NOVARTIS

Clinical Development

LEE011

Protocol CLEE011X2201 / NCT02300987

A randomized, blinded, placebo-controlled, phase II trial of LEE011 in patients with relapsed, refractory, incurable teratoma with recent progression

Authors	[redacted]
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List of abbreviations

ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUCinf	Area Under the Curve from Time Zero to Infinity
AUClast	Area Under the Curve from Time Zero to the Last Measureable Concentration Time
BOR	Best Overall Response
BSEP	Bile Salt Export Pump
BUN	Blood Urea Nitrogen
CDK	Cyclin-Dependent Kinase
CHF	Congestive Heart Failure
CI	Confidence Interval
Cmax	Maximum Plasma Concentration after a Single Dose
CNS	Central Nervous System
CPL	Clinical Program Lead
CR	Complete Response
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DLT	Dose-Limiting Toxicity
DMC	Data Monitoring Committee
DOR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
[redacted]	[redacted]
EOT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
[redacted]	[redacted]
FMO3	Flavin-Containing Monooxygenase 3
GCP	Good Clinical Practice
GCT	Germ Cell Tumor

[redacted]

GI	Gastrointestinal
GLP	Good Laboratory Practice
GTS	Growing Teratoma Syndrome
HA	Health Authority
HIV	Human Immunodeficiency Virus
HPF	High Powered Field
HR	Heart Rate or Hazard Ratio
IB	Investigator's Brochure
IC_{50}	Concentration resulting in 50% Inhibition
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
LPLV	Last Patient First Visit
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
MT	Malignant Transformation
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition Scan
NSGCT	Non-Seminomatous Germ Cell Tumor
NYH	New York Heart
ORR	Overall Response Rate
OS	Overall Survival
PD	Pharmacodynamic or Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per Protocol Set
PRBC	Packed Red Blood Cells
pRB	Retinoblastoma Protein
[redacted]	[redacted]
PR	Partial Response or Interval between P Wave and QRS Complex
[redacted]	[redacted]
PT	Prothrombin Time
PVC	Premature Ventricular Contraction
QD	Daily
[redacted]	[redacted]
QRS	Part of ECG Wave representing Ventricular Depolarization
QT	Measure of time between the Q Wave and the T Wave in Cardiology
QTcB	QT corrected with Bazett's formula
QTcF	Q-T interval in the ECG (corrected according to the formula of Fridericia)
RAP	Report and Analysis Plan
RB	Retinoblastoma gene
RBC	Red Blood Cell

[redacted]

RECIST v1.1	Response Evaluation Criteria for Solid Tumors Version 1.1
RR	Interval between R waves
SAE	Serious Adverse Event
SEER	Surveillance, Epidemiology and End-Result
SD	Stable Disease
SEC	Study Evaluation Completion
T1/2	Half Life
Tmax	Time to Reach Maximum (peak) Plasma Concentration
TSH	Thyroid-Stimulating Hormone
TTP	Time to Progression
ULN	Upper Limit of Normal
US	United States
VES	Visit Evaluation Schedule
WBC	White Blood Cell
[redacted]	[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 (e.g.: q28 days)
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 21 CFR Part 312.3 and is synonymous with “investigational new drug.”
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment arms of a study
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Placebo	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
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 drug	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study drug in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Treatment arm	A treatment arm defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

[redacted]

Amendment 3 (18-Aug-2017)

Amendment rationale

The purpose of this amendment is:

- To add language to facilitate unblinding of patient treatment status.
- To add language to allow patients receiving LEE011 to discontinue treatment in CLEE011X2201 and transfer to a Novartis rollover clinical trial (CLEE011X2X01B) which will continue to provide treatment with LEE011.
- To add language to allow placebo patients to crossover to LEE011 treatment if the investigator believes it is in the best clinical interest of the patient.

Enrollment to this study was halted on 20-Nov-2015. Based on the small number of patients enrolled prior to the enrollment halt, the primary endpoint will not be obtained and therefore it is no longer necessary for patients to continue to receive placebo. With this in mind, ongoing patients will be unblinded in order to permit crossover to LEE011 for those patients receiving placebo.

