have been measured with the same method as the one used at Screening, otherwise the radiological response for index lesions at that assessment will be "Unknown (UNK)".

iv Evaluation of non-index lesions (including nodal, splenic and/or hepatic nodules and other extranodal lesions)

At each reassessment, a non-index lesion (or a group of non-index lesions) will be given one of the following designations:

- Normalization (non-index nodal lesion has regressed to normal size; non-index extranodal lesion is no longer present). Normalization of non-index nodal lesions should be determined based on their size at Screening.
- Improved, stable or worsened, but without unequivocal evidence of disease progression (non-index lesion is present but there is not sufficient worsening to declare PD based on the existing non-index lesions).
- Unequivocal evidence of disease progression (worsening of existing non-index lesions is sufficient to declare PD)
- Not assessed

Then, this status for each non-index lesion (or group of non-index lesions) will lead to a global response for non-index lesions (Table 4-5):

[redacted]

Table 4-5 Response criteria for non-index lesions (nodal, splenic and/or hepatic nodules and other extranodal lesions)

Response Criteria	Evaluation of non-index lesions
Complete Response (CR)	Complete normalization of all non-index nodal and extranodal lesions: Radiological regression to normal size of all lymph nodes and complete disappearance of all extranodal (including splenic and/or hepatic nodules) lesions
Stable Disease (SD)	Failure to attain the criteria needed for CR and failure to fulfill the criteria for PD
Progressive Disease (PD)	Unequivocal disease progression of any existing non-index lesions (nodal or extranodal)

In case of a missing status of any of the non-index lesions, the radiological response for non-index lesions at that assessment will be "Unknown (UNK)", unless progression was seen.

All lesions must have been measured with the same method as the one used at Screening, otherwise the radiological response for non-index lesions at that assessment will be "Unknown (UNK)".

v New lesions

The appearance of

- any new nodal lesion ≥15 mm in any axis. New nodal lesion is defined by:
  - either a previously normal lymph node becoming > 15 mm in any axis,
  - or a previously identified abnormal lymph node showing an increase of at least 50% in the long axis,
  - as assessed by investigator

OR

- any discrete extranodal (including splenic and/or hepatic nodules) lesions reliably appearing on CT scan or MRI after Screening

is always considered as Progressive Disease (PD) and has to be recorded as a new lesion in the appropriate module of the eCRF. Determination of new lymphoma involvement in organs other than lymph nodes or liver or spleen should be confirmed histologically and the site must document that in a comment to the corresponding eCRF.

vi Overall radiological response

Overall radiological response is calculated as shown in Table 4-6.

[redacted]

Table 4-6 Overall radiological response at each assessment

Index lesions	Non-index lesions[1]	New lesions	Overall radiological response
CR	CR	No	CR
CR	SD	No	PR
PR	CR or SD	No	PR
SD	CR or SD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1] If no non-index lesions are present at Screening, then this column is not used in evaluating overall radiological response.

If the evaluation of any of the index or non-index lesions identified at Screening could not be made during follow-up or if the index or non-index response is "Unknown (UNK)", the overall response status at that assessment must be "Unknown (UNK)" unless progression or a new lesion was seen.

vii Evaluation of overall disease response

The evaluation of overall disease response at each assessment is a composite of the individual radiological responses (index and non-index lesions, new lesions), laboratory test (bone marrow) and clinical responses (lymphoma related clinical symptoms).

viii Bone marrow re-assessment at time of radiological CR

In order to confirm a Complete disease response (CR), bone marrow biopsy or aspirate may be required when a radiological CR has been achieved. Details are provided in the Study Protocol. The infiltrate of lymphoma in bone marrow must have cleared on repeat bone marrow biopsy or aspirate. Patients who achieve a CR by other criteria but who have persistent morphologic positive or inconclusive bone marrow involvement will be considered partial responders. New or recurrent bone marrow involvement anytime during the follow up will be considered PD. Bone marrow biopsy or aspirate will be performed after the first assessment of CR or when clinically indicated.

The biopsy sample of bone marrow must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry.

ix Overall disease response

If a patient has an overall radiological response of CR then this response must be confirmed by bone marrow biopsy or aspirate (if required as per the Study Protocol), presence of normal liver and spleen size, and evaluation of lymphoma related B-symptoms. The patient's overall response will be calculated as follows:

A patient will be deemed to have overall disease response of CR if bone marrow biopsy or aspirate becomes negative for tumor involvement (if the bone marrow was involved by lymphoma at Screening) and the liver and spleen are normal in size and there are no lymphoma related B-symptoms in addition to radiological CR.

[redacted]

If assessments of any of the following: lymphomatous infiltration of bone marrow (If required as per the Study Protocol), or evaluation of B-symptoms is not done, unknown or indeterminate or B-symptoms are still present when the overall radiological response is assessed as CR or the liver or spleen are enlarged, then the overall disease response will be assessed as PR until evaluation of these factors have shown normalized results and recorded on the corresponding eCRF.

For patients whose radiological response is anything other than CR, assessment of bone marrow, liver, spleen and B-symptoms will not be required in evaluating overall response and overall disease response is the same as radiological response. However any new or recurrent bone marrow involvement at any time during follow-up will be considered PD.

Of note, appearance of B-symptoms or enlarged spleen or liver will not in themselves constitute documentation of progression. They are however expected to be associated with progressive disease. Every effort should be made to document that evidence radiologically and report the corresponding tumor assessments. Such tumor assessments are expected to be performed within 2 months of appearance of B-symptoms or enlarged spleen or liver.

5 References (available upon request)

Cheson BD (2007a) The international harmonization project for response criteria in lymphoma clinical trials. Hematol Oncol Clin N Am 21:841-854.

Cheson BD (2009) The case against heavy PETing. J Clin Oncol 27:1742-1743.

Cheson BD, Horning SJ, Coiffier B, et al (1999) Report of an International Workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 17:1244-1253.

Cheson BD, Pfistner B, Juweid ME, et al (2007b) Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586.

FDA Guideline (2005) Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.

[redacted]

14.3 Appendix C: Ann Arbor staging classification

Not applicable. Please refer to BGJ398XUS04 Protocol Version 02

Stage	Area of involvement
I	Single lymph node group
II	Multiple lymph node groups on the same side of the diaphragm
III	Multiple lymph node groups on both sides of the diaphragm
IV	Multiple extranodal sites or lymph nodes and extranodal disease
X	Bulk disease > 10 cm
E	Extranodal extension or single isolated site of extranodal disease
Class A are patients who experience no B symptoms	
Class B are patients experience unexplained fever of ≥ 38°C; unexplained, recurrent drenching night sweats; or unexplained loss of >10% body weight within the previous 6 months	

[1] Cotswolds modification of Ann Arbor staging system adapted from 2007 NCCI guidelines for non-Hodgkin's lymphoma

[redacted]

14.4 Appendix D: Rai Staging System [a]

Stage	Area of involvement	Risk Status
0	Lymphocytosis, lymphocytes in blood >15 x 10^9/L and >40% lymphocytes in bone marrow	Low
I	Stage 0 with enlarged node(s)	Intermediate
II	Stage 0-1 with splenomegaly, hepatomegaly, or both	Intermediate
III[b]	Stage 0-II with hemoglobin < 11.0 g/dL or hematocrit <33%	High
IV[b]	Stage 0-III with platelets <100 x 10^9/L	High

[a] Research originally published in Blood. Rai KR,et al. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46(2):219-234. (c) The American Society of Hematology

[b] Immune-mediated cytopenias are not the basis for these stage definitions.

[redacted]

14.5 Appendix E: Criteria for Response assessment in Acute Myeloid Leukemia (based on IWG and Cheson)

Disease assessments will be based on standardized response criteria as defined by the International Working Group (IWG) for AML (Cheson et al 2003).

Response classification in AML at a given evaluation time (Cheson 2003)	
Response category	**Definition#**
Complete remission (CR)	**Bone marrow** < 5% blasts no blasts with Auer rods **Peripheral blood** neutrophils ≥ 1.0 x 10^9/L platelets ≥ 100 x 10^9/L ≤ 1% blasts No evidence of extramedullary disease (such as CNS or soft tissue involvement). Transfusion independent (see Section 7.2.1.4.5). In case all criteria for CR apply and the patient receives platelet and/or neutrophil transfusions, the patient will be assessed as CRi.
Complete remission with incomplete blood count recovery (CRi)	**Bone marrow** < 5% blasts no blasts with Auer rods **Peripheral blood** neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L ≤ 1% blasts No evidence of extramedullary disease (such as CNS or soft tissue involvement). Transfusion-independent (see Section 7.2.1.4.5). Exception: Platelet and neutrophil transfusions are allowed.
Partial Remission (PR)	**Bone marrow** 50% or greater decrease (absolute range 5-25% blasts) < 5% of blasts contain Auer rods **Peripheral blood** neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L No evidence of extramedullary disease (such as CNS or soft tissue involvement).
Treatment failure	Treatment failure includes those patients for whom treatment has failed to achieve PR, CRi or CR throughout the treatment.
Relapse from CR or CRi*	Only in patients with a CR or CRi: Reappearance of blasts in peripheral blood (> 1%) OR ≥ 5% blasts in bone marrow OR (Re-)appearance of extramedullary disease

[redacted]

Response classification in AML at a given evaluation time (Cheson 2003)	
Response category	**Definition#**
No response	In case a patient does not achieve CR, CRi, PR or relapse for an individual response assessment.
Unknown	In case the response assessment was not done, the baseline assessment was not done, the assessment was incomplete or was not done within the respective time frame.
# If not defined otherwise, all of the criteria apply. * Cheson et al (2003) does not specify relapse after PR but this may be considered in Phase I or II protocols.	

14.5.1 Exploratory AML response categories according to IWG

Response category	**Definition**
Cytogenetic complete remission (CRc)	All criteria for CR plus no cytogenetic abnormalities
Molecular complete remission (CRm)	All criteria for CRc plus no leukemic cells by RQ-PCR assay

[redacted]

14.6 Appendix F: Criteria for Response assessment in Acute Lymphoblastic Leukemia (based on NCCN Guidelines Version 1.2013)

Response classification in ALL for Blood and Bone Marrow at a given evaluation time	
Response category	**Definition[#]**
Complete remission (CR)	No circulating blasts or extramedullary disease (such as lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass, CNS or soft tissue involvement) Trilineage hematopoiesis (TLH) and < 5% blasts neutrophils ≥ 1.0 x 10^9/L platelets ≥ 100 x 10^9/L No recurrence for 4 weeks
Complete remission with incomplete blood count recovery (CRi)	**Peripheral blood** Recovery of platelets but < 100 x 10^9/L or neutrophils is < 1.0 x 10^9/L.
Progressive Disease (PD)	Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease.
Treatment failure	Treatment failure includes those patients for whom treatment has failed to achieve a CR at the end of treatment
Relapse from CR or CRi[*]	Only in patients with a CR or CRi: Reappearance of blasts in peripheral blood (> 1%) OR ≥ 5% blasts in bone marrow OR (Re-)appearance of extramedullary disease
No response	In case a patient does not achieve CR, CRi, PR or relapse for an individual response assessment.
Unknown	In case the response assessment was not done, the baseline assessment was not done, the assessment was incomplete or was not done within the respective time frame.
[#] If not defined otherwise, all of the criteria apply.	

[redacted]

14.7 Appendix G: Criteria for Response assessment in Chronic Myelogenous Leukemia (based on NCCN Guidelines Version 4. 2013)

Response classification in CML for hematologic, cytogenetic, and molecular evaluation at a given evaluation time	
Response category	**Definition#**
Complete hematologic response (CR)[1]	Complete normalization of peripheral blood counts with leukocyte count < 10 x 10^9/L platelets < 450 x 10^9/L No immature cells such as myelocytes, promyelocytes, or blasts in peripheral blood No signs and symptoms of disease with disappearance of splenomegaly
Cytogenetic response[2,3]	**Complete** No Ph-positive metaphases **Partial** 1% - 35% Ph-positive metaphases **Major** 0% - 35% Ph-positive metaphases (complete + partial) **Minor** > 35% Ph-positive metaphases
Molecular response[4,5]	**Complete** No detectable BCR-ABL mRNA by QPCR using an assay with a sensitivity of at least 4.5 logs below standardized baseline. **Major** ≥ 3 log reduction in international scale of BCR-ABL mRNA
Treatment failure	Treatment failure includes those patients for whom treatment has failed to achieve a complete hematologic response (CR) throughout treatment.
No response	In case a patient does not achieve CR, PR or relapse for an individual response assessment.
Unknown	In case the response assessment was not done, the baseline assessment was not done, the assessment was incomplete or was not done within the respective time frame

If not defined otherwise, all of the criteria apply.

1. Federl S et al: Chronic myelogenous leukemia: Biology and therapy. Ann Intem Med 1999; 131:207-219.

2. A minimum of 20 metaphases should be examined.

3. O'Brien SG, et al: Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.

4. Hughes TP, et al: Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnoses chronic myeloid leukemia. N Engl J Med 2003;349:1423-1432

5. Hughes T, et al: Monitoring CML patients responding to treatment with tyrosine kinase inhibitors; review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006;108:28-37

[redacted]

14.8 Appendix H: Criteria for Response assessment in Chronic Lymphocytic Leukemia (based on modified IWG guidelines)

Disease assessments will be based on standardized response criteria as defined by the modified IWG guidelines for CLL. Response in CLL must meet the criteria in both Group A and Group B. Group A criteria defines tumor load. Group B criteria defines the function of the hematopoietic system (or marrow).

Response Definition for Chronic Lymphocytic Leukemia[1]

Group A Response for Tumor Burden			
Response	**Nodal Masses**	**Organomegaly**	**Bone Marrow**
CR	None > 1.5 cm	No splenomegaly No hepatomegally	Normocellular >30% Lymph. No B lymphoid nodules
CRi	None > 1.5 cm	No splenomegaly No hepatomegally	Hypocellular marrow
PR	Decrease ≥50%	Spleen/Liver decrease ≥50	50% reduction in marrow infiltrate, or B-lymphoid nodules
Group B Response for hepatopoietic system[2]			
Response	**Platelet count**	**Hemoglobin**	**Neutrophils**
CR	>100 x 10^9/L	>11 g/dL	>1.5 x 10^9/L
CRi	If meets criteria from Group A but does not meet criteria from Group B		
PR	>100 x 10^9/or increase ≥50% over baseline	>11 g/dL or increase ≥50% over baseline	>1.5 x 10^9/L or >50% improvement over baseline
SD	Failure to attain CR/CRi/PR or PD		
Relapsed disease or PD	Appearance of any new lesions; at least one of the above criteria. Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease		

1. Hallek M, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia updating the National Cancer Institute-Working Group 1996 Guidelines. Blood 2008; 111:5446-5456
2. All values are without transfusion or hepatopoietic growth factors

[redacted]

14.9 Appendix I: Criteria for Response assessment in Myelofibrosis (based on modified IWG-MRT guidelines and European LeukemiaNet (ELN) consensus report)[1]

Response category	Definition
CR	Bone marrow*: Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF† and Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥ 1 X 10^9/L and <UNL; Platelet count ≥100 X 10^9/L and <UNL; <2% immature myeloid cells‡ and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
PR	Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥1 X 10^9/L and <UNL; platelet count ≥100 X 10^9/L and <UNL; <2% immature myeloid cells‡ and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH or Bone marrow*: Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF†, and peripheral blood: Hemoglobin ≥85 but <100 g/L and <UNL; neutrophil count ≥1 X 10^9/L and <UNL; platelet count ≥50, but <100 X 10^9/L and <UNL; <2% immature myeloid cells‡ and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Clinical improvement (CI)	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia§
Anemia response	Transfusion-independent patients: a ≥20 g/L increase in hemoglobin level‖ Transfusion-dependent patients: becoming transfusion-independent^
Spleen response#	A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable** or A baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≥50%** A baseline splenomegaly that is palpable at <5 cm, below the LCM, is not eligible for spleen response A spleen response requires confirmation by MRI or computed tomography showing ≥35% spleen volume reduction
Symptoms response	A ≥50% reduction in the MPN-SAF TSS††
Progressive disease‡‡	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm or Leukemic transformation confirmed by a bone marrow blast count of ≥20% or A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 X 10^9/L that lasts for at least 2 weeks

[redacted]

Response category	Definition
Stable disease	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI, or Loss of anemia response persisting for at least 1 month or Loss of spleen response persisting for at least 1 month
Recommendations for assessing treatment-induced cytogenetic and molecular changes	
Cytogenetic remission	At least 10 metaphases must be analyzed for cytogenetic response evaluation and requires confirmation by repeat testing within 6 months window CR: eradication of a preexisting abnormality PR: ≥50% reduction in abnormal metaphases (partial response applies only to patients with at least ten abnormal metaphases at baseline)
Molecular remission	Molecular response evaluation must be analyzed in peripheral blood granulocytes and requires confirmation by repeat testing within 6 months window CR: Eradication of a pre-existing abnormality PR: ≥50% decrease in allele burden (partial response applies only to patients with at least 20% mutant allele burden at baseline)
Cytogenetic/molecular relapse	Re-emergence of a pre-existing cytogenetic or molecular abnormality that is confirmed by repeat testing

[1] Tefferi et al. (2013) Revised response criteria for myelofibrosis: International Working (IWG-MRT) and European LeukemiaNet (ELN) consensus report Group-Myeloproliferative Neoplasms Research and Treatment. Blood; 2013 122: 1395-1398

EMH, extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven nonhepatosplenic EMH); LCM, left costal margin; UNL, upper normal limit.

[†]Grading of MF is according to the European classification

Thiele et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica. 2005;90:1128.

It is underscored that the consensus definition of a CR bone marrow is to be used only in those patients in which all other criteria are met, including resolution of leukoerythroblastosis. It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histologic remission.

[‡]Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, <5% immature myeloid cells is allowed.

[§]See above for definitions of anemia response, spleen response, and progressive disease. Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥20 g/L decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or absolute neutrophil count, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In addition, assignment to CI requires a minimum platelet count of ≥25 000 X 10^9/L and absolute neutrophil count of ≥0.5 X 10^9/L.

[||]Applicable only to patients with baseline hemoglobin of<100 g/L. In patients not meeting the strict criteria for transfusion dependency at the time of study enrollment (see as follows), but have received transfusions within the previous month, the pre-transfusion hemoglobin level should be used as the baseline.

^Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of

[redacted]

Response category	Definition
packed red blood cells (PRBC), in the 12 weeks prior to study enrollment, for a hemoglobin level of <85 g/L, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent patients requires absence of any PRBC transfusions during any consecutive "rolling" 12-week interval during the treatment phase, capped by a hemoglobin level of ≥85 g/L. #In splenectomized patients, palpable hepatomegaly is substituted with the same measurement strategy. **Spleen or liver responses must be confirmed by imaging studies where a ≥35% reduction in spleen volume, as assessed by MRI or CT, is required. Furthermore, a ≥35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination. ††Symptoms are evaluated by the MPN-SAF TSS.[1] The MPN-SAF TSS is assessed by the patients themselves and this includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0-100 scale). Symptoms response requires ≥50% reduction in the MPN-SAF TSS. ‡‡Progressive disease assignment for splenomegaly requires confirmation my MRI or computed tomography showing a ≥25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to post-treatment measurements.	

14.10 Appendix J: Criteria for Response assessment in polycythemia vera (based on modified IWG-MRT guidelines and European LeukemiaNet (ELN) consensus report)[1]

Response categories	Required criteria
Complete remission	A. Durable resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement† AND B. Durable peripheral blood count remission, defined as Ht lower than 45% without phlebotomies; platelet count ≤400 X 10^9/L, WBC count <10 X 10^9/L, AND C. Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND D. Bone marrow histological remission defined as the presence of age-adjusted normocellularity and disappearance of tri-linear hyperplasia, and absence of >grade 1 reticulin fibrosis
Partial remission	A. Durable resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement† AND B. Durable peripheral blood count remission, defined as Ht lower than 45% without phlebotomies; platelet count ≤400 X 10^9/L, WBC count <10 X 10^9/L, AND C. Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND D. Without bone marrow histological remission defined as persistence of tri-linear hyperplasia.
No response	Any response that does not satisfy partial remission
Progressive disease	Transformation into post-PV myelofibrosis, myelodysplastic syndrome or acute leukemia‡

Molecular response is not required for assignment as complete response or partial response. Molecular response evaluation requires analysis in peripheral blood granulocytes. Complete response is defined as eradication of a preexisting abnormality. Partial response applies only to patients with at least 20% mutant allele burden at baseline. Partial response is defined as ≥ 50% decrease in allele burden.

WBC, white blood cell.

Large symptom improvement (≥10-point decrease) in MPN-SAF TSS.[2]

For the diagnosis of post-PV myelofibrosis, see the IWG-MRT criteria[3]; for the diagnosis of myelodysplastic syndrome and acute leukemia, see WHO criteria.

[1] Barosi G, et al; Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood 2013 121: 4778-4781

[2] Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs [published correction appears in J Clin Oncol. 2012;30(36):4590]. J Clin Oncol. 2012;30(33):4098-4103

[3] Barosi G, Mesa RA, Thiele J, et al; International Working Group for Myelofibrosis Research and Treatment (IWG-MRT). Proposed criteria for the diagnosis of post-polycythemia vera and postessential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. Leukemia. 2008;22(2):437-438

[redacted]

14.11 Appendix K: Criteria for Response assessment in Essential thrombocythemia (based on modified IWG-MRT guidelines and European LeukemiaNet (ELN) consensus report)[1]

Response category	Definition
Complete remission	A. Durable resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement,† AND B. Durable peripheral blood count remission, defined as: platelet count ≤400 X 10^9/L, WBC count <10 X 10^9/L, absence of leukoerythroblastosis, AND C. Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND D. Bone marrow histological remission defined as disappearance of megakaryocyte hyperplasia and absence of >grade 1 reticulin fibrosis.
Partial remission	A. Durable resolution of disease-related signs including palpable hepatosplenomegaly, and large symptoms improvement, AND B. Durable peripheral blood count remission, defined as: platelet count ≤400 X 10^9/L, WBC count <10 X 10^9/L, absence of leukoerythroblastosis, AND C. Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND D. Without bone marrow histological remission, defined as the persistence of megakaryocyte hyperplasia.
No response	Any response that does not satisfy partial remission
Progressive disease	Transformation into PV, post-ET myelofibrosis, myelodysplastic syndrome or acute leukemia‡

Molecular response is not required for assignment as complete response or partial response. Molecular response evaluation requires analysis in peripheral blood granulocytes. Complete response is defined as eradication of a preexisting abnormality. Partial response applies only to patients with at least 20% mutant allele burden at baseline. Partial response is defined as ≥50% decrease in allele burden.

WBC, white blood cell.

†Large symptom improvement (≥10-point decrease) in MPN-SAF TSS.[3]

‡For the diagnosis of PV see World Health Organization criteria (WHO)[4]; for the diagnosis of post-ET myelofibrosis, see the IWG-MRT criteria[2]; for the diagnosis of myelodysplastic syndrome and acute leukemia, see WHO criteria.[4]

[1] Barosi G, et al; Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood 2013 121: 4778-4781

[2] Barosi G, Mesa RA, Thiele J, et al; International Working Group for Myelofibrosis Research and Treatment (IWG-MRT). Proposed criteria for the diagnosis of post-polycythemia vera and postessential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. Leukemia. 2008;22(2):437-438.

[3] Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs [published correction appears in J Clin Oncol. 2012;30(36):4590]. J Clin Oncol. 2012;30(33):4098-4103.

[4] Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC; 2008.

[redacted]

14.12 Appendix L: Criteria for Response assessment in Myelodysplasia (based on modified IWG guidelines)[1]

Category	Response Criteria
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines* Persistent dysplasia will be noted* Peripheral blood • Hgb ≥ 11 g/dL • Platelets ≥ 100 x 10^9/L • Neutrophils ≥ 1.0 x 10^9/L • Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: • Return to pretreatment bone marrow blast percentage • Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets • Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete - Disappearance of the chromosomal abnormality without appearance of new ones Partial - At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: • Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts • 5%-10% blasts: ≥ 50% increase to > 10% blasts • 10%-20% blasts: ≥ 50% increase to > 20% blasts • 20%-30% blasts: ≥ 50% increase to > 30% blasts Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hgb by > 2 g/dL • Transfusion dependence
*Dysplastic changes should consider the normal range of dysplastic changes (modification).	
[1] Cheson, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. blood-2005-10-4149.	

[redacted]

14.13 Appendix M: Myeloproliferative Neoplasm (MPN) Symptom Assessment Form Total Symptom Score (MPN-SAF-TSS)

Name: _____ Date: _____

Fill out the form below to track the burden of your symptoms.

For each symptom, please **circle the number** that best describes how severe that symptom is, on a scale of 0 to 10, with **0 being absent or as good as it can be** and **10 being worst imaginable**. Make sure you circle a number for every symptom. Be sure to **share your answers** with your hematologist or other healthcare professional.

Symptom - 1 to 10, 0 if absent and 10 being worst imaginable

Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past **24 hours**

Fatigue

0	1	2	3	4	5	6	7	8	9	10

(ABSENT) (WORST IMAGINABLE)

Circle the one number that describes how much difficulty you have had with each of the following symptoms during the **past week**

Filling up quickly when you eat (early satiety)

0	1	2	3	4	5	6	7	8	9	10

(ABSENT) (WORST IMAGINABLE)

Abdominal discomfort

0	1	2	3	4	5	6	7	8	9	10

(ABSENT) (WORST IMAGINABLE)

Inactivity

0	1	2	3	4	5	6	7	8	9	10

(ABSENT) (WORST IMAGINABLE)

Problems with concentration - compared to before my diagnosis

0	1	2	3	4	5	6	7	8	9	10

(ABSENT) (WORST IMAGINABLE)

Night sweats

0	1	2	3	4	5	6	7	8	9	10

(ABSENT) (WORST IMAGINABLE)

Itching (pruritus)

0	1	2	3	4	5	6	7	8	9	10

(ABSENT) (WORST IMAGINABLE)

[redacted]

Bone pain (diffuse, not joint pain or arthritis)										
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

(ABSENT) (WORST IMAGINABLE)

Fever (> 37.8°C or 100°F)										
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

(ABSENT) (WORST IMAGINABLE)

Unintentional weight loss last 6 months										
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

(ABSENT) (WORST IMAGINABLE)

To help you get a clear overall picture of how you are feeling, you can add up all your scores to calculate your Total Symptom Score. **Total** ☐

[1] Adapted from Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs [published correction appears in J Clin Oncol. 2012;30(36):4590]. J Clin Oncol. 2012;30(33):4098-4103

[redacted]

14.14 Appendix N: Eastern Cooperative Oncology Group (ECOG) performance status

Score	Performance status
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, e.g. light housework, 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

[redacted]

14.15 Appendix O: International Myeloma Working Group (IMWG) uniform response criteria for multiple myeloma

Response	IMWG Criteria
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[3] by immunohistochemistry or immunofluorescence[4]
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[3]
VGPR	Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-component plus urine M-component < 100 mg per 24 hr
PR	> 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by >90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable,[5] a > 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, > 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was > 30% In addition to the above listed criteria, if present at baseline, a > 50% reduction in the size of soft tissue plasmacytomas is also required
SD	Not meeting criteria for CR, VGPR, PR, or progressive disease
PD[5]	Increase of > 25% from lowest response value in any one or more of the following: Serum M-component and/or (the absolute increase must be > 0.5 g/dL)[6] Urine M-component and/or (the absolute increase must be > 200 mg/24 h) Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL Bone marrow plasma cell percentage; the absolute percentage must be > 10%[7] Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[6] It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice Development of new soft tissue plasmacytomas or bone lesions Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] Decrease in haemoglobin of > 2 g/dL [1.25 mmol/L] Rise in serum creatinine by 2 mg/dL or more [177 mmol/L or more]

[1.] BGM Durie et al. International uniform response criteria for multiple myeloma. Leukemia (2006) 1-7.

[2.] Adapted from Durie BGM, et al. Leukemia 2006; 20: 1467-1473; and Kyle RA, Rajkumar SV. Leukemia 2008;23:3-9

[redacted]

Response	IMWG Criteria
Note: A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.	
[3.] Confirmation with repeat bone marrow biopsy not needed.	
[4.] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.	
[5.] All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.	
[6.] For progressive disease, serum M-component increases of >1 gm/dL are sufficient to define relapse if starting M-component is >5 g/dL.	
[7.] Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.	
[8.] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.	

14.16 Appendix P: List of concomitant medications

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or BGJ398.

The following lists are based on the Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: 29 Oct 2012), which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft guidance.

14.16.1 Drugs to be used with caution while on study

Category	Drug Names
Sensitive CYP3A Substrates	Alpha-dihydroergocryptine, aplaviroc, aprepitant, atorvastatin, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, indinavir, levomethadyl, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simvastatin, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil, vicriviroc
Moderate inhibitors of CYP3A4	Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, imatinib, Schisandra sphenanthera, tofisopam, verapamil
Moderate inducers of CYP3A4	Bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, talviraline, thioridazine, tipranavir
Medications which alter the pH of the GI tract[1]	Proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids.
Medications that have possible risk of TdP/QT prolongation	Dronedarone, eribulin, lapatinib, sunitinib, nilotinib, tamoxifen, gatifloxacin, gemifloxacin, levofloxacin, ofloxacin, roxithromycin, telithromycin, clozapine, iloperidone, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, dolasetron, granisertron, ondansetron, escitalopram, venlafaxine, Ranolazine, voriconazole, amantadine, foscarnet, isradipine, moexipril, nicardipine, fingolimod, tacrolimus, atazanavir, felbamate, famotidine, fosphenytoin, alfuzosin, chloral hydrate, indapamide, lithium, octreotide, pasireotide, oxytocin, ranolazine, tizanidine, vardenafil

[redacted]

Category	Drug Names
Medications that have conditional risk of TdP/QT prolongation	Amisulpride, amiptriptyline, clomipramine, desipramine, doxepin, fluoxetine, imipramine, nortriptyline, paroxetine, protriptyline, sertraline, trazodone, trimipramine, ciprofloxacin, trimethoprim-sulfa, diphenhydramine, fluconazole, itrazonazole, ketoconazole, ritonavir, galantamine, solifenacin
BCRP substrates	Rosuvatstatin, methotrexate, irinotecan, atorvastatin, simvastatin, topotecan, sulfasalazine

[1] BGJ398 should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent.

Reference:

FDA Guidance for Industry, Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Accessed 10 November 2013 fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf.

Indiana University School of Medicine's "Clinically Relevant" table (2009). medicine.iupui.edu/clinpharm/ddis/clinicalTable.aspx. Accessed 14 July 2011

University of Washington's Drug Interaction Database (2013) druginteractioninfo.org

Drug-Drug Interactions (DDI) Database: Novartis Oncology Clinical Pharmacology Internal Memorandum, Final (v04), 12-Oct-2012

[redacted]

14.17 Appendix Q: List of prohibited medication

14.17.1 List of prohibited medication while on study

Category	Drug Names
Strong inducers of CYP3A4	Avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort
Strong Inhibitors of CYP3A4	Clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, voriconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, grapefruit juice, juice from Seville oranges
Medications which increase serum phosphorus and/or calcium	Calcium, phosphate, vitamin D, parathyroid hormone (PTH)
Narrow Therapeutic index substrates of CYP3A4	Quinidine, astemizole, terfanadine, cyclosporine, sirolimus, tacrolimus, diergotamine, cisapride, ergotamine, pimozide, alfentanil, fentanyl thioridazine, diergotamine, dihydroergotamine, ergotamine
Medications with established potential for QT prolongation or Torsades de pointes	Amiodarone, Anagrelide, Arsenic trioxide, Astemizole (Off US mkt), Azithromycin, Bepridil (Off US mkt), Chloroquine, Chlorpromazine, Cisapride (Off US mkt), Citalopram, Clarithromycin, Cocaine, Disopyramide, Dofetilide, Domperidone (Not on US mkt), Dronedarone, Droperidol, Erythromycin, Escitalopram, Flecainide, Grepafloxacin (Off market worldwide), Halofantrine, Haloperidol, Ibutilide, Levofloxacin, Levomethadyl (Off US mkt), Mesoridazine (Off US mkt), Methadone, Moxifloxacin, Ondansetron, Pentamidine, Pimozide, Probucol (Off US mkt), Procainamide (Oral off US mkt), Quinidine, Sevoflurane, Sotalol, Sparfloxacin (Off US mkt), Sulpiride (Not on US Mkt), Terfenadine (Off US mkt), Thioridazine, Vandetanib

[redacted]

14.18 Appendix R: Bayesian Adaptive Design Framework for the Modular phase II study to link targeted therapy to patients with pathway activated tumors

14.1.1.0 Introduction

This document outlines the adaptive design framework to be used for this study and all modules.

Although the selected tumor types may vary by trial, this document outlines the design and analysis approach based on 8 example tumor cohorts:

- Lung NSCL
- Bladder
- Breast
- Colorectal
- GIST
- HNSCC
- Ovarian
- Sarcoma

Other tumor types may be considered for trials if 1) 4 or more patients are enrolled in the cohort, and 2) a reasonable estimate of the clinical benefit rate is available.

The primary endpoint is clinical benefit rate (CBR) in each cohort, with clinical benefit being assessed at 16 weeks. All patients will receive the experimental treatment for that particular trial.

14.1.1.1 Primary analysis

We let Yi be the response indicator for the ith subject, and let Rg be the assumed probability of response within a control population and $\pi g = Pr(Yi = 1 \mid gi = g)$ be the underlying probability of response for group g within the trial. We transform to the logit scale for modeling purposes. Let θg be the mean log odds treatment effect, i.e.:

$$\theta_g = \log\left(\frac{\pi_g}{1-\pi_g}\right) - \log\left(\frac{R_g}{1-R_g}\right).$$

Thus, θg is the group specific logistic regression coefficient for group g. The primary analysis is a set of group specific tests that $\theta g>0$, meaning that the experimental treatment is better than the assumed control rate for that group. Thus, we wish to test the set of hypotheses

$H0g : \theta g \leq 0$

$H1g : \theta g > 0$

We proceed in a Bayesian fashion, assigning a prior distribution (discussed below) and computing the posterior probability of H1g within each group g. If, at the final analysis,

[redacted]

$$Pr(\theta g>0 \mid data) > 0.80$$

Then group g will be declared a success (thus, the final analysis produces a separate decision for each group). The trial also allows for early stopping of groups, described below.

14.1.1.2 Trial logistics

Each trial will enroll all available subjects in all cohorts for 2 years unless a cohort cap is reached, or a cohort is stopped early, or the trial is stopped early by Novartis. Each trial will enroll no more than 30 evaluable subjects in each cohort. Interim monitoring will be conducted starting after the first 30 patients are enrolled overall (across all cohorts), and continuing each 13 weeks thereafter till study enrollment closure. After that, one CBR analysis will be done after database lock. At each interim data review, response information for the various cohorts will be evaluated to determine the current $Pr(\theta g>0 \mid data)$ within each cohort, with sufficiently high/low values used to stop the cohort for success/futility. A minimum of 10 patients will be required in a cohort before it may discontinue enrollment for futility, and a minimum of 15 patients are required before discontinuing a cohort for efficacy. If a cohort stops enrolling early, the remaining cohorts will continue until the end of 2 years or until the other cohorts reach their own early stopping criteria. The final analysis will occur after the database lock for the primary CSR.

Each trial will enroll subjects in all listed cohorts. In addition, should other cohorts be identified throughout the trial, the following mechanism will be used. If another cohort is identified, it will not be placed into the statistical analysis unless 3 subjects enroll within the cohort (thus, the trial may enroll multiple additional cohorts, but a cohort will only be added to the list if at least 3 patients enroll from that cohort). Thus, it is possible (but not viewed as likely) that multiple additional cohorts may be added to the trial if the trial has sufficient enrollment in multiple additional cohorts. In addition to sufficient enrollment, the sponsor must have a reasonable estimate of the control clinical benefit rate.

Subjects within any cohort which does not reach the minimum enrollment will be excluded from the interim and final analyses. As the study continues, early interim data reviews may be based on fewer cohorts than later interim data reviews, as the interim data reviews will include whatever cohorts have satisfied the criteria at the time of the data review.

14.2.2.0 Statistical modeling

We let Yi be the response indicator for the ith subject, and let Rg be the probability of response within a control population and $\pi g = Pr(Yi = 1 \mid gi = g)$ be the underlying probability of response for group g within the trial. We transform to the logit scale for modeling purposes. Let θg be the mean log odds treatment effect, i.e.:

$$\theta_g = \log\left(\frac{\pi_g}{1-\pi_g}\right) - \log\left(\frac{R_g}{1-R_g}\right).$$

The statistical design borrows information across groups with a hierarchical model. The hierarchical model allows dynamic borrowing of information between groups such that more borrowing occurs when the groups are consistent and less borrowing occurs when the groups differ. In this way, the model is a compromise between the two alternate extremes of either a

[redacted]

completely pooled analysis or a separate analysis in each group. We additionally incorporate a clustering mechanism that allows borrowing within clusters but treats clusters separately. This minimizes borrowing across groups that are quite different in terms of CBR.

The purpose of such an analysis (discussed in more detail in the appendix) is to produce higher power or lower type I error in situations where we see some commonality (identical effects are not required) among the groups. The model will borrow more in situations where the groups appear similar than situations where the groups appear different.

14.2.2.1 Hierarchical model with clustering

Our hierarchical approach involves two stages. The goal of both stages is to allow the data to drive the amount of borrowing across groups. If the data indicate a large amount of borrowing is appropriate (due to similar results), the model will borrow more and thus increase the overall power of the trial within each group. In contrast, if the data indicate a small amount of borrowing is appropriate (due to dissimilar results) the model will adjust and each group will stand more on its own. This "dynamic" borrowing property is distinct from other approaches which use a fixed informative prior or apriori assume an amount of borrowing across groups. Here the approach includes two stages to identify the appropriate amount of borrowing based on the data.

The first stage of model places the groups into distinct clusters. The purpose of this stage is to minimize borrowing of information across groups that appear to be quite different. Thus, for example, should 2 of the groups appear similar while the others differ significantly, the model may place a large probability on two clusters, one containing the two similar groups with the other containing the remaining groups. The model incorporates the uncertainty of the data in this determination, producing a probability distribution over the possible clusterings. Thus, in our example, the model may consider it highly likely that the 2 similar groups are in one cluster with the remaining groups in another, but it would also retain lower probabilities on the possibility all groups are in one cluster (e.g. we are simply seeing differences in the two groups by chance) as well as other possibilities. The complete analysis averages over this uncertainty. This clustering approach is implemented through a Dirichlet Process Mixture (DPM) model, described in the appendix.

At the second stage, we place hierarchical models over the groups within each cluster (thus, conditional on the clustering, there is no borrowing of information across clusters, only within clusters). The hierarchical model assumes that the θ_g have an across groups distribution

$$\theta g \sim N(\mu, \tau 2)$$

The across group mean μ and variance $\tau 2$ are unknown, and hence have a prior distribution which is combined with the data to produce estimates of μ and $\tau 2$.

The variance component τ controls the degree of borrowing among groups. Small values of τ result in a greater degree of borrowing while large values of τ correspond to less borrowing. The parameter τ is estimated using the data, so the observed between group variation is a key component of the model behavior.

Combined, the two stages allow groups with similar results to borrow information between them (they will have a high probability of being in the same cluster) while groups with

[redacted]

different results with borrow far less information between them (they will have a low probability of being in the same cluster).

Details of the two stages may be found in the appendix.

14.3.3.0 Evaluation of trial success and futility

Interim monitoring will occur after the first 30 patients are on the study for 16 weeks (112 days), then every 13 weeks thereafter till study enrollment closure. At each interim data review, the groups will be evaluated for early futility and early success by comparing posterior quantities for the response rate to pre-specified early stopping criteria.

14.3.3.1 Early futility

If there is less than 10% probability that the response rate in a group exceeds the historical rate Rg, then the group will stop enrollment early for futility. Formally, enrollment will stop early for futility if:

$$Pr(\pi g > Rg) < 0.10.$$

A group is only eligible for early stopping once a minimum of 10 patients has been evaluated for response in that group.

14.3.3.2 Early success

If there is at least 95% probability that the response rate in a group exceeds the historical rate, then the group will stop enrollment early for success. Formally, enrollment will stop early for success if:

$$Pr(\pi g > Rg) > 0.95.$$

A minimum of 15 subjects will need to be evaluated prior to declaring a group to be efficacious.

14.3.3.3 Final analysis

In addition, recall the final analysis will occur when both accrual and follow-up are complete in all groups, or after the database lock for the primary CSR. If, at the completion of the trial, there is at least 80% probability that the response rate in a group exceeds the historical rate, then the group will be considered a success. Formally:

$$Pr(\pi g > Rg) > 0.80.$$

14.4.4.0 Simulation

We evaluated type I error and power for each of the 8 possible groups under a variety of possible “truths” indicating various possible true underlying probabilities within each group.

14.4.4.1 Assumptions

Accrual – Two scenarios for the assumed two-year expected accrual are investigated: 1) 10 subjects per group and 2) 5 subjects per group. Note that these are averages, the actual number

[redacted]

of available patients is simulated as a Poisson distribution with the specified mean. Also note that the group cap of 30 applies, and thus if the number of available patients in a group exceeds 30, only the first 30 available patients in that group will be enrolled in the study.

Dropouts – We assume no dropouts for the purpose of this simulation.

Control Rates –Table 14-1 shows the assumed control clinical benefit rates for each group.

Table 14-1 Assumed control CBR values used in the simulations

Tumor Type	Assumed Control Rate (Rg)
Lung LSCL	0.45
Bladder	0.47
Breast	0.50
Colorectal	0.38
GIST	0.50
HNSCC	0.45
Ovarian	0.47
Sarcoma	0.40

We consider four possible scenarios, or possible "truths" in the simulation. These consisted of a null scenario (where the treatment has no effect for any group), an alternative scenario (where the treatment is effective in all groups), a scenario where the treatment was effective in two of the groups, and a scenario where the treatment was effective in half of the groups.

Treatment Rates - The treatment rates for each scenario are shown in the table below. Values identical to the control are shown in red, while values greater than the assumed control rate are shown in green.

	Null	Alternative	Two	Half
Lung LSCL	0.45	0.71	0.45	0.45
Bladder	0.47	0.73	0.47	0.47
Breast	0.50	0.75	0.50	0.50
Colorectal	0.38	0.65	0.38	0.38
GIST	0.50	0.75	0.50	0.75
HNSCC	0.45	0.71	0.45	0.71
Ovarian	0.47	0.73	0.73	0.73
Sarcoma	0.40	0.67	0.67	0.67

Simulation Details – For each scenario we simulated 1000 trials. For each interim within each trial, we ran 50,000 MCMC iterations after a 1,000 MCMC iteration burnin.

14.4.4.2 Results

A total of 8 scenarios were simulated (two accrual scenarios and four possible 'truths' for the clinical benefit rate). The probability of group success for each group is provided for each scenario in the below two tables.

Table 14-2 provides the probability of group success for each of the cohort – assuming expected accrual of 10 subjects/cohort and 5 subjects/cohort separately

[redacted]

Table 14-2 Probability of group success for each cohort

Two-year expected accrual: 10 subjects/cohort				
Group	Null	Alternative	Two	Half
Lung LSCL	0.158	0.915	0.208	0.305
Bladder	0.131	0.918	0.232	0.322
Breast	0.147	0.909	0.233	0.312
Colorectal	0.138	0.921	0.200	0.276
GIST	0.162	0.921	0.233	0.826
HNSCC	0.139	0.906	0.217	0.834
Ovarian	0.145	0.929	0.786	0.829
Sarcoma	0.135	0.939	0.758	0.852
Two-year expected accrual: 5 subjects/cohort				
Group	Null	Alternative	Two	Half
Lung LSCL	0.132	0.803	0.204	0.258
Bladder	0.140	0.830	0.196	0.265
Breast	0.160	0.807	0.232	0.261
Colorectal	0.135	0.794	0.194	0.278
GIST	0.155	0.826	0.212	0.688
HNSCC	0.140	0.820	0.190	0.657
Ovarian	0.151	0.819	0.587	0.652
Sarcoma	0.139	0.799	0.579	0.667

Entries in red represent groups where the treatment effect is 0 (e.g. the treatment is ineffective). Thus, entries in red are type I errors. Entries in green appear where the treatment is effective, and thus indicate the power of the design.

Generally, type I error is controlled below 0.20 under the null scenario (the borrowing compensates for the multiple interim data reviews) and power is an increasing function of the expected sample size (power is higher in the higher accrual situation across treatment rate scenarios). In the alternative scenario there remains decently high probability of success even in the lower accruing situations. When fewer groups are effective in truth, the scenarios “half” and “two” are harder to discern. Note in any particular trial there should be a mix of high and low enrolling groups, thus some groups may enroll closer to 10 subjects while others may only enroll five. This would produce a power value somewhere between the two tables.

Power is reduced and type I error is inflated when the truth is a mixture of effective and ineffective treatment effects across the groups. Generally power is a function of the sample size.

Appendix 1 - Modeling details

Recall at the first stage the groups are clustered according to a Dirichlet Process Mixture Model.

The number of clusters is not assumed to be known in advance but will instead be inferred from the data using Dirichlet Process Mixtures (DPM). The DPM looks across all the possible

[redacted]

clusterings of the groups and assigns a probability to each based on the data. The prior distribution in a DPM is governed by a parameter α. When α is small, the prior favors large clusters. As α tends to zero, the prior tends to place all its mass on a single cluster containing all the groups. As α increases, the prior places more mass on clusterings with a large number of clusters. As α becomes very large, the prior places all of its mass on having a separate cluster for each group (that is, no borrowing across groups). Thus, by specifying extreme values of the prior one could force the groups into one cluster or force the groups to be analyzed in separate clusters. Here we choose a moderate version of α=2 (common values might be anywhere between 0.5 and 5) and allow the data more control over the clustering.

The details of the prior are as follows. Let zg represent the cluster to which group g belongs. Then zg ~ Categorical(p), where p is the vector such that pk is the probability that a group belongs to cluster k and $\sum_{k=1}^{\infty} p_k = 1$. We construct p using a stick-breaking process:

$$p_k = \beta_k \prod_{i=1}^{k-1} (1 - \beta_i)$$

and

$$\beta k \sim \text{Beta}(1, \alpha).$$

A large value of α thus removes a very small amount of probability for p, resulting in many clusters, while a small value of α tends to produce probabilities near 1 for the first cluster.

Conditional on the clustering, we fit a hierarchical model which has an across groups distribution

$$\theta g \sim N(\mu, \tau 2)$$

As discussed above, this across group distribution states that within a cluster we expect to see some variation in the parameters, with that variation governed by τ. When τ is small, there is minimal variation across groups within a cluster, and thus within the cluster the model would approach pooling. In contrast, when τ is large we expect large amount of across group variation, and thus even though the groups are in the same cluster the θg values may be quite different. Apriori we have no way of knowing τ, so we estimate it using the data combined with the prior distributions

$$\mu \sim N(0, 1.82)$$

and

$$\tau 2 \sim IG(3,0.5),$$

where IG(α, β) is the inverse gamma distribution defined by:

$$f(x|\alpha, \beta) = \frac{\beta^{\alpha} e^{-\beta/x}}{x^{\alpha+1}\Gamma(\alpha)}.$$

When the entire model is implemented (via Markov Chain Monte Carlo) we consider the full joint distribution of the clustering combined with the hierarchical model parameters. We average over the entire range of the uncertainty in the parameters to produce the posterior

[redacted]

distribution for each group parameter θg, which is then used to drive the decisions in the model.

[redacted]