NOVARTIS

Clinical Development

Ribociclib (LEE011)

Protocol CLEE011XUS03 / NCT02187783

Modular phase II study to link targeted therapy to patients with pathway activated tumors: Module 8 – Ribociclib for patients with CDK4/6 pathway activated tumors

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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
BCC	Basal cell carcinoma
BCRP	Breast cancer resistance protein
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
[redacted]	[redacted]
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 & Patient Safety
CNS	Central Nervous System
CPK	Creatine phosphokinase
CR	Complete Response
CRC	Colorectal Cancer
CrCl	Creatinine clearance
CRO	Contract Research Organization
CRPC	Castrate Resistant Prostate Cancer
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
FDA	Food and Drug Administration
FAS	Full Analysis Set
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
FFPE	Formalin fixed paraffin embedded
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 gonadotrophin
HCV	Hepatitis C Virus
HDL	High density lipoprotein
hERG	human Ether-à-go-go Related Gene
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
hr	hour
IB	Investigators Brochure
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

[redacted]

IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine system
IWG	International working group
KA	Keratoacanthoma
LDL	Low density lipoprotein
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated ERK Kinase
mg	milligram
MI	Myocardial infarction
MM	Multiple Myeloma
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
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
PK	Pharmacokinetics
PLT	Platelets
PR	Partial Response
PSA	Prostate-specific antigen
PT	Prothrombin time
PTEN	Phosphatase and tensin homolog
QD	*quaque die*/once a day
QTc	QT corrected
QTcF	Q-T interval in the ECG (corrected according to the formula of Fridericia)
RAP	Report Analysis Plan
RBC	Red Blood Cells
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended phase two dose

[redacted]

RU	Resource utilization
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SC	Steering Committee
SCC	Squamous cell carcinoma
SCT	Stem cell transplant
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
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
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. Ribociclib will be dosed once daily, 3 weeks on and 1 week off. The first dose of ribociclib defines Day 1 of the treatment cycle.
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. Ribociclib 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. Ribociclib 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	Ribociclib (LEE011)
Study treatment discontinuation	Point/time when patient permanently stops taking ribociclib, for any reason.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

[redacted]

Amendment 3 (10-Apr-2017)

Study CLEE011XUS03 was initiated in August 2014 and closed to enrollment on May 8, 2015 with 106 patients enrolled. As of April 6, 2017, one patient remains on study.

Amendment rationale

The main purpose of this amendment is to introduce language to allow for the one ongoing patient to rollover onto a Novartis sponsored Rollover Study for patients receiving LEE011.

Protocol changes

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.

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.

Section 4.2 Definition of End of Study: Further defines the end of study to include termination by the study or another clinical study becoming available for the patients to transfer.

Section 7.1.3.2 Criteria for premature patient withdrawal (EOT phase completion): Clarified that patients who rollover to another study will have EOT procedures performed but will not have further follow up on the current study.

Throughout the document: Changed the name of Novartis Drug Safety and Epidemiology Department (DS&E) to Novartis Chief Medical Office & Patient Safety (CMO&PS).

Amendment 2

Study CLEE011XUS03 was initiated in August 2014 and as of April 2nd, 2015, a total of 78 patients have been dosed.

Amendment rationale

The main purpose of the amendment is to align safety and general program information across ribociclib studies.

The amendment contains changes to:

1. Reduce the frequency of disease assessments from every 8 weeks to every 16 weeks for patients who have completed 16 weeks on treatment. This change will bring the disease assessment close to standard of care after the primary endpoint.
2. Clarify that survival follow-up may be discontinued if the primary endpoint is not met.
3. Definition of end of study, to clarify when data will be reported.
4. Align the inclusion and exclusion criteria to the requirements across ribociclib studies.
5. Include specific dose modification guidance for cases of hepatic toxicity in order to better manage patient safety: dose adjustments as well as additional follow up for bilirubin and/or transaminases increase have been detailed and separated from the dose modification guidance for other adverse events.

[redacted]

6. Guidance for management of QTc prolongation has been extended to all AEs regardless of the grades to better manage patient safety.
7. Update the protocol requirements for consistency with the most recent preclinical information:
   a. In the initial rat ADME study cited in previous IB version, thyroid had the highest exposure in albino animals only. As a precaution, thyroid function was monitored in all clinical study protocols. A most recent study (DMPK 1300792) using p.o. dosing in partially pigmented animals with a longer observation period showed the highest distribution to the melanin-containing structures and not to the thyroid gland. In addition, no clinically significant thyroid adverse events have been reported in clinical trials so far. Based on this information, the risk to thyroid gland is removed from the reference safety information for the compound and thyroid laboratory monitoring in clinical protocols are no longer mandated.
   b. In the 15-week rat toxicity study, kidney has been identified as an additional organ of toxicity for LEE011. In order to better characterize this potential side effect, as well as improve the management of the safety of the patients, monthly urinalysis has been added as well as blood urea nitrogen assessment with each chemistry panel.
8. Concomitant medications: bisphosphonate and denosumab, palliative radiotherapy, concomitant medications requiring caution and prohibited concomitant therapy sections have been updated to better manage concomitant medication use.
9. [redacted]
10. Bayesian adaptive design for the Modular Phase II Study to link Targeted Therapy to Patients with Pathway Activated Tumors. In a single arm trial without control arm, the quality of the inferences depend strongly on historical data used to create a credible estimate of the baseline control rate. For this study this required an estimate of the patient population that would be enrolled. A control estimate was initially formed for each group based on the population estimate which differed from the patient population was enrolled in terms of previous line of therapy (heavily pretreated). In order to 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 study rather than rely on the pre-trial assumptions. The appendix has been changed to be standard across the Modules rather than being study specific.
11. This amendment also includes minor editorial changes as described in the list of changes below.

Protocol changes

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.

[redacted]

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.

- Section 1.2.1.1.2 Nonclinical pharmacokinetics and metabolism of ribociclib: Provides the most recent nonclinical pharmacokinetics information on ribociclib.
- Section 1.2.1.2 Clinical experience with ribociclib: Provides status update on clinical experience with ribociclib.
- Section 1.2.1.2.1 Clinical safety of ribociclib: Provides the most recent available safety information on ribociclib.
- Protocol summary, Section 4.1.1, Table 7-1: reduced the frequency of disease assessments after 16 weeks on treatment from every 8 weeks to every 16 weeks.
- Protocol summary, Section 4.1.2, Table 7-1, section 7.1.4.3: provides updated information on how survival follow-up will be handled.
- [redacted]
- Section 4.2: provides updated definition of end of study, and clarifies when the study data will be reported.
- Section 5.2, number 13f: provides most recent inclusion bilirubin values available for ribociclib.
- Section 5.3: provides updated exclusion values based on clinical experience with ribociclib.
- Section 6.3.3: provides the most recent criteria for interruption and re-initiation of ribociclib based on available clinical experience.
- Section 6.4, Appendix A: provides updated information on concomitant medication based on available clinical experience.
- [redacted]
- Table 7-1, Section 7.2.2.6.1, Table 7-2: provides updated information ECG plan.
- Section 10.5.1: added information to clarify how ORR will be presented if the sample size is small.
- Section 10.8: provides updated information on sample size calculation.
- Appendix R: provides revised Bayesian Adaptive Design for the Modular Phase II Study to Link Targeted Therapy to Patients with Pathway Activated Tumors.
- Changed LEE011 to ribociclib through-out the protocol.

Amendment 1

Amendment Rationale

The amendment contains changes to clarify that tumor aberration resulting from CDK4/6 pathway activation is required for study. Other changes in the protocol include updates to the inclusion and exclusion criteria, addition of confirmatory requirement for solid tumor

[redacted]

assessment responses of PR or greater and updates to in text appendix references. The changes were implemented to make protocol clear, standardize leukemia requirements and update hyperlinks.

Changes to the Protocol

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

- Protocol title has been revised to state: "Modular phase II study to link targeted therapy to patients with pathway activated tumors: Module 8 - LEE011 for patients with CDK4/6 pathway activated tumors".
- Protocol Summary: the title, brief title, purpose and rationale, [redacted], study design and efficacy assessment sections were revised to clarify CDK 4/6 pathway activation and streamline the summary.
- Section 2.1: the study purpose was streamlined to reflect the protocol title.
- [redacted]
- Sections 4.1.2, 7.2.4.2.2 and Table 7-3: revised to remove ambiguity from collection timepoint for optional tumor sample at disease progression.
- Sections 5.2 and 5.3: updated for leukemia patients.
- Sections 7.2.1.1 and 10.4: added disease assessment confirmatory requirement for solid tumor patients who achieved a response of PR or greater.
- Section 11.3: updated contraception requirement for males to make it consistent with section 5.3, #30.
- Updated appendix references and hyperlinks, and removed typographical errors throughout the protocol.

[redacted]

Protocol summary

Protocol number	CLEE011
Title	Modular phase II study to link targeted therapy to patients with pathway activated tumors: Module 8 - Ribociclib for patients with CDK4/6 pathway activated tumors
Brief title	Ribociclib for patients with CDK4/6 pathway activated 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 ribociclib demonstrates sufficient efficacy in CDK4/6 pathway activated 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 ribociclib 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. 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.
Table	T1-1 o 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]	
Study design	This is a phase II, open label study to determine the efficacy and safety of treatment with LEE011 in patients with a diagnosis of select solid tumors or hematological malignancies that have been pre-identified (prior to study consent) to have CDK 4/6 pathway activation , and whose disease have 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 the relevant gene aberrations to treatment with CDK4/6 inhibitor, LEE011. Pre-identification of the pathway aberration status will be performed locally at a CLIA certified laboratory prior to participation on the trial. 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
[redacted]	

	before any screening activities take place. Once eligibility (inclusion/exclusion criteria) has been confirmed by Novartis, the patient will initiate therapy with ribociclib single-agent. The patient may not receive any additional anti-cancer therapy during treatment with ribociclib. Patients will continue to receive study treatment until disease progression (assessed by investigator per RECIST 1.1 or appropriate hematologic response criteria), 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. 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. The frequency of disease assessment will be reduced to every 16 weeks after patients have completed 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. 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 study primary efficacy endpoint is not met, Novartis may discontinue survival follow-up for this study.
Population	The study population consists of approximately 70-90 adult patients with a diagnosis of a solid tumor or hematological malignancy that have been pre-identified as having relevant CDK4/6, cyclin D1/3, or p16 aberrations. 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 ribociclib. Tumors currently being studied under some key Novartis-sponsored trials will be excluded. These include breast cancer (except triple negative), mantle cell lymphoma, teratoma, castrate resistant prostate cancer (CRPC), melonoma and liposarcoma. Additional tumor types may be excluded during the course of the study at the discretion of Novartis. Patients must have archival tissue available for submission to allow for molecular testing related to pathway activation. If tissue is not available or is insufficient the patient must be willing to undergo a fresh tumor biopsy to allow for these analyses. Enrollment is meant to encompass select solid tumors and hematologic malignancies that have the relevant CDK4/6, cyclin D1/3 or p16 aberrations and 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. such as ovarian, mesothelioma, breast (triple negative), colorectal, biliary, pancreatic neuroendocrine cancer, and lymphomas (excluding mantle cell lymphoma) (enrollment will not be strictly limited to those particular cancers). 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 (except breast cancer (triple negative will be enrolled), teratoma, CRPC, melanoma, and liposarcoma) or hematologic malignancies (except mantle cell lymphoma,) and is in need of treatment because of

[redacted]

	progression or relapse. Patient's tumor has been evaluated and pre-identified as having a tumor with relevant CDK4/6, cyclin D1/3, or p16 aberration. The qualifying alteration must be assessed and reported by a CLIA-certified laboratory 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
Exclusion criteria	Patient has received prior treatment with ribociclib Patients with primary Central Nerve System (CNS) tumors or CNS tumor involvement 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 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	Ribociclib will be dosed on a flat scale of 600 mg once daily, 3 weeks on and 1 week off. A complete treatment cycle is defined as 28 days.
Efficacy assessments	Clinical benefit rate (CBR), overall response (OR), progression free survival (PFS), overall survival (OS) and duration of response (DOR) based on local investigator assessment per RECIST 1.1 for solid tumors or appropriate hematological response criteria. 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. The frequency of disease assessment will be reduced to every 16 weeks after patients have completed 16 weeks on treatment.
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)
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, mutations, amplifications, signature, CDK4, CDK6, CDK4/6, cyclin D1, CCND1, cyclin D3, CCND3, p16 mutation, CDKN2A, LEE011, breast cancer, ovarian cancer, colon cancer, mesothelioma, pancreatic neuroendocrine

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Overview of G1 to S phase transition in mammalian cells

Normal mammalian cells proliferate in response to extracellular signals by transitioning through a series of tightly controlled phases that culminate in cell division. The commitment to transition from G1 to S phase and the initiation of cell cycle progression is regulated by the retinoblastoma protein (pRb). In the absence of appropriate growth stimuli, pRb, in its unphosphorylated state, binds and inhibits the activity of the E2F family of transcription factors, preventing these proteins from activating the genes required for S phase transition (Oretega, Malumbres and Barbacid 2002, Shapiro 2006). Upon mitogen stimulation, signaling through pathways such as the MAPK and PI3K pathways increases the abundance of D-cyclins, which bind and activate cyclin-dependent kinases (CDKs) 4 and 6 (CDK4/6). Cyclin D-bound CDK4/6 then phosphorylates the pRb protein to deactivate it and release bound E2F. Once freed, E2F activates S phase-specific genes in order to start cell cycle progression. Full deactivation of pRb requires its sequential phosphorylation at different sites by both cyclin D-CDK4/6 and cyclin E-CDK2. The phosphorylation events mediated by CDK4/6 are prerequisites for those catalyzed by CDK2 (Lundberg and Weinberg 1998). The kinase activity of CDK4/6 is in turn inhibited by p16, encoded by the INK4a gene (Kamb et al 1994, Ortega, Malumbres and Barbacid 2002). The CIP/KIP proteins, inhibitors of cyclin E-CDK2, also bind to the cyclin D-CDK4/6 complex, and this results in further activation of CDK2 by sequestering CIP/KIP proteins from their target (Sherr and Roberts 1999). Cyclin D-CDK4/6 is therefore a key enzyme complex that regulates the G1 to S phase transition.

1.1.2 Alterations in the D-cyclin-CDK4/6-INK4a-pRb pathway in human malignancies:

The D-cyclin-CDK4/6-INK4a-pRb pathway is universally disrupted in cancer to favor cell proliferation. Eighty percent of human neoplasms maintain functional pRb but harbor aberrations that increase the activity of CDK4/6 to effectively inactivate pRb function. These aberrations include genetic or epigenetic changes that directly increase the kinase activity of CDK4/6 or defects that activate the upstream regulators (Ortega, Malumbres and Barbacid 2002, Shapiro 2006). One of the most common events is the inactivation of p16 via mutations, deletion and epigenetic silencing. p16 inactivation is frequently observed in a significant portion of non-small cell lung cancer (NSCLC), melanoma, pancreatic cancer and mesothelioma (Cheng et al 1994, Cowgill and Muscarella 2003, Fountain et al 1995, Gazzeri et al 1998). Moreover, a specific mutation of the CDK4 gene (CDKR24C), that confers resistance to p16 binding, has been shown to play a causal role in rare cases of familial melanoma, suggesting that unchecked CDK4 activity is a key event in these cancers (Molven et al 2005).

Translocations of the genes encoding D-cyclins to the immunoglobulin heavy chain locus are found in a majority of mantle cell lymphomas (MCLs) and in many cases of multiple

[redacted]

myeloma (Bergsagel and Kuehl 2003). These translocations lead to constitutive expression of D-cyclins, which result in enhanced CDK4/6 kinase activity and unchecked cell proliferation (Amin et al 2003). Amplification of cyclin D1 and overexpression of the protein have also been reported in approximately 50% of squamous cell esophageal cancers (Huang et al 2007) and in 20-30% of breast cancers (Arnold and Papanikolau 2005, Sutherland and Musgrove 2004), suggesting that activation of this pathway may play a role in the growth of these tumors. Furthermore, many of the receptor-mediated growth pathways that are activated in human cancers increase D-cyclin transcription and expression to drive cell proliferation. In mouse breast cancers driven by activated Ras or Her2/Neu oncogenes, cyclin D1 and CDK4 have been shown to be necessary for the tumorigenic phenotype in both initiation and maintenance phases, demonstrating that Cyclin-D1/CDK4 is the key effector enzyme complex for Ras- or Her2/Neu-driven cancers (Landis et al 2006, Yu Geng and Sicinski 2001). Other activating aberrations of mitogen pathways such as V600E B-Raf in the MAPK pathway and PTEN deletions in the PI3K pathway also increase D-cyclins to achieve unchecked proliferation, suggesting that CDK4/6 may also be crucial for the cancers bearing these alterations (Garcia-Echeverria 2009, Gray-Schopfer Dias and Marais 2005). Finally, the genes encoding CDK4 and 6 are amplified in a subset of human neoplasms. The CDK4 gene is amplified in 100% of liposarcomas along with the MDM2 gene, while CDK6 is frequently amplified in T-lymphoblastic lymphoma and/or acute lymphoblastic leukemia (Nagel et al 2008, Sirvent et al 2007).

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

1.2.1 Overview of Ribociclib

Ribociclib is an investigational agent that is an orally bioavailable, small molecule inhibitor of CDK4/6. LEE011 exhibits highly specific inhibitory activity against CDK4/cyclinD1 and CDK6/cylinD3 complexes, with concentration resulting in 50% inhibition (IC_{50}) values of 10 nM and 39 nM, respectively, in isolated enzyme assays. It is inactive against the majority of other kinases.

1.2.1.1 Non-clinical experience

1.2.1.1.1 Pharmacology of Ribociclib

Ribociclib inhibits the growth of many tumor cell types *in vitro* and *in vivo* including ER+ BC. In a panel of human breast cancer cell lines, dose-dependent inhibition of proliferation was observed in ER+ BC cell lines, with IC_{50} < 1μM being observed for most ER+ BC lines. Regardless of the various genetic aberrations that may be present in the cancer cells, the anti-tumor activity of ribociclib requires the presence of functional retinoblastoma protein (Rb).

1.2.1.1.2 Non-clinical pharmacokinetics and metabolism of Ribociclib

Four different species were used to investigate the pharmacokinetics (PK) of ribociclib: mouse, rat, dog and monkey. Ribociclib showed high clearance (CL) in the mouse, rat, dog and monkey. The volume of distribution was large across species and the terminal elimination half-life (T1/2) was moderate in rodents and monkey (~2 to 5 h) and longer in dog (18 h).

[redacted]

Bioavailability was low to moderate in rat (37%) and cynomolgus monkey (17%), and moderate in mouse (65%) and dog (64%). Following oral administration, time to reach maximal plasma concentrations (Tmax) occurred between 2 to 4 h across species. Gender-dependent toxicokinetics were observed in rats with higher exposure to LEE011 in males as compared to females and with higher exposure to the metabolite, LEQ803.

Plasma protein binding was moderate in all species (unbound fraction (fu) in human: 30%).

In a rat (absorption, distribution, metabolism and excretion (ADME)) study, extensive distribution of [3H]LEE011 and its metabolites was seen. In pigmented rats, radioactivity was specifically found in melanin-containing structures, and the highest exposure to total radiolabeled components was observed in eye ciliary body, eye choroid, meninges, tactile hair and hair follicles. Radioactivity was not detected in the brain. Tlast (last observation timepoint) was ≤ 48h for most tissues, but long (168 to 840h) for lymph nodes, preputial gland, testis, eye and meninges. At one week ≤ 0.04% of the dose was retained in the carcass.

LEQ803 (N-demethylation) was a prominent metabolite found in mouse, rat, dog, monkey and human hepatocytes. This metabolite retains some pharmacologic activity and interacts with human Ether-a-go-go Related Gene (hERG) channels in vitro. In male rats, unchanged LEE011 (24.7% of [3H]AUC0-24h) and its metabolite M11 (26.3% of [3H]AUC0-24h) were the major components in plasma. In rats, LEE011 was eliminated mainly by metabolism. The major metabolism pathway was direct sulfation of LEE011 to M8 and its excretion into the bile. Direct LEE011 secretion accounted for 18.2% of the total plasma clearance.

Results from the ADME (male rats) study showed that 3H-components were predominantly excreted with bile (61.4% of dose). Minor urinary excretion was observed (5.9% of dose after p.o.). The majority of the administered dose (87.3%) was excreted within 24 h via urine, feces (enteric secretion) and bile.

In vitro, LEE011 was a reversible inhibitor of cytochrome P450 (CYP) enzymes CYP1A2, CYP2E1 and CYP3A4 and a time-dependent inhibitor of CYP3A4. No pregnane X-receptor (PXR)-mediated CYP3A4 induction was observed. *In vitro* inhibition of drug transporters was observed with LEE011 for organic anion transporting polypeptide 1B1 (OATP1B1), breast cancer resistance protein (BCRP), organic cation transporter 1 (OCT1), OCT2, multidrug andtoxin extrusion protein 1 (MATE1), MATE2K and bile salt export pump (BSEP). At therapeutic doses, LEE011 may affect substrates of CYP3A4, BSEP, MATE1, OCT2 and/or BCRP depending on the dose and concentrations achieved *in vivo*.

Elimination of LEE011 is dominated by oxidative metabolism mainly via CYP3A4 with a minor contribution by flavin-containing monooxygenase 3 (FMO3). The elimination of LEE011 may be affected by co-administered drugs that inhibit or induce CYP3A4. Although LEE011 is a substrate of the P-glycoprotein (P-gp) efflux transporter and subject to active uptake into hepatocytes, these processes are likely not clinically relevant due to the high passive permeability of LEE011.

1.2.1.1.3 Safety pharmacology and toxicology of Ribociclib

In vitro, LEE011 did not show mutagenic or phototoxic potential. Safety pharmacology studies conducted did not reveal any effects on CNS or respiratory functions. In the dog telemetry study, prolongation of the average QT and QTc was observed with the potential to

[redacted]

induce PVCs at higher exposure levels. LEE011 and LEQ803 likely contributed to the QT prolonging effects seen *in vivo*.

In rats and dogs, ribociclib induced bone marrow hypocellularity, lymphoid depletion, atrophy of the skin and intestinal mucosa, decreased bone formation and testicular atrophy. These effects are considered to be related to the pharmacological inhibition of cell replication in these tissues due to CDK4/6 inhibition. The liver, bile system and gall bladder (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile) were identified as additional target organs of toxicity which are not likely related to the primary pharmacology of ribociclib. Correlating hematological and/or biochemistry changes were seen for the effects described in the bone marrow, lymphoid system and liver. All of the described changes were fully reversible in rats and dogs.

Based on the mechanism of action and preclinical toxicology studies conducted, the major potential toxicities for ribociclib include myelosuppression, hepatic toxicity, and prolongation of the QT interval. The risk of these toxicities may be amplified by concomitant administration of strong inhibitors of CYP3A4.

1.2.1.2 Clinical experience

1.2.1.2.1 Clinical safety

As of 24-Apr-2014, 132 patients have been treated with single agent LEE011 in the FIH phase I study; 85 patients have been treated in the dose escalation part and 47 patients in the dose expansion part of the study.

Patients with advanced solid tumors or lymphomas were treated with increasing doses of LEE011 orally, once daily (qd) for 21 days followed by a 1-week rest (28-day cycle). Doses ranging from 50 mg to 1200 mg were evaluated on this schedule. In addition, continuous dosing of LEE011 at 600 mg was evaluated (qd for 28 days of a 28-day cycle). Treatment has been discontinued in 111 (84%) patients; the primary reasons for treatment discontinuation were: disease progression (96 [72%] patients); AEs (8 [6%] patients); withdrawal of consent (3 [2%] patient); and loss to follow up (1 [1%] patient).

The most frequently reported AEs (≥10%), regardless of grade, causality and LEE011 dose were: fatigue (53.8%); nausea (50.8%); neutropenia (47.7%); leukopenia (46.2%); anemia (37.1%); vomiting (34.8%); thrombocytopenia (34.1%); diarrhea (32.6%); lymphopenia (30.3%); decreased appetite, hyperglycemia (21.2% each); constipation (19.7%); hypoalbuminemia (18.9%); dyspnea (18.2%); cough (16.7%); fever, increased creatinine (15.9% each); abdominal pain, AST increase, edema, headache (15.2% each); back pain (14.4%); dizziness (13.6%); ECG QT prolonged (11.4%); blood alkaline phosphatase increased and hypocalcemia (10.6% each).

For either continuous or intermittent dosing, the onset of neutropenia (most frequently Grade 2) occurs by Day 15, reaching a nadir in the third or fourth week with recovery during the week of drug holiday. Some patients require additional time for recovery (7 to 14 days). QT changes become evident in the first cycle by Day 8 and later (once steady state is reached), are associated with the maximum drug levels between 1 to 8 h post-dose, and remain stable or improve in subsequent cycles.

[redacted]

Asymptomatic Grade 2 QTcF prolongation was observed with increasing frequency when increasing the dose starting at 600 mg: twelve patients (18%) in the 600 mg cohort, three patients (21%) in the 750 mg cohort, four patients (31%) in the 900 mg cohort, and two patients (67%) in the 1200 mg cohort. Two patients (3%) at 600 mg and two patients (15%) at 900 mg had asymptomatic QTcF prolongation that resulted in a QTcF interval of 500 ms or more. As compared to baseline value, QTcF prolongation was at least 30 msec in 2 patients (50%) at 250mg, 2 (40%) at 350 mg and 400 mg, 46 (73%) at 600 mg, 10 (71%) at 750 mg, 11 (85%) at 900 mg and 2 (67%) at 1200 mg; and at least 60 msec as compared to baseline in respectively 16%, 0%, 39% and 67% of patients at 600 mg, 750 mg, 900 mg and 1200 mg. One grade 1 atrioventricular block of first degree was reported as related to LEE011 given at the dose of 140 mg. No other cardiac abnormalities were observed as related adverse events in any patient.

There have been no deaths related to study drug reported on study [CLEE011X2101].The following serious adverse events shown in Table 1-1 have been reported with a suspected causal relationship in study [CLEE011X2101] as of 19-Aug-2014. For a complete list of AEs, all grades and Grade 3/4 that are suspected to be related to LEE011 refer to the Investigator Brochure.

Table 1-1 Serious adverse events with a suspected causal relationship with LEE011 single agent

Serious suspected adverse events which have occurred with LEE011 (single agent)	
System Organ Class Preferred Term	**Preferred Term**
Blood and lymphatic system disorders	Anaemia, Febrile neutropenia, Neutropenia,Thrombocytopenia
Gastrointestinal disorders	Diarrhoea, Nausea
General disorders and administration site conditions	Generalized oedema
Infections and infestations	Herpes simplex
Investigations	**Blood creatinine increased**

Events in bold indicate those events which are newly included since the previous edition of the reference safety information.

1.2.1.2.2 Clinical efficacy

Preliminary anti-tumor activity of ribociclib from trial [CLEE011X2101] was assessed across all dose levels. Out of 114 evaluable, 3 partial responses were observed at the 600 mg dose level; one each in BRAF/NRAS wild type with CCND1 amplified melanoma, and head and neck acinar carcinoma with CDKN2A loss (both on the 3 weeks on/1 week off regimen), and ER+/HER2-, PIK3CA mutant, CCND1 amplified breast cancer (on the continuous daily dosing regimen) [LEE011 Investigator Brochure]. Stable disease (SD) was the best overall response in 41 (37%) patients. Stable disease ≥4 cycles and ≥6 cycles was observed in 26 (24%) and 17 (15%) patients, respectively. Six patients with SD ≥4 cycles received treatment for >1 year, of these 2 patients were on study for >2 years (Jeffrey R Infante ASCO 2014 abstract 2528).

[redacted]

1.2.1.2.3 Clinical pharmacokinetics

As of 28-Mar-2014, PK data were available from approximately 128 patients from the first-inhuman (FIH) study CLEE011X2101. Following oral dosing, LEE011 was rapidly absorbed with median Tmax ranging from 1 to 5 hours. LEE011 plasma exposure exhibited slightly over-proportional increases in exposure across the dose range tested (50 to 1200 mg), with no clear evidence of time-dependent auto-inhibition of its clearance mediated by CYP3A4. Steady-state was generally reached by Day 8 and the mean effective T1/2 based on accumulation ratio (i.e., T1/2,acc) ranged from 15.9 to 32.6 hours across the dose range tested.

The accumulation ratio based on AUC obtained in a dosing interval (Racc) across the studied doses ranged from 1.55 to 2.52. Details on the human pharmacokinetics of LEE011 can be found in the LEE011 Investigator Brochure.

A food effect study was conducted in 24 healthy subjects ([CLEE011A2111]). Compared to the fasted state, oral administration of a single 600 mg dose of LEE011 DiC with a high-fat, high-calorie meal decreased the rate of absorption of LEE011 resulting in a 23% decrease in Cmax (geometric mean ratio: 0.775; 90% confidence interval [CI]: 0.700, 0.858) and a median difference in Tmax of 2 hours. However, there was no effect on the extent of absorption of LEE011 as the overall exposure (AUCinf) was unaffected under fed conditions (geometric mean ratio: 0.994; 90% CI: 0.925, 1.070). A similar trend was observed for LEQ803, an active metabolite of LEE011, with a decrease in Cmax (102 to 69.7 ng/mL), a delay in median Tmax (2.50 to 6.00h), and no substantial effect on overall exposure (2970 to 2750 ng*h/mL). Based on these data, LEE011 DiC can be taken without regard to meals.

A drug-drug interaction (DDI) study with ritonavir (a strong CYP3A4 inhibitor) and rifampicin (a strong CYP3A4 inducer) conducted in healthy subjects [CLEE011A2101] indicated that concurrent use of strong CYP3A4 inhibitors or strong CYP3A4 inducers may markedly affect LEE011 exposure and should be avoided. Details can be found in Section 5.1.5 of the Investigator Brochure.

A DDI cocktail study with midazolam (a sensitive CYP3A4 substrate) and caffeine (a sensitive CYP1A2 substrate) was conducted in healthy subjects [CLEE011A2106]. PK data indicate that LEE011 (400 mg) is a moderate inhibitor of CYP3A4 (≥ 2-fold but < 5-fold increase in AUC), but did not have a substantial effect on CYP1A2 substrates in humans. Concurrent use of sensitive CYP3A4 substrates with a narrow therapeutic index should be avoided. Concurrent use of CYP1A2 substrates is not expected to lead to clinically important DDIs. Details can be found in the LEE011 Investigator Brochure Section 5.1.5.

1.2.1.2.4 Clinical pharmacodynamics

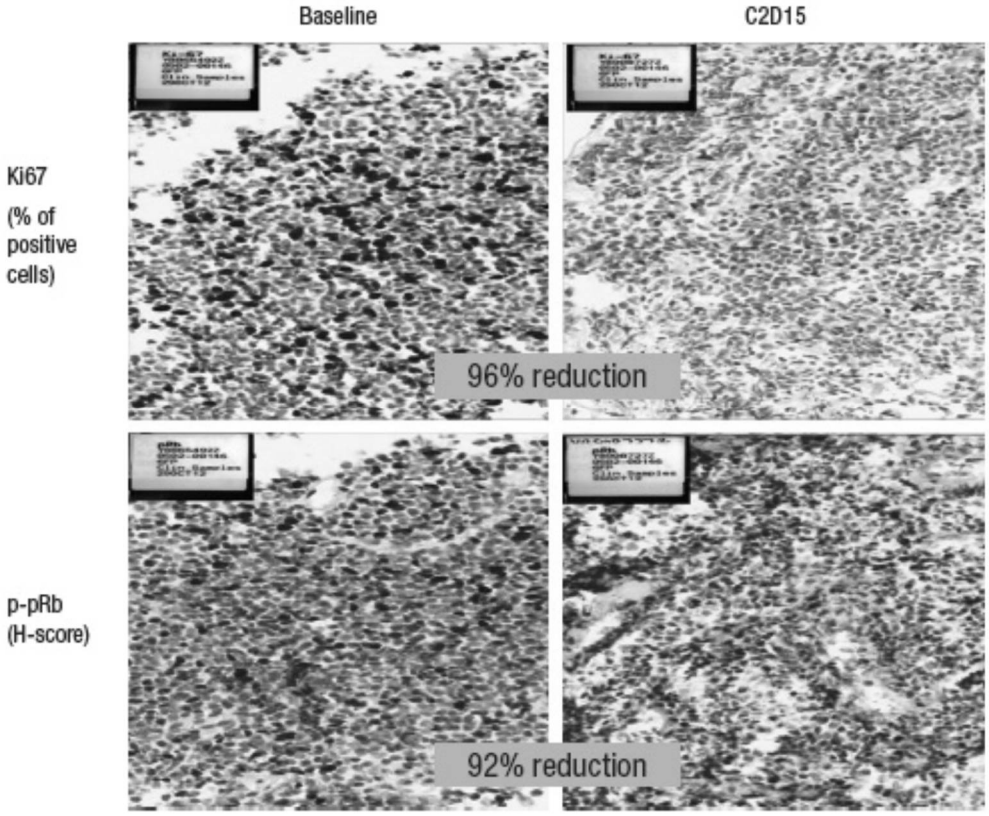
Paired skin biopsies from 55 patients treated with LEE011 at doses ranging from 50 to 900 mg and paired tumor biopsies from 20 patients (16 patients at 600 mg, 2 patients at 900 mg, and 1 patient each at 70 and 750 mg) were assessed for changes in Ki67 and pRb levels. Preliminary results indicate the following: in skin biopsies, reductions in Ki67 from baseline were observed across all dose levels with a more consistent trend from 400 mg onwards; in tumor biopsies, reductions in Ki67 from baseline were observed in 18/20 patients; however, limited samples and varied tumor types prevent conclusions about any dose-response

[redacted]

relationship from being drawn. Changes in pRb were not significant or consistent in either skin or tumor samples, possibly due to varied tumor types.

LEE011 was shown to decrease Ki67 and pRb in tumor tissue from a patient with mantle cell lymphoma treated with LEE011 daily [CLEE011X2101] (see Figure 1-3). Neutropenia and thrombocytopenia are also considered to be on target inhibition of rapidly dividing cells.

Figure 1-1 Pharmacodynamic response in tumor tissue from a patient with mantle cell lymphoma treated with LEE011



Change from baseline in Ki67 and p-pRb positive cells in tumor biopsies at C2D15 in a patient with mantle cell lymphoma treated with 900mg LEE011 in the phase I clinical trial [CLEE011X2101]. Left panels present positive immunostaining (brown color) for 2 PD markers: Ki67 and pRb. Right panels show a decrease of these markers following treatment of LEE011 (day 15 of cycle 2).

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-activations but do not have access to targeted drug treatment. This is a signal seeking study to match patients with CDK4/6 amplification or mutations, cyclin D1/3 amplifications, or p16

[redacted]

mutation to treatment with the CDK4/6 inhibitor, ribociclib. Pre-identification of the relevant gene mutation or amplification status will be performed locally at a CLIA certified laboratory prior to participation on the trial.

The purpose of this signal seeking study is to determine whether treatment with ribociclib demonstrates sufficient efficacy in CDK4/6 pathway-activated solid tumors and/or hematologic malignancies to warrant further study. Breast cancer (triple negative will be enrolled), liposarcoma, teratoma, castrate resistant prostate cancer (CRPC), melanoma and mantle cell lymphoma will be excluded from this exploratory study because these indications may be studied under key Novartis-sponsored ribociclib trials. Triple negative breast cancer will be allowed to enroll in this study. Additional tumor types may be excluded during the course of the study in the case of early futility or success based upon an interim analysis.

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; 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. Therefore, in patients with a best response of SD or better, an optional tumor sample at the time of disease progression could be obtained for genomic analysis.

[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 ribociclib in patients with a diagnosis of solid tumors or hematological malignancies that have been pre-identified (prior to study consent) to have relevant aberrations and whose disease has progressed on or after standard treatment.

2.3 Rationale for dose and regimen selection

In the first in human study of single agent ribociclib in adult patients with solid tumors [CLEE011X2101], the MTD of ribociclib was determined at 900 mg QD with a 3 weeks on/1 week off schedule. The recommended dose for future development is 600 mg QD with a 3 weeks on/1 week off schedule which has an acceptable safety profile, lower risk for QTcF prolongation, adequate exposures, and preliminary evidence of clinical activity, [LEE011 Investigator's Brochure]. The starting dose 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 ribociclib 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.	Clinical benefit rate (e.g. defined as CR or PR or SD ≥ 16 weeks for solid tumors)	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
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]		

4 Study design

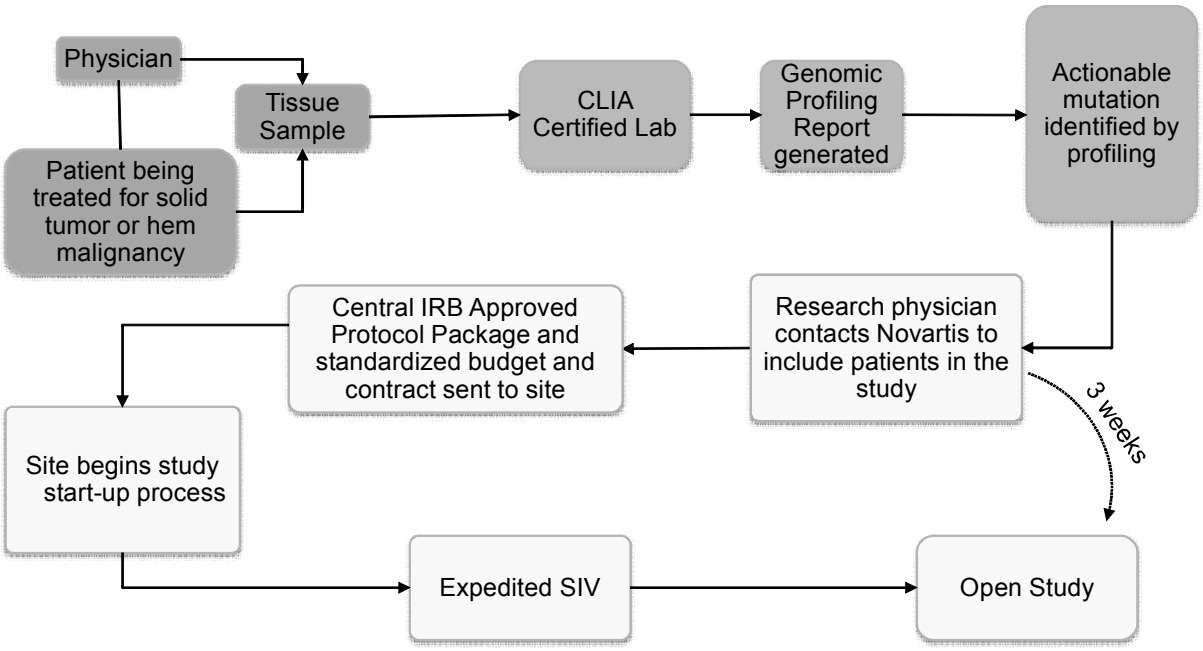
4.1 Description of study design

This is a phase II, open label study to determine the efficacy and safety of treatment with ribociclib in patients with a diagnosis of solid tumors or hematological malignancies that have been pre-identified (prior to study consent) to have CDK4/6 amplifications or mutations, cyclin D1/3 amplifications, or p16 mutation and 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 relevant gene aberration. Eligibility is based on the gene aberration status as assessed in a local, CLIA certified laboratory. The results of this testing must be known prior to signing the ICF and before formal screening begins. 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. After the eligibility criteria is met, the patient will initiate therapy with ribociclib single-agent. The patient may not receive any additional anti-cancer therapy during treatment with ribociclib.

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), 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. 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. The frequency of disease assessment will be reduced to every 16 weeks after patients have completed 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.

For patients with a best response of SD or better who discontinue study treatment due to disease progression, an optional tumor sample should be obtained for genomic analysis. This tumor sample must be obtained within 28 days of stopping the study treatment and no more than 14 days after starting another treatment for their cancer (at a time most convenient for the patient); exceptions may be made after discussion with the sponsor. [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 the survival follow-up as described in Section 7.1.4.3 , when the last patient on study has died, been lost to follow up, or withdraws consent, whichever occurs first, or if the study is terminated early or another clinical study becomes available that can continue to provide LEE011 in this patient population and all patients ongoing are eligible to be transferred to that clinical study.

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 clinical study report (CSR). Additional data for patients continuing to receive study treatment past the data cutoff date for the CSR will be reported once all patients have discontinued treatment or been lost to follow-up.

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.

[redacted]

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 70-90 adult patients with a diagnosis of a solid tumor or hematological malignancy with a CDK 4/6 mutation or amplification, cyclin D 1/3 amplification, or p16 mutation. 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. This is a signal seeking study, attempting to identify additional patient populations who may benefit from treatment with single agent ribociclib. Tumors currently being studied under some key Novartis-sponsored trials will be excluded. These include breast cancer (except triple negative), liposarcoma, teratoma, CRPC, melanoma and mantle cell lymphoma. Additional tumor types may be excluded during the course of the study at the discretion of Novartis.

Patients must have archival tissue available for submission to allow for molecular testing related to pathway activation. If tissue is not available or is insufficient the patient must be willing to undergo a fresh tumor biopsy to allow for this analysis. [redacted]

We expect that the study will enroll patients whose tumors have already been pre-identified such as ovarian, mesothelioma, breast (triple negative), colorectal, biliary, pancreatic neuroendocrine cancer, and lymphomas (excluding mantle cell lymphoma) (enrollment will not be strictly limited to those particular cancers). 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.

[redacted]

3. Patient has a confirmed diagnosis of a solid tumor (except breast cancer (however, triple negative will be included), liposarcoma, CRPC, melanoma and teratoma) or hematological malignancy (except mantle cell lymphoma). Additional tumor types may be excluded during the course of the study at the discretion of Novartis.
4. Patient is in need of treatment because of progression or relapse defined as:
   a. radiological progression for solid tumor and lymphoma
   b. 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 of the following. The qualifying alteration must be assessed and reported by a CLIA-certified laboratory.
   a. CDK4 amplification or mutation
   b. CDK6 amplification or mutation
   c. Cyclin D1 (CCND1) amplification
   d. Cyclin D3 (CCND3) amplification
   e. p16 (CDKN2A) mutation
6. Patient must have archival tissue available for submission to allow for molecular testing related to pathway activation. If the tissue is not available or is in sufficient, 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 sample may not be required if the patient had their genomic profiling performed at the same laboratory that will be used for confirmatory analysis, and the patient consents to allow Novartis use that data as their 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. **Diffuse large B cell lymphoma only**: Patient has received or is ineligible for autologous stem cell transplant.
9. Patients must have measurable disease as per appropriate guidelines:
   a. **Solid Tumors:** by RECIST 1.1 (Appendix B)
   b. **Lymphoma**: Patient has at least one measurable nodal lesion (≥2 cm) according to International Working Group (IWG) 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 C)
   c. **Symptomatic Multiple Myeloma:** by International Myeloma Working Group (IMWG)
      i. Serum M-component of ≥1 gm/dL
      ii. Urine M-component of ≥200 mg/24 h
      iii. 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

[redacted]

d. Leukemia only: Relapsed/refractory leukemia for which no standard therapy options are anticipated to result in a durable remission:

i. 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.

ii. 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)].

iii. For patients with Chronic Myeloid Leukemia (CML) only accelerated and blast phase CML will be allowed.

10. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status≤ 1 (Appendix K).
11. Patient has a life expectancy of at least 16 weeks.
12. Patients must have adequate bone marrow as described below:
    a. Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L (no growth factor within past 14 days) (not applicable for leukemia patients)
    b. Platelets (PLT) ≥ 100 x 10^9/L (no platelet transfusion within past 14 days) (not applicable for leukemia patients)
    c. Hemoglobin (Hgb) ≥ 9 g/dL (no blood transfusion within past 14 days) (not applicable for leukemia patients
    d. International Normalized Ratio (INR) ≤ 1.5
13. All patients must have adequate organ function defined as described below:
    a. Potassium, total calcium (corrected for serum albumin), magnesium, sodium and phosphorus within normal limits (WNL). Supplementation is allowed to meet eligibility requirements
    b. Serum creatinine ≤ 1.5 mg/dL or creatinine clearance ≥50 mL/min
    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. Alkaline phosphatase (AP) ≤ 2.5 x ULN
    e. Albumin ≥ 2.0 g/dl
    f. Total bilirubin ≤ ULN; or total bilirubin ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN in patients with well-documented Gilbert's syndrome.
14. For leukemia patients, peripheral blast counts < 50,000 blasts/mm^3
15. Must be able to swallow ribociclib capsules.

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 ribociclib.
2. Patients with a known hypersensitivity to ribociclib or to its excipients.

[redacted]

3. Patients with primary CNS tumor or CNS tumor involvement. However, patients with metastatic CNS tumors may participate in this study if 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 enzyme inducing anti-convulsive medications (that were started for brain metastases)
   e. Patient with no leptomeningeal involvement
4. Patients with clinical evidence of active CNS leukemia
5. Patients who have received allogeneic SCT and/ or have active GVHD
6. Patients who have received autologous SCT within the last 3 months
7. Patients with diarrhea ≥ CTCAE grade 2.
8. Patients with neuropathy ≥ CTCAE grade 2.
9. Patients with acute or chronic pancreatitis.
10. Patients with external biliary drains.
11. Patients with clinically significant uncontrolled heart disease and/or recent events , including any of the following:
    a. History of acute syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis with 12 months prior to screening
    b. History of documented congestive heart failure (New York Association functional classification III-IV)
    c. Documented cardiomyopathy
    d. Left ventricular ejection fraction (LVEF) ≤ 50% as determined by MUGA scan or ECHO
    e. History of any cardiac arrthythmias, e.g., ventricular, supraventricular, nodal arrhythmias or conduction abnormality within 12 months of screening.
    f. Congenital long QT syndrome or family history of long QT syndrome.
    g. Systolic blood pressure (SBP) > 160 mmHg or < 90 mmHg at screening.
    h. Bradycardia (heart rate <50 at rest), by ECG or pulse, at screening.
    i.
12. On screening, inability to determine the QTcF interval on the ECG (i.e.: unreadable or not interpretable) or QTcF >450ms (using Fridericia's correction).
13. Patients with uncontrolled diabetes mellitus.
14. Impairment of GI function or GI disease that may significantly alter the absorption of ribociclib (e.g. severe ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
15. Any other condition that would, in the Investigator's judgment, cause unacceptable safety risks, 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, active or uncontrolled fungal, bacterial or viral infections, etc).

[redacted]

16. 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.
17. 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.
18. Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.

Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).

19. 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.
20. Patients not able to discontinue their current anti-cancer therapy prior to first dose of study drug.
21. Patients currently receiving warfarin or other coumarin-derived anticoagulant for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH) or fondaparinux is allowed.
22. Participation in a prior investigational study with 30 days prior to enrollment or within 5 half-lives of the investigational product, whichever is longer.
23. Patients who have received radiotherapy ≤ 4 weeks prior to starting the study drug or limited field radiation for palliation ≤ 2 weeks prior to starting study drug, and who have not recovered to grade 1 or better from related side effect of such therapy (exceptions include alopecia) and /or in whom ≥ 25% of the bone marrow was irradiated.
24. 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.
25. 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 (curatively resected cervical cancer).
26. 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).

[redacted]

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.

27. Patients who have received investigational agents within ≤ $5t_{1/2}$ of the agent (or ≤ 4 weeks when half-life is unknown) prior to starting study drug.
28. Patient is currently receiving any of the following substances and cannot be discontinued 7 days prior to starting study drug (Refer to Appendix A):
    a. Known strong and moderate inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges.
    b. Medications with known risk to prolong the QT interval or induce Torsades de Pointes.
    c. Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.
    d. Herbal preparations and dietary supplements.
29. Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory).
30. Patient has a history of non-compliance to medical regimen.
31. 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.
32. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception (defined below). Highly effective contraception must be used by both sexes (female patients and their male partners) during study treatment and for **8 weeks** after the last dose of study medication.

    Highly effective contraception methods include:
    a. 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
    b. 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
    c. Male partner sterilization (at least 6 months prior to screening). The vasectomized male partner should be the female study patient's sole partner
    d. Combination of the following (a+b or a+c, or b+c):
        i. 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.
        ii. Placement of a non-hormonal intrauterine device (IUD) or non-hormonal intrauterine system (IUS)
        iii. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

Note : In case of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment

Women of child-bearing potential (sexually mature) who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months), must have a negative serum pregnancy test ≤ 14 days prior to starting study drug.

Post-menopausal women are allowed to participate in this study and do not require pregnancy or hCG laboratory test. 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 six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks prior to entry in the study. 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.

33. Fertile males must be willing to use contraception. Fertile males must use condom with spermicide (double barrier method). Highly effective contraception, as defined above, must be used by both sexes (male patients and their female partners) during study treatment and for 21 days after the last dose of study medication 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 for this trial is ribociclib.

Novartis Drug Supply Management or its designee will provide ribociclib as 200-mg hard gelatin capsules as individual patient supply, packaged in bottles or blisters. Ribociclib will be dosed on a flat scale and not be adjusted to body weight or body surface area.

6.1.1 Dosing regimen

Ribociclib will be dosed on a flat scale of 600 mg (e.g., 3 x 200 mg capsules) once daily for 3 weeks on/1 week off. 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

[redacted]

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Ribiciclib	Capsule for oral use	600 mg/day	Daily (3 weeks on/1 week off)

6.1.1.1 Ribociclib administration

The following general guidelines should be followed for administration.

- Patients should be instructed to take their daily dose with a large glass of water (~250 ml) and swallow the required number of capsules at approximately the same time on each day. The capsules should be consumed over as short a time as possible (e.g. 1 capsule every 2 minutes) and can be taken without regard to meals. However, dietary habits around the time of dosing should be as consistent as possible throughout the study.
- 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.
- Patients should be instructed to swallow the capsules whole and not to chew or crush them.
- Any doses that are missed should be skipped and should not be replaced or made up during the next scheduled dosing or on a subsequent day, whichever applies.
- Patients must avoid consumption of grapefruit, pomelos, pomegranates, star fruits, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4/5 interaction with the study medications. Orange juice is allowed.
- 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.
- If patient forgets to take his/her daily dose of ribociclib within 6 hours of the usual dosing time, then that day's dose should be omitted and the patient should continue treatment with the next scheduled dose
- The investigator (or his/her designee) must instruct the patient to take ribociclib 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 ribociclib 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 ribociclib capsules/tablets to the investigative site at each visit.

[redacted]

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 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). 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), death and/or treatment is discontinued due to any other reason. 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 LEE011 administration must be recorded on the Dosage Administration Record eCRF.

Ribociclib 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 ribociclib 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 6.3.3, provided this toxicity resolved to ≤ CTCAE grade 1, unless otherwise specified.

6.3.2 Permitted study treatment adjustments for Ribociclib

For patients who are unable to tolerate the protocol-specified dosing schedule, dose reductions or interruptions are permitted to manage drug-related toxicities.

- When dose reduction is necessary, the dose of ribociclib may be reduced to 400 mg.
- If an additional dose reduction is required, ribociclib may be reduced to 200 mg.
- Once the ribociclib dose is reduced it cannot be re-escalated.

[redacted]

- All dose reductions should be based on the worst preceding toxicity.
- Patients are allowed only 2 dose reductions (to 400 mg and 200 mg) as specified in (Table 6-2).

Table 6-2 Ribociclib dose modifications

LEE011 Dose Level	LEE011 Dose	Frequency
Starting dose level (0)	600 mg po	Daily (3 weeks on/1 week off)
Dose level – 1	400 mg po	Daily (3 weeks on/1 week off)
Dose level – 2	200 mg po	Daily (3 weeks on/1 week off)

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-week intervals, until resolution or stabilization of the event, whichever comes first. The maximum time allowed for treatment interruption due to toxicity is 21 days (3 weeks) from the intended dosing day. If interruption is > 21 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 ribociclib treatment

If the administration of ribociclib must be interrupted because of an unacceptable toxicity, ribociclib 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 >21 days (counting from the first day when a dose was missed) must discontinue the study treatment.

Table 6-3 Ribociclib related toxicity management guidelines

Toxicity	Grade	Dose Adjustment and Management Recommendations
Thrombocytopenia	Grade 1 ≥75 x 10^9/L	No dose adjustment required.
	Grade 2 ≥50 x 10^9/L – <75 x 10^9/L	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the same dose.
	Grade 3 ≥25 x 10^9/L - <50 x 10^9/L	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the same dose level. If toxicity recurs at grade 3: temporary dose interruption until recovery to grade ≤1 and reduce ribociclib to the next lower dose level.
	Grade 4 <25 x 10^9/L	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 4: discontinue ribociclib.
Absolute neutrophil count (ANC)	Grade 1 ≥1.5 x 10^9/L	No dose adjustment required.
	Grade 2 ≥1.0 - <1.5 x 10^9/L	No dose adjustment required.

[redacted]

Toxicity	Grade	Dose Adjustment and Management Recommendations
	Grade 3 ≥0.5 - <1.0 x 10^9/L	Dose interruption until recovery to ≥1.0 x 10^9/L. Re-initiate ribicoclib at the same dose level. If toxicity recurs at grade 3: temporary dose interruption until recovery to ≥ 1.0 x 10^9/L. If resolved within ≤ 7 days, then maintain dose level. If resolved >7days, then reduce ribociclib dose to the next lower dose level.
	Grade 4 <0.5 x 10^9/L	Dose interruption until recovery to ≥ 1.0 x 10^9/L. Re-initiate LEE011 at the next lower dose level. If toxicity recurs at grade 4: temporary dose interruption until recovery to ≥1.0 x 10^9/L and reduce LEE011 at the next lower dose level.
Febrile neutropenia	Grade 3 ANC <1.0 x 10^9/L with [a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour]	Dose interruption until improvement of ANC ≥ 1.0 x 10^9/L and no fever. Restart at the next lower dose level. If febrile neutropenia recurs, discontinue ribociclib.
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib.
Anemia (Hemoglobin)	Grade 1 ≥10.0 – LLN g/dL	No dose adjustment required.
	Grade 2 ≥8.0 – <10.0 g/dL	No dose adjustment required.
	Grade 3 <8.0 g/dL	Dose interruption until recovery to grade ≤ 2. Re-initiate ribociclib at the same dose.
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib.

Table 6-4 Recommendations for dose modification in case of hepatic toxicities

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
TOTAL BILIRUBIN without ALT/AST increase above baseline value	
Grade 1 (>ULN – 1.5 x ULN) (confirmed 48-72hrs later)	Maintain dose level with LFTs monitored bi-weekly
Grade 2 (> 1.5 – 3.0 x ULN)	Dose interruption of ribociclib If resolved to ≤ grade 1 in ≤ 21 days, then maintain dose level If resolved to ≤ grade 1 in > 21 days or toxicity recurs, then reduce 1 dose level If toxicity recurs after two dose reductions, discontinue ribociclib
Grade 3 (> 3.0 – 10.0 x ULN)	Dose interruption of ribociclib If resolved to ≤ grade 1 in ≤ 21 days, lower 1 dose level of ribociclib If resolved to ≤ grade 1 in > 21 days or toxicity recurs, discontinue ribociclib

[redacted]

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
TOTAL BILIRUBIN without ALT/AST increase above baseline value	
Grade 4 (> 10.0 x ULN)	Discontinue ribociclib
Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gall bladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤ 1 x ULN) due to hemolysis or Gilbert Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.	
AST or ALT	
AST or ALT without bilirubin elevation > 2 x ULN	
Same grade as baseline or increase from baseline grade 0 to grade 1 (confirmed 48 – 72 hrs later)	No dose adjustment required with LFTs monitored per protocol if same grade as baseline or bi-weekly in case of increase from baseline grade 0 to 1
Increase from baseline grade 0 or 1 to grade 2 (> 3.0 – 5.0 x ULN) or from baseline grade 2 to grade 3 (> 5.0 – 20.0xULN)	Dose interruption of ribociclib If resolved to ≤ baseline value in ≤ 21 days, then maintain dose level If resolved to ≤ baseline value in > 21 days or toxicity recurs, then reduce 1 dose level If toxicity recurs after two dose reductions or recovery to ≤ baseline value is > 28 days, discontinue ribociclib
Increase from baseline grade 0 or 1 to grade 3 (> 5.0 – 20.0 x ULN)	Dose interruption of ribociclib until resolved to ≤ baseline value, then lower 1 dose level of ribociclib If recovery to ≤ baseline value is > 28 days, discontinue ribociclib If toxicity recurs, discontinue ribociclib
Grade 4 (> 20.0 x ULN)	Discontinue ribociclib
AST or ALT and concurrent Bilirubin	
AST or ALT ≥ grade 2 (> 3 x ULN) in patients with normal values at baseline and total bilirubin > 2 x ULN or AST or ALT ≥ grade 3 (> 5 x ULN) in patients with grade 1 or 2 at baseline, and total bilirubin > 2 x ULN	Discontinue ribociclib
Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new or progressive liver metastasis, and alcohol intake.	

6.3.3.1 Additional follow-up for hepatic toxicities

Hepatic toxicity monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT. For patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only.

Close observation is recommended in case of AST, ALT, and/or bilirubin increase requiring dose interruption, which involves:

- Repeating liver enzyme and serum bilirubin tests **two or three times weekly**. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize or return to normal values.

[redacted]

- Obtaining a more detailed history of current symptoms.
- Obtaining a more detailed history of prior and/or concurrent diseases.
- Obtaining a history of concomitant drug use (including non-prescription medications, herbal and dietary supplements), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; hepatotropic virus infections (CMV, EBV or HSV); autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.
- Assessing cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure as possible etiologies for liver dysfunction.

Table 6-5 Dose modification guidance in case of QT Prolongation

Grade	Dose Modification
For all grades	Check the quality of the ECG. Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If below the lower limit of normal, interrupt ribociclib administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. Check compliance with correct dose and administration of ribociclib.
Grade 1 QTc 450-480 ms	No dose adjustment required.
Grade 2 QTc 481-500 ms	Interrupt ribociclib Perform a repeat ECG 1 hour after the QTcF of ≥ 481 ms If QTcF <481 ms, restart ribociclib at the same dose. No dose adjustment required for first occurence. If QTcF remains ≥481 ms, repeat ECG as clinically indicated until QTcF returns to < 481 ms. Restart ribociclib at the same dose level. No dose adjustments required for first occurrence. If QTcF ≥ 481 ms recurs, ribociclib should be reduced by 1 dose level. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patient who has therapy interrupted due to QTcF ≥ 481 ms.
Grade 3 QTc ≥ 501 ms on at least two separate ECGs	Interrupt LEE011 Consider consulting a local cardiologist Perform a repeat ECG one hour after the first QTcF of ≥ 501 ms. If QTcF remains > 501 ms, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 481 ms. If QTcF returns to < 481 ms, ribociclib will be reduced by 1 dose level. Refer to Table 6-2 for dosing schedule. Repeat ECGs 7 days and 14 days after dose resumption for any patient who had therapy interrupted due to QTcF ≥ 501 ms If QTcF of ≥ 501 ms recurs, discontinue ribociclib

[redacted]

Grade	Dose Modification
Grade 4 [QT/QTc ≥ 501 or > 60 ms change from baseline] and [Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia]	Discontinue ribociclib Obtain local cardiologist consultation Perform a repeat ECG 1 hour after the first QTcF of ≥ 501 ms If QTcF remains ≥ 501 ms, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 501 ms.

6.3.3.2 Management of all other adverse reactions

Consider performing an analysis of serum potassium, calcium, phosphorus, and magnesium for all adverse reactions that are potentially associated with electrolyte imbalance (e.g. diarrhea, nausea/vomiting). If electolyte values are below the lower limit of normal, interrupt ribociclib administration, correct electrolyte with supplements as soon as possible, and repeat electrolyte testing until documented normalization of the electolytes.

Table 6-6 Ribociclib dose adjustment and management recommendation for all other adverse reactions

Grade	Dose Adjustment and Management Recommendations
1	No dose adjustment recommended. Initiate appropriate medical therapy and monitor.
2	Dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate LEE011 at the same dose. If the same toxicity recurs at grade 2, interrupt LEE011 until recovery to grade ≤1. Re-initiate LEE011 at the next lower dose level.
3	Dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate LEE011 at the next lower dose level. If toxicity recurs at grade 2: temporary dose interruption until recovery to grade ≤1 and reduce LEE011 dose the next lower dose level. If toxicity recurs at grade 3, discontinue LEE011.
4	Discontinue LEE011 and treat with appropriate medical therapy.

6.3.3.3 Adjustment of starting dose in special populations

Renal impairment

Insufficient data are available to provide a dosage to provide a dosage recommendation for ribociclib for patients with renal impairment. Patients with baseline renal impairment are excluded from the study (serum creatinine > ULN or creatinine clearance < 50mL/min). Patients who experience renal impairment of grade 2 or higher during the treatment period should discontinue treatment and should be followed safety assessments.

Elderly

Physicians should exercise caution in monitoring the effects of ribociclib in the elderly. Insufficient data are available to provide a dosage recommendation.

6.3.4 Follow-up for toxicities

Patients who complete treatment or whose treatment is interrupted or permanently discontinued due to an AE must be followed at least once a week for 4 weeks, and then at 4

[redacted]

weeks intervals until resolution or stabilization of the event. All patients will be followed for onset of any new serious adverse events for 30 days following the last dose of study treatment.

6.3.5 Anticipated risks and safety concerns of the study

Appropriate eligibility criteria, as well as specific dose modifications and stopping rules are included in this protocol. Refer to Section 6.3.1 and Section 6.3.2 for details.

6.4 Concomitant medications

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted, except as specifically prohibited. Refer to LEE011 Investigator's Brochure and Appendix A for information on possible drug-drug interactions.

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

Medications required to treat AEs, manage cancer symptoms, concurrent stable diseases and supportive care agents, such as packed red blood cells (PRBC), pain medications, anti-emetics and anti-diarrheals are allowed. The use of any other potential new concomitant medications may be discussed between the investigator and the sponsor on a case by case basis. Hematopoietic growth colony stimulating factors may be used therapeutically or as secondary prophylaxis.

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 (other than study drug) and significant 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 study, and until 30 days after the last dose of study drug, must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies eCRFs.

6.4.1.1 Bisphosphonates and denosumab

Bisphosphonates and denosumab are permitted for the treatment of osteoporosis and prevention of skeletal related events for patients with bone metastases. Chronic concomitant bisphosphonate/denosumab therapy for the prevention of bone metastasis is not permitted.

6.4.1.2 Palliative radiotherapy

Palliative radiation is permitted if done solely for bone relief. It should not be delivered to a target lesion and it should not encompass more than 25% of irradiated bone marrow.

Refer to the ribociclib (LEE011) Investigator's Brochure, Table 1 and Table 2, for information on possible interaction with other drugs.

[redacted]

6.4.2 Concomitant therapy requiring caution

The following therapies are permitted in this study; however, they should be used with caution. This list is not comprehensive and is only meant to be used as a guide. These medications should be excluded from patient use if possible. If they must be given, then use with caution and consider a ribociclib interruption if the concomitant medication is only needed for a short time:

- Moderate inhibitors or inducers of CYP3A4/5
- Sensitive substrates of CYP3A4/5 with wide therapeutic index
- Sensitive substrates of the renal transporters, MATE1 and OCT2
- Sensitive substrates of BCRP
- Known inhibitors of BSEP
- Medications that carry a possible risk for QT prolongation

6.4.3 Prohibited concomitant therapy

The following medications are prohibited during treatment in this study (Appendix A). This list is not comprehensive and is only meant to be used as a guide:

- Strong inhibitors or inducers of CYP3A4/5
- Substrates of CYP3A4/5 with narrow therapeutic window
- Medications with a known risk for QT prolongation
- Other investigational and antineoplastic therapies
- Primary prophylactic hematopoietic growth factors
- Herbal medications. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using all herbal medications at least 7 days prior to first dose of study treatment.
- Patients should be instructed not to take grapefruit products/juice, or Seville (sour) oranges/juice while taking study drug and preferably 7 days before the first dose due to potential CYP3A4/5 interaction. Oranges juice is 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.

[redacted]

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 ribociclib on an outpatient basis. The investigator shall provide the patient with instructions for ribociclib administration according to the protocol.

6.6.1 Study drug packaging and labeling

Ribociclib will be supplied as 200 mg or 50 mg hard gelatin capsules (refer to Table 6-6).

Medication labels will comply with US legal requirements and are printed in the local language. The label contains LEE011 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 6-6 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Ribociclib (LEE011)	Capsules or tablets (200 mg or 50 mg) in bottles or blisters	Labeled as LEE011 Dosing frequency: once-a-day, 3 weeks on/1 week off

6.6.2 Drug supply and storage

Each site will be supplied by Novartis with oral ribociclib. Study drug must be received by a designated personnel 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, ribociclib 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 ribociclib at home.

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

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.

[redacted]

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.

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**	**777**	**501**	**701**
Cycle days[1]			**-28 to -1**	**1**	**15**	**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 & 7.2.4.1	X						X[13]		
Informed consent	D	7.1.1	X								
[redacted]											
PATIENT HISTORY											
Demography	D	7.1.1.3	X								
Inclusion/exclusion criteria	D	5.2 & 5.3	X								
Eligibility checklist	S	7.1.1.1	X								
End of phase disposition	D	7.1.3.1 & 7.1.1.2	X						X		
Relevant medical history/ current medical conditions	D	7.1.1.3	X								
Diagnosis and Extent of cancer	D	7.1.1.3	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**	**777**	**501**	**701**
Cycle days[1]			**-28 to -1**	**1**	**15**	**1**	**15**	**1**		**EOT + 30 (±4) days**	**EOT + every 3 months[2]**
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		
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		
ECOG performance status	D	7.2.2.4	X	X[4]		X		X	X		
IMAGING AND OTHER ASSESSMENTS											
Cardiac imaging (MUGA/ECHO)	D	7.2.2.6.2	X	If clinically indicated							
ECG	D	7.2.2.6.1	X[12]	X	X	X		X	X		
MRI (optional)	S										
LABORATORY ASSESSMENTS											
Hematology	D	7.2.2.5.1	X	X[4]	X	X	X	X	X		
Biochemistry (including liver function tests)	D	7.2.2.5.2	X	X[4]	X	X	X	X	X		
Thyroid function test	D	7.2.2.5.3	X	X[4]	Every 3 cycles starting at C3D1, and if clinically indicated				X		
Coagulation	D	7.2.2.5.4	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**	**777**	**501**	**701**
Cycle days[1]			**-28 to -1**	**1**	**15**	**1**	**15**	**1**		**EOT + 30 (±4) days**	**EOT + every 3 months[2]**
Urinalysis	D	7.2.2.5.5	X	X[4]		X		X	X		
Pregnancy test[6]	D	7.2.2.5.6	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											
Ribociclib administration	D	6.1.1		Daily (3 weeks on/1 week off)							
Survival	D	7.1.4.3									X[15]
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 1st 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**	**777**	**501**	**701**
Cycle days[1]			**-28 to -1**	**1**	**15**	**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	7.2.1.1.4	X	Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) for the 1st 16 weeks of treatment and every 16 weeks (±4 days) thereafter					X		
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 1st 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 1st 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 1st 16 weeks of treatment and every 16 weeks (±4 days) thereafter					X		
Bone Marrow Biopsy or aspirate	D	7.2.1.2.4	X	To confirm response of CR[10]							

[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**	**777**	**501**	**701**
Cycle days[1]			**-28 to -1**	**1**	**15**	**1**	**15**	**1**		**EOT + 30 (±4) days**	**EOT + every 3 months[2]**
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 1st 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)							
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 1st 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 1st 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 1st 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**	**777**	**501**	**701**
Cycle days[1]			**-28 to -1**	**1**	**15**	**1**	**15**	**1**		**EOT + 30 (±4) days**	**EOT + every 3 months[2]**
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 1st 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							
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 1st 16 weeks of treatment and every 16 weeks (±4 days) thereafter							
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, MF, PV and ET											

[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**	**777**	**501**	**701**
Cycle days[1]			**-28 to -1**	**1**	**15**	**1**	**15**	**1**		**EOT + 30 (±4) days**	**EOT + every 3 months[2]**
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							
History/assessment of chromosomal abnormalities/Karyotype	S	7.2.1.4.4	X[11]								
Evaluation of transfusion dependency	D	7.2.1.4.5	X	X	X	X	X	X	X		
Myeloproliferative Neoplasm (MPN) Symptom Assessment	D	Appendix Q	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	777	501	701
Cycle days[1]			-28 to -1	1	15	1	15	1		EOT + 30 (±4) days	EOT + every 3 months[2]

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.
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 a 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. The frequency of disease assessment will be reduced to every 16 weeks after patient have completed 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
10. To confirm complete responses in patients with bone marrow tumor involvement prior to study treatment
11. History must be present in the patient's source documents. Additional testing to confirm is not required and should be done based on the investigator's judgment
12. Screening ECGs should performed ≤ 7 days from C1D1
13. For patients with a best response of SD 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
14. [redacted]
15. Survival follow-up may be discontinued if the primary efficacy endpoint is not met.

[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. The results of this testing must be known prior to signing the ICF and before formal screening begins. 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 ribociclib.

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 is insufficient, 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. [redacted]

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 to use that data as their baseline molecular analysis results.

For the purposes of enrollment, the patient's pathway activation status is based on the presence of known aberrations identified in Section 5.2.

Patients who fail to start on treatment within 28 days of screening 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.

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 <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 ineligible and a screening failure.

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, eligibility should be confirmed prior to the subject receiving the first dose of study drug.

[redacted]

7.1.1.2 Information to be collected on screening failures

Patient who sign the ICF, but are not started on treatment for any reason will be considered a screen failure. For screen failure patients, the reason for not proceeding with treatment 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 starting 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 include:

- Pathway aberration status as identified in section 5.2
- 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 7.2.2.4)
- Laboratory evaluations (e.g., hematology, coagulation, biochemistry, urinalysis, liver function monitoring) (See Section 7.2.2.5)
- [redacted]
- Serum pregnancy (See Section 7.2.2.5.6)
- Cardiac assessment (See Section 7.2.2.6)
- Disease evaluations (See Section 7.2.1.)

[redacted]

- Radiological assessments (e.g., CT scan) if clinically indicated (See Section 7.2.1)

7.1.2 Treatment period

Patients will be treated with ribociclib (600 mg, orally) 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. The frequency of disease assessment may be reduced to every 12 weeks for patients who have at least 4 post-baseline disease assessments and are clinically stable (except MM patients).
- Laboratory assessments performed as part of the screening evaluations, more than 4 days prior to the first dose of study treatment, must be repeated on the first dosing day.
- [redacted]

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 7 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.

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.

For patients with a best response of SD or better who discontinue study treatment due to disease progression, an optional tumor sample should be obtained for genomic analysis.

For solid tumor patients with at least ≥ 20% reduction in overall tumor assessment (PR or better for hematological tumors) who discontinue study treatment due to disease progression,

[redacted]

[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
    - Interruption of study treatment for > 21 days, regardless of reason, from the intended day of the next scheduled dose

Patients that transition into the rollover clinical trial will perform end of treatment procedures. However, follow-up for safety, survival and disease progression will not be performed.

[redacted]

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

All patients will be followed for survival status every 3 months regardless of treatment discontinuation reason (except if consent is withdrawn). Survival information will be collected every 3 months until 2 years after the last patient has enrolled in 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.

If the primary efficacy end-point is not met, Novartis may discontinue survival follow-up for this study.

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.

7.2 Assessment types

[redacted]

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 B.

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 based on RECIST 1.1 must be confirmed at least 4 weeks after initial observation. If the two assessments differ, the best overall response will be determined by Table 3-3 of Appendix B.

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 B).

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, 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 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 $\leq$ 4 days prior to the first dose of ribociclib, however tumor assessments $\leq$ 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). The frequency of disease assessment will be reduced to every 16 weeks after the 1st 16 weeks on treatment.

7.2.1.2 Lymphoma

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

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

[redacted]

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 of 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 C 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, 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. The frequency of disease assessment may be reduced to every 16 weeks after the 1st 16 weeks on treatment.

Refer to Section 7.2.1.1.4 for requirements

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 C. 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 conformed for lymphoma involvement (the site must document the histological confirmation (yes or no) on the corresponding eCRF) and photographed (color photography using 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

[redacted]

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 C 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 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 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 C for lesion measurements.

7.2.1.3 Symptomatic multiple myeloma

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

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) refer to Table 7-1 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).

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

Response for AML will be evaluated using the revised recommendations of the International Working Group (IWG) as noted in Cheson 2003 (Appendix F). Response for ALL will be evaluated using guidelines adapted from NCCN Guidelines Version 2.2012 (Appendix H). CML will be evaluated using guidelines adapted from NCCN Guidelines Version 13 2013 (Appendix I). The response for CLL will be evaluated using the revised recommendation of the IWG as noted in Hallek 2008 (Appendix J). The response for myelodysplasia (MDS) will

[redacted]

be evaluated using the revised recommendation of the IWG as noted in Cheson 2006 (Appendix P). 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 N and Appendix O respectively). The response for myelofibrosis (MF) will be evaluated using IWG-MRT as noted in Tefferi 2013 (Appendix M).

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.

Clinical evaluations and disease assessments for CLL will be performed periodically as is indicated in Table 7-1, based on the lymphoma 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 E). 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

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 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 as hematology 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.

[redacted]

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 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.

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 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, 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.

[redacted]

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 within 4 days prior 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, before administration of ribociclib at Day 1 of each cycle, and EOT. 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 first dosing does not need to be repeated at Cycle 1 Day 1. Height will be collected at screening only.

7.2.2.4 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 K). ECOG performance assessment performed within 4 days of first dosing does not need to be repeated at Cycle 1 Day 1.

7.2.2.5 Laboratory evaluations

Clinical laboratory analyses (Hematology, biochemistry, coagulation, urinalysis, pregnancy test, thyroid function 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 within 4 days of first dosing do not need to be repeated at Cycle 1 Day 1.

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.

7.2.2.5.1 Hematology

Hematology tests are to 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 according to the Visit Schedule outlined in Table 7-1. The hematology panel includes hematocrit, hemoglobin, platelet count, total red blood cells (RBC), total white blood cells (WBC) count, and a WBC differential including neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

7.2.2.5.2 Biochemistry

Biochemistry tests are to 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 according to the Visit Schedule outlined in Table 7-1. The full biochemistry panel includes albumin, amylase, bicarbonate, calcium, creatinine, glucose, lactate dehydrogenase (LDH), lipase, magnesium, potassium, total protein, , phosphorus, sodium, urea or blood urea nitrogen (BUN), uric acid, 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.

7.2.2.5.3 Thyroid Panel

Thyroid test will be performed at screening, C1D1, every 3 cycles starting at C3D1, and EOT, and during the treatment phase if clinically indicated. Thyroid panel test include TSH, free T3, and free T4.

7.2.2.5.4 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.

7.2.2.5.5 Urinalysis

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

[redacted]

7.2.2.5.6 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 either study drug), and at EOT. Women of child-bearing potential must additionally undergo a monthly urine pregnancy test during the treatment phase.

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 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

Standard triplicate 12 lead ECG assessments will be performed after the patient has been resting for 5-30 min prior to each time point indicated in Table 7-2 below. The triplicate ECGs should be taken approximately 2 minutes apart. The combined QTcF values from triplicate ECGs will be averaged to provide a single value for each patient. If an abnormal ECG or QTcF value of ≥ 481 ms is obtained at any time during the study, study treatment must be interrupted, repeat the ECG measurements and follow management guidelines detailed in Table 6-5.

Table 7-2 ECG Collection Plan

Cycle/ Visit[3]	Day	Time	ECG Type
Screening	-7 to 1	Any time	12 Lead[1]
1	1	Pre-dose	12-Lead
1	1	2, 4 and 6 h post-dose	12-Lead
1	15	Pre-dose	12 Lead
1	15	2, 4 and 6 h post-dose	12 Lead
2	1	Pre-dose	12 Lead
2	1	2 h post-dose	12 Lead
3	1	Pre-dose	12 Lead
3	1	2 h post-dose	12 Lead
Cycles 4 and subsequent cycles[2]	1	Pre-dose	12 Lead
End of treatment		Any time	12 Lead
Unscheduled sample		Anytime	12 Lead
Triplicate 12 lead ECG is not required at screening. For C4D1 and subsequent visits, the ECG will be measured only at pre-dose, except when clinically indicated. For patients with QTcF ≥ 481ms at any time, interrupt study treatment and follow the procedures described in the "Ribociclib Dose Modification section". If treatment is resumed, repeat ECGs 7 days and 14 days after dose resumption (and then as clinically indicated). During subsequent cycles, perform predose ECG for every cycle, and 2 h post dose starting at every 3rd cycle after thereafter.			

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

[redacted]

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.

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

MUGA (multiple gated acquisitions) scan or echocardiogram (ECHO) will be used to assess LVEF at screening and during the treatment phase as clinically indicated to assess signs or symptoms of cardiotoxicity. In case of clinically significant abnormalities, they should be reported on the Adverse Events eCRF.

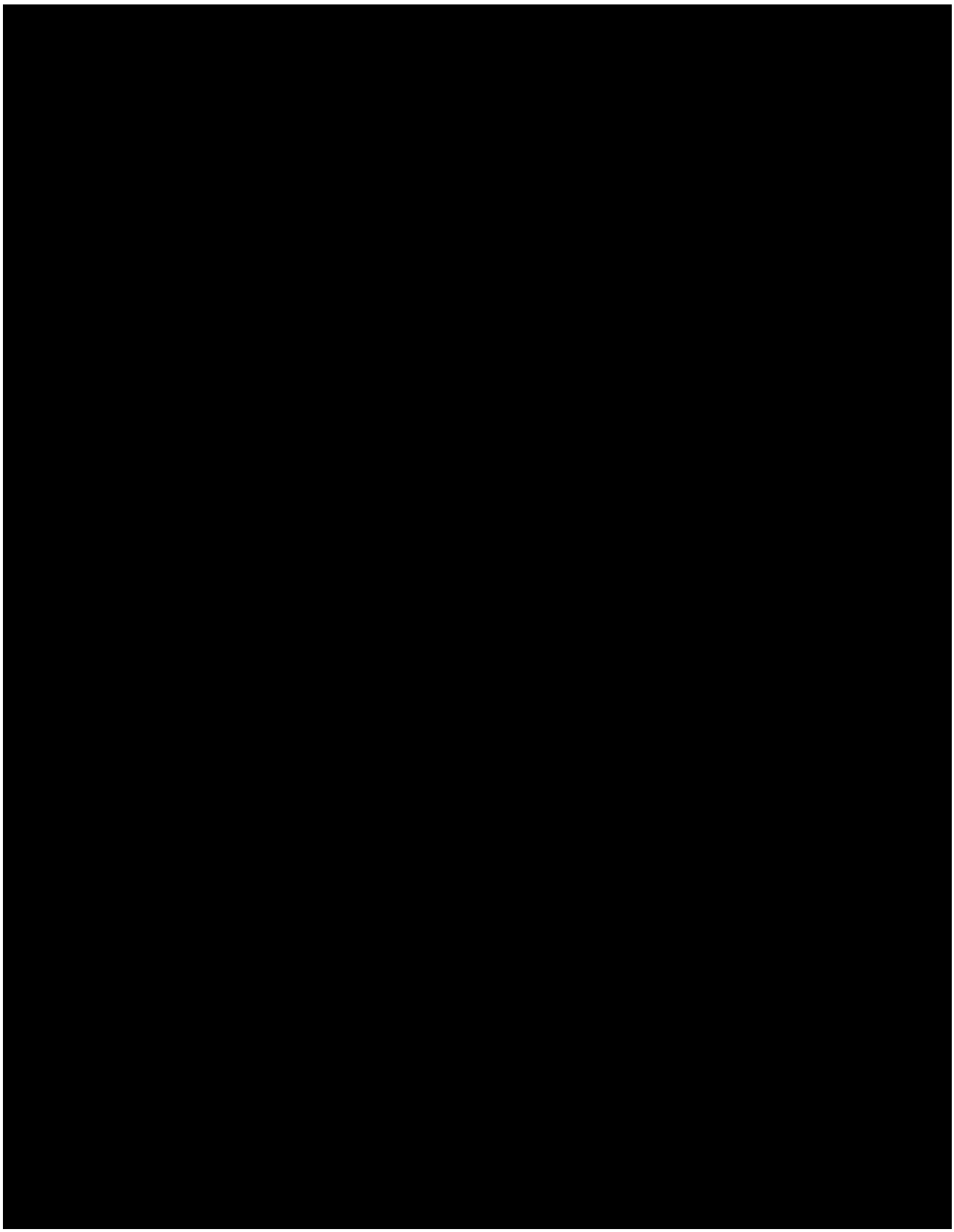
In case a patient develops left ventricular systolic dysfunction while on study treatment dose adjustment guidelines described in Section 6.3 must be followed.

7.2.3 Pharmacokinetics

Not Applicable.

[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.

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 or as per Cheson's guidelines for hematological malignancies), 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.

[redacted]

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
    - 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

[redacted]

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 each specific study treatment (if there is more than one 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 local Novartis Chief Medical Office & 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, 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 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.

[redacted]

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.

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.

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 violations 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. 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.

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 study drug.

FAS will be used for the analysis of 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.

[redacted]

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. 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, preferred term and treatment arm 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 objective is to assess clinical benefit associated with ribociclib 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 $\geq$ 16 weeks. For hematologic tumors other appropriate hematological response criteria will apply and are included in the appendices.

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

10.4.1 Variable

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

[redacted]

10.4.2 Statistical hypothesis, model, and method of analysis

The study will enroll patients from at least 8 tumor cohorts, with each tumor cohort containing possible tumors of interest as shown in Appendix R.

We 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 within the trial. We transform to the logit scale for modeling purposes. Let θ_g be the mean log odds treatment effect, i.e.:

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

Thus, θ_g 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 treatment is better than the assumed control rate for that group. Thus, we wish to test the set of hypotheses

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

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

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

$$\Pr(\theta_g>0 \mid \text{data}) > 0.80$$

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..

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 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 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.

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

[redacted]

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 τ^2 are unknown, and hence have a prior distribution which is combined with the data to produce estimates of μ and τ^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 different results with borrow far less information between them (they will have a low probability of being in the same cluster).

Details of the hierarchical model is 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 evaluation are planned to occur after the first 30 patients overall (across all groups) have been dosed for at least 16 weeks or discontinued, and then every 13 weeks thereafter until the end of the study. An additional CBR evaluation will be performed at the end of the study.

Early Futility

If there is less than 10% probability that the response rate in a subgroup 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 have been evaluated for response in that group.

Early Success

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

[redacted]

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

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 groups. 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:

$$\Pr(\pi_g > R_g) > 0.80.$$

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.

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 Complete Response (CR) 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 (ORR, PR plus CR) and its 95% exact confidence interval will be provided for each patient group. In the event where sample size in each patient group is small (<10), only ORR summary for entire study cohort will be presented.

10.5.2 Other secondary efficacy objectives

The secondary 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
- To assess safety and tolerability

[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 applies only to patients whose best response was PR or CR. 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.

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 system organ class and/or preferred term, maximum severity (based on CTCAE v4.03), type of adverse event, relationship to the study treatment by treatment group. 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.

Adverse events will be summarized by presenting the number and percentage of patients by system organ class and/or preferred term, the maximum severity (based on CTCAE v4.03) and treatment arm. Adverse events related to study treatment will also be summarized. In

[redacted]

addition, adverse events of related nature may be analyzed by categories regrouping the relevant preferred terms, as appropriate.

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 treatment arm. 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 data reviews will occur for the primary endpoint of clinical benefit rate only as required by the Bayesian Hierarchical design. The first interim data review will be performed after the first 30 patients overall (across all groups) have been dosed for at least 16 weeks or discontinued, and then every 13 weeks thereafter, 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 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 Table 4.2.1 and Table 4.2.2 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

[redacted]

included the expected variable accrual by simulating a Poisson process with expected accrual also shown in the appendix.

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 8 weeks after the final dose of study treatment. Fertile males must agree to adhere to contraception requirement until at least 21

[redacted]

days 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.

[redacted]

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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[redacted]

14 Appendices

Appendix A: 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 ribociclib.

The following lists are not comprehensive and are only meant to be used as a guide. The 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 P450 Drug Interaction Table

(http://medicine.iupui.edu/clinpharm/ddis/main-table/) and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012) (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (http://www.druginteractioninfo.org/). For current lists of medications that may cause QT prolongation and/or torsades de pointes (TdP), refer to the CredibleMeds® website (https://crediblemeds.org/). Please contact the medical monitor with any questions.

1 Prohibited Medications

Table 14-1 List of prohibited medications during LEE011 treatment

Category	Drug Name
Strong CYP3A4/5 inhibitors	Boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, voriconazole
Strong CYP3A4/5 inducers	Avasimibe[2,3], carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[3]
CYP3A4/5 substrates with NTI[1]	Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine
Medications with a known risk for QT prolongation[4]	Amiodarone, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, flecainide, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, moxifloxacin, pentamidine, pimozide, probucol, procainamide, quinidine, sotalol, sparfloxacin, terfenadine, thioridazine, vavdetanib
Herbal preparations/ medications	Herbal preparations/medications are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kaya, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.
Other investigational and antineoplastic therapies	Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while on study medication. If such agents are required for a patient then the patient must be discontinued from study drug.

[redacted]

Category	Drug Name
[1] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes). [2] Herbal product [3] P-gp inducer [4] Source: www.crediblemeds.org	

Table 14-2 List of medications to be used with caution[1] during study drug treatment

Category	Drug Name
Moderate CYP3A4/5 inhibitors	Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus paradisi fruit juice), imatinib, Schisandra sphenanthera[2], tofisopam, verapamil
Moderate CYP3A4/5 inducers	Bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, talviraline, thioridazine, tipranavir
P-gp inhibitors	captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar (GF120918), erythromycin, felodipine, fexofenadine, fluvoxamine, milk thistle (silybum marianum), nelfinavir, nifedipine, nitrendipine, paroxetine, quercetin, ranolazine, Schisandra chinensis, talinolol, telaprevir, telmisartan, ticagrelor, tolvaptan, valspodar (PSC 833), verapamil
P-gp inducers	Any known P-gp inducers
Sensitive CYP3A4/5 substrates[2]	Alpha-dihydroergocryptine, aplaviroc, aprepitant, atorvastatin, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, sildenafil, simvastatin, ticagrelor, tolvaptan, triazolam, vardenafil, vicriviroc
Strong BSEP inhibitors	Bosentan, fusidate, glibenclamide, lovastatin, sulindac, troglitazone (TGZ-sulfate)
BCRP substrates	Daunorubicin, doxorubicin, rosuvastatin, sulfasalazine, topotecan
CYP1A2 substrates with NTI[3]	Theophylline, tizanidine
Medications that carry a possible risk for QT prolongation[4]	Alfuzosin, amantadine, atazanavir, chloral hydrate, clozapine, dolasetron, dronedarone, eribulin, escitalopram, famotidine, felbamate, fingolimod, foscarnet, fosphenytoin, gatifloxacin, gemifloxacin, granisertron, iloperidone, indapamide, isradipine, lapatinib, levofloxacin, lithium, moexipril, nicardipine, nilotinib, octreotide, ofloxacin, ondansetron, oxytocin, paliperidone, pasireotide, quetiapine, ranolazine, risperidone, roxithromycin, sertindole, sunitinib, tacrolimus, tamoxifen, telithromycin, tizanidine, vardenafil, venlafaxine, voriconazole, ziprasidone
MATE1 and OCT2 substrates[5]	Acyclovir, amantadine, amiloride, cephalexin, cephradine, cimetidine, famotidine, fexofenadine, memantine, metformin (also a substrate for OCT1, MATE1 amd <ATE2K), pindolol, procainamide, ranitidine and varencicline
[1] Any drug mentioned in the above list should be contraindicated if they are excluded based on any other exclusion criteria as specified in Section 6.4.2 of the Study Protocol or listed in Table 14-1 and Table 14-2. [2] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor. [3] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes). [4] Source: www.crediblemeds.org [5] Source: FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis and implications for Dosing and Labeling (February 2012) and Yonezawa and Inui (2011) Importance -of the multidrug and toxin extrusion MATE/SLC47A family to pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics. Br J Pharmacology 164:1817-25	

Appendix B: 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).

2 Measurability of tumor lesions at baseline

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

2.1 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).

2.2 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.

2.2.1 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

2.2.2 Cystic lesions

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

[redacted]

2.2.3 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.

3 Specification by methods of measurement

3.1 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.

3.1.1 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.

3.1.2 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.

3.2 Response criteria

3.2.1 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.

3.2.2 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).

3.2.3 New lesions

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

- 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

[redacted]

- 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

3.2.4 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.

4 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.

Table 3-1 Time point response: patients with target (± 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

[redacted]

Target lesions	Non-target lesions	New lesions	Overall lesion response
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.

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

[redacted]

5 References (available upon request)

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Appendix C: 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

1.1 Definitions

1.1.1 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:

2.1 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

2.2 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:
  - If it is thought to be disease related, it will constitute a **non-measurable nodal lesion**

[redacted]

- 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.

2.3 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

3.1 Measurement of lesions

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

3.1.1 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

3.1.2 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, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI,

[redacted]

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.

3.1.3 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.

3.1.4 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).

[redacted]

B-symptoms are defined as follows:

- 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 5-1. 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).

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, immunohistochemistry 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	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

[redacted]

Response	Definition	Nodal Masses	Spleen. Liver	Bone Marrow
		identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy		

4.1 Evaluation of Index Lesions (nodal and extranodal)

4.1.1 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 4.1.2).

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.

4.1.2 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 4.1.5: 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

[redacted]

Response Criteria[1]	Evaluation of 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.

4.1.3 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.

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)".

4.1.4 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.

[redacted]

- 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):

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)".

4.1.5 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.

4.1.6 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.

4.1.7 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).

4.1.8 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.

4.1.9 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, 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, 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]

Appendix D: Ann Arbor staging classification

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	

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

[redacted]

Appendix E: 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)	
II	Stage 0-1 with splenomegaly, hepatomegaly, or both	Intermediate
III[b]	Stage 0-II with hemoglobin < 11.0 g/dL or hematocrit <33%	Intermediate
IV[b]	Stage 0-III with platelets <100 x 10^9/L	High
		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]

Appendix F: 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
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.	

[redacted]

Appendix H: 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]

Appendix I: 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

Appendix J: 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 define 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]

Appendix K: 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]

Appendix L: International Myeloma Working Group (IMWG) uniform response criteria for multiple myeloma[1]

Response	IMWG Criteria
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[2] by immunohistochemistry or immunofluorescence[3]
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[2]
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,[4] 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)[5]
	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%[6]
	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).[5] 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]

[redacted]

Response	IMWG Criteria

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

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

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.

2. Confirmation with repeat bone marrow biopsy not needed.

3. 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.

4. 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.

5. For progressive disease, serum M-component increases of >1 gm/dL are sufficient to define relapse if starting M-component is >5 g/dL.

6. Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

[redacted]

Appendix M: 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
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	

[redacted]

Response category	Definition
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 109/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 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.

[redacted]

Response category	Definition
#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.	
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.	

[redacted]

Appendix N: 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	Durable resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement† AND 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 Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND 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	Durable resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement† AND 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 Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND 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]

Appendix O: 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	Durable resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement,† AND 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 Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND Bone marrow histological remission defined as disappearance of megakaryocyte hyperplasia and absence of >grade 1 reticulin fibrosis.
Partial remission	Durable resolution of disease-related signs including palpable hepatosplenomegaly, and large symptoms improvement, AND 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 Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND 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.

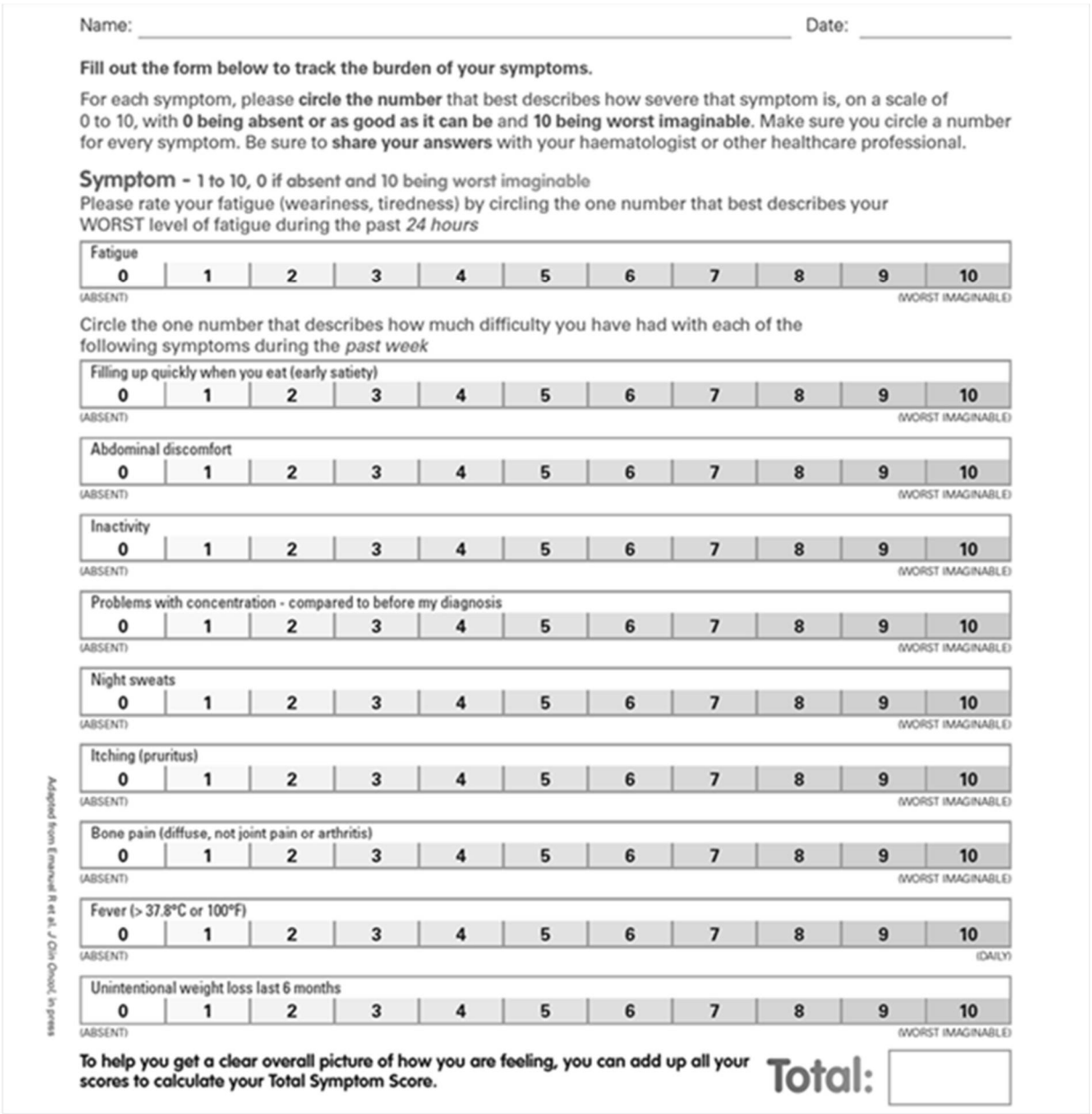
[redacted]

Appendix P: 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. (2005) Clinical application and proposal for modification of the InternationalWorking Group (IWG) response criteria in myelodysplasia. blood-2005-10-4149.	

[redacted]

Appendix Q: 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 haematologist 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)

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)										(DAILY)

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:** _____

Adapted from Emanuel R et al. J Clin Oncol; in press

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]

Appendix R: Bayesian Adaptive Design Framework for the Modular Phase II Study to Link Targeted Therapy to Patients with Pathway Activated Tumors.

1 Introduction

This document outlines the adaptive design framework to be used for all trials within Novartis's Modular Phase II study to link targeted therapy to patients with pathway activated tumors.

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

- Lung NSC
- 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.

1.1 Primary Analysis

We 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 within the trial. We transform to the logit scale for modeling purposes. Let θ_g be the mean log odds treatment effect, i.e.:

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

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 for that group. Thus, we wish to test the set of hypotheses

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

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

[redacted]

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

$$\Pr(\theta_g>0 \mid \text{data}) > 0.80$$

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.

1.2 Trial Logistics

The 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. The 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 at the end of the study. At each interim data review, response information for the various groups will be evaluated to determine the current $\Pr(\theta_g>0 \mid \text{data})$ 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 groups reach their own early stopping criteria. The final analysis will occur after the analysis of the analysis of the study data for the primary CSR.

The 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 possible cohorts within the "other" category, 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 3 subject 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.

2 Statistical Modeling

We let Y_i be the response indicator for the i^{th} subject, and let R_g be the 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 within the trial. We transform to the logit scale for modeling purposes. Let θ_g be the mean log odds treatment effect, i.e.:

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

[redacted]

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 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 Section 5) 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.

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 τ^2 are unknown, and hence have a prior distribution which is combined with the data to produce estimates of μ and τ^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.

[redacted]

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 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 Section 5.

3 Evaluation of Trial Success and Futility

Interim monitoring will occur after the first 30 patients are on study for 16 weeks, 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.

3.1 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.

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:

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

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

3.3 Final Analysis

In addition, recall the final analysis will occur when both accrual and follow-up are complete in all groups. 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:

$$\Pr(\pi_g > R_g) > 0.80.$$

[redacted]

4 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.

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 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 4.1.1 shows the assumed control clinical benefit rates for each group.

Table 4.1.1 Assumed control rates

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

Table 4.1.1 – Assumed control CBR values used in the simulations.

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 4.1.2. Values identical to the control are shown in bold, while values greater than the assumed control rate are italicized.

Table 4.1.2 Treatment rates

	Null	Alternative	Two	Half
Lung NSC	**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*

[redacted]

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.

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 scenarios in the tables below.

Table 4.2.1 Probability of group success for each cohort assuming expected accrual of 10 subjects/cohort

Two-year expected accrual: 10 subjects/cohort				
Group(Exp N)	Null	Alternative	Two	Half
Lung NSC	**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*

Table 4.2.2 Probability of group success for each cohort assuming expected accrual of 5 subjects /cohort

Two-year expected accrual: 5 subjects/cohort				
Group	Null	Alternative	Two	Half
Lung NSC	**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 bold represent groups where the treatment effect is 0 (e.g. the treatment is ineffective). Thus, entries in bold are type I errors. Italicized entries appear where the treatment is effective, and thus indicate the power of the design.

Generally, type I error is controlled at 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 enrolling groups. 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 cohorts, thus some cohorts may enroll closer to 10 subjects while other may only enroll five. This would produce a power value somewhere between the two tables.

[redacted]

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

5 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 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 z_g represent the cluster to which group g belongs. Then $z_g \sim$ Categorical($\boldsymbol{p}$), where $\boldsymbol{p}$ is the vector such that p_k is the probability that a group belongs to cluster k and $\sum_{k=1}^{\infty} p_k = 1$. We construct $\boldsymbol{p}$ 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 $\boldsymbol{p}$, 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

$$\theta_g \sim N(\mu, \tau^2)$$

[redacted]

As discussed above, this across groups 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 θ_g 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 distribution for each group parameter θ_g, which is then used to drive the decisions in the model.

[redacted]