Other changes implemented in this amendment:

- To update the preclinical safety pharmacology and toxicology sections to include recent data on teratogenicity of LEE011.
- To correct minor typographical and grammatical errors throughout the document.

Study status:

The CLEE011X2201 study started enrollment on 26-February-2015. Enrollment to this study was halted on 20-Nov-2015. Prior to recruitment halt, a total of 10 patients were enrolled. As of 18-Aug-2017, there are 4 patients on treatment, 3 of which are blinded and 1 has crossed over to LEE011 treatment.

Changes to the protocol

- Section 1.2.1.3 – updated preclinical safety pharmacology and toxicology
- Section 4.1 – revised treatment procedures after early study termination
- Section 4.1.2 – added language to facilitate unblinding of ongoing patients and allow placebo patients to crossover to LEE011 treatment if the investigator believes it is in the best clinical interest of the patient
- Section 4.1.3, 4.1.4 and 4.1.5 – revised follow-up procedures after early study termination
- Section 4.1.6 – revised crossover treatment procedures after study termination and following patient enrollment to a LEE011 rollover clinical trial (CLEE011X2X01B)
- Section 4.3 – added language to permit patient rollover to CLEE011X2X01B
- Section 4.3 – revised to align with Section 10.4 regarding when a primary CSR will be produced
- Section 7.1.3 – added transfer to a LEE011 rollover clinical trial (CLEE011X2X01B) as a reason for end of treatment
- Section 7.1.3 – changed parent/guardian decision to patient/parent/guardian decision

[redacted]

- Section 7.1.5.1 – revised follow-up procedures following patient enrollment to a LEE011 rollover clinical trial (CLEE011X2X01B)
- Section 7.1.5.2 and 7.1.5.3 – revised follow-up procedures after early study termination
- Section 10 – revised to clarify CSR reporting after early study termination or patient enrollment to a LEE011 rollover clinical trial (CLEE011X2X01B)
- Section 14.1.30 and 14.1.31 – added transfer to a LEE011 rollover clinical trial (CLEE011X2X01B) as a reason for end of treatment and study phase completion
- Section 14.1.30 and 14.1.31 – changed parent/guardian decision to patient/parent/guardian decision

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Health Authorities (HAs). The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised informed consent that takes into account the changes described in this protocol amendment.

Amendment 2

Amendment rationale

The main purpose of this amendment is to address recently observed safety findings. These safety findings and the resulting changes follow:

1. Updates to monitoring and dose adjustment guidelines for QTcF prolongation in order to improve patient safety based on program standard language recommendations have been implemented. As a result, new guidelines for management of QTcF prolongation were instituted throughout the LEE011 program in order to improve safety. These changes include:
   a. additional ECG assessments
   b. the addition of continued ECG monitoring for all cycles in the event of a patient QTcF $\geq$ 481 ms at any time before Cycle 9 Day 1
   c. in the event of QTcF prolongation:
      i. follow-up of electrolyte abnormalities until normalization
      ii. mandated site review of concomitant medications
      iii. mandated site review of dosing regimen
2. Recent data suggests a potential risk of hepatic toxicity (drug induced liver injury [DILI] indicated by an increase of transaminases, in isolation or with bilirubin increase) in patients treated with LEE011. Updates to monitoring and dose adjustment guidelines for hepatobiliary toxicities including ALT, AST, and total bilirubin have been added and separated from the dose modification guidance for other adverse events.
3. Further clarification to withdrawal of consent and lost to follow-up process

[redacted]

4. DNA sequencing of cancer related genes has been removed because similar data in patients receiving single agent LEE011 has already been generated, thus this analysis would have been of limited utility.

Changes to the protocol

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

- All inclusion and exclusion criteria contained in section 5.2 and section 5.3 were added to the protocol summary for consistency
- Section 1.2.3 - Clinical pharmacokinetics of LEE011 updated with the most recent available data
- [redacted]
- Inclusion criteria #4 – clarification of inclusion criterion
- Exclusion criteria #2 – clarification of exclusion criterion
- Exclusion criteria #15 – added phosphorus and sodium as electrolytes correctable by oral supplementation to be consistent with LEE011 protocol guidelines
- Table 6-3 – table revised to detail study drug adjustments and management recommendation for hematological adverse reactions
- Table 6-4 – table added to detail study drug dose adjustment and management recommendations for hepatic toxicities
- Section 6.2.1.1 – added to include additional follow-up guidance for hepatic toxicities
- Section 6.2.1.2 – added to include additional follow-up guidance for QTc prolongation
- Section 6.2.1.3 – added to include additional guidance for all other adverse reactions
- Table 6-6 – added to clarify dose adjustment and management recommendations by CTCAE grade
- Section 7.1 - study flow and visit schedules have been updated to include additional ECGs
- Section 7.1.3 Discontinuation of study treatment – renamed section and clarified section
- Section 7.1.4 – Withdrawal of Consent – section added for clarification
- Section 7.1.5 – Follow-up Period – added clarification
- Section 7.2.2.5.2 – added sodium and phosphorus to the list of labs included in “clinical chemistries”
- Section 7.2.2.6.1. – added ECGs to be completed in triplicate at screening
- Section 7.2.4 – deleted next generation sequencing
- Table 7-4 – added additional ECG collection plan per recommended guidance for LEE011 program
- Table 7-6 – deleted DNA sequence of cancer related genes (by next generation sequencing) and reduced number of slides needed

[redacted]

- Section 10.1.1 – The Full Analysis Set definition was updated to include the clarification of the grouping of patients undergoing crossover from placebo to LEE011 after RECIST progression.
- Sections 10.2, 10.3.2 and 10.6.1.3.2.- updated to include the addition of FAS2 analysis,

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Amendment 1

Amendment rationale

In order to investigate a more homogeneous patient population, patients with pathologic evidence of malignant transformation will no longer be included in this study.

The median progression-free survival (PFS) expectation for patients receiving placebo has been adjusted from 3 months to 2 months, in response to feedback from investigators. The median PFS expectation for the LEE011 treatment arm remains 6 months. The trial was modified from 90 patients to 42 patients. It remains adequately powered (alpha = 0.05, power = 80%).

The interim analysis for efficacy will no longer be performed due to the changes in the baseline assumption of median PFS leading to a smaller study sample size. Based on the small sample size, it is not considered beneficial to perform are in interim analysis of the PFS data. Note, safety data will continue to be reviewed during the course of the study.

In order to maintain consistency throughout the LEE011 program cardiac imaging (MUGA/ECHO) will be required at screening and end of treatment (EOT) visits for all patients to more completely evaluate underlying cardiac disease.

The following additional changes have been made:

- New safety and efficacy data from the newest edition of the IB for LEE011 were included as necessary. Obsolete data was excluded from the protocol.
- Typographical and grammatical errors were corrected throughout the protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. All inclusion and exclusion criteria contained in section 5.2 and section 5.3 were added to the protocol summary for consistency.

Section 1.1.2 – Epidemiology – deleted information regarding malignant transformation

[redacted]

Section 1.1.3 – Current treatment – deleted information regarding malignant transformation

Section 1.2.1.3 – Safety pharmacology and toxicology – changes reflect clarity and consistency between other LEE011 protocols

Section 1.2.2 – Clinical experience – updated information about AEs from [LEE011 Investigator Brochure]

Section 1.2.2.1 Safety and efficacy of LEE011 – updated information from [LEE011 Investigator Brochure]

Section 1.2.3 – Clinical pharmacokinetics of LEE011 – updated information from [LEE011 investigator brochure]

Section 2.2 – Rationale for Study Design – deleted stratification for malignant transformation patients

Section 3 – Objective and endpoint – added duration of response (DOR) for consistency to statistical section 10

Section 4.1 – Study Design – removed malignant transformation and reduced the number of patients to be enrolled in the trial from 90 to 42

Figure 4-1 Study design – revised to remove malignant transformation stratification and provide clarity to overall study design

Section 4.2 – Timing of interim analyses and design adaptations – the interim analysis was removed

Section 5.2 Inclusion criteria – Inclusion criterion #5 – malignant transformation patients excluded from protocol

Section 5.3 Exclusion Criteria – Exclusion criterion #3 –Pathologic evidence of malignant transformation patients added as exclusion criteria

Section 5.3 Exclusion Criteria – Exclusion criterion #14 – removed as this is a drug in capsule packaging and there are no excipients

Section 6.3.3 Prohibited concomitant therapy – revised for clarity and consistency with other LEE011 protocols

Table 7-1 – Visit Evaluation Schedule – removed urinalysis and added cardiac imaging

Table 7-3 – Local clinical laboratory – deleted urinalysis as other LEE011 studies have collected data with no safety signal concern.

Section 7.2.2.6.2 – Cardiac Imaging – ECHO or MUGA scans added at screening and EOT visits.

Table 7-4 – ECG collection plan – removed C2D21 pre dose and 4 hr post dose time points as other LEE011 studies have collected data with no safety signal concern

[redacted]

Section 8.6 – Data Monitoring Committee – revised to delete interim analysis

Section 10 – Statistical methods and data analysis – various modifications to remove malignant transformation stratification, remove the interim analysis and to change the number of PFS event for the primary efficacy analysis

Section 14 – Table 14-8 – List of medications to be used with caution during treatment with LEE011 – medications removed and added based on new information.

IRB

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[redacted]

Protocol summary:

Protocol number	CLEE011X2201
Title	A randomized, blinded, placebo-controlled, phase II trial of LEE011 in patients with relapsed, refractory, incurable teratoma with recent progression
Brief title	Study of the efficacy and safety of LEE011 in patients with relapsed, refractory, incurable teratoma with recent progression
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The primary purpose of this study is to determine the anti-tumor activity of LEE011 for relapsed/refractory, progressive teratoma for which there is no curative therapy. Targeting the D-Cyclin-CDK axis to inhibit teratoma growth is driven by biological rationale, supporting clinical evidence, and the need for effective targeted therapy in this indication. Evidence of anti-tumor activity in this study will be used to inform future development of LEE011 in other tumors where this pathway may be critical for tumorigenesis.
Primary Objective(s) and Key Secondary Objective	To assess the efficacy of LEE011 compared to placebo in patients with relapsed/refractory teratoma with recent progression
Secondary Objectives	To assess other measures of efficacy of LEE011 compared with placebo To assess safety and tolerability of LEE011 compared with placebo
Study design	This is a multi-center, randomized, double blind (investigator and patient), placebo controlled phase II study to determine the efficacy and safety of treatment with LEE011 versus placebo in patients with progressive relapsed, refractory incurable teratoma. Eligible patients will be randomized at a 2:1 ratio to LEE011 or placebo. Study drug (LEE011 or placebo) will be administered orally once daily for 21 days followed by one week break (28-day cycle). The dose of LEE011 will be 600 mg.
Population	The study will be conducted in approximately 42 patients with relapsed/refractory/incurable teratoma with recent progression.
Inclusion criteria	1. Age ≥ 15 years old at time of informed consent. 2. Diagnosis of teratoma for which no additional standard surgical or medical therapy exists 3. Availability of an archival or newly obtained tumor sample (collected at diagnosis or progression) with accompanying pathology report ● Patients without an archival tumor sample may be permitted to participate after discussion between Novartis and the investigator 4. Patients must have completed at least 1 prior line of chemotherapy for germ cell tumor (except patients who present with primary, pure teratoma who need not have received any previous chemotherapy) 5. Radiographic progression, defined by RECIST v.1.1, after the last cancer treatment and within 12 weeks prior to enrollment, compared with scans within 1 year of enrollment. 6. Measurable or evaluable extra-cranial disease as defined by RECIST v.1.1 7. Patients must have ECOG performance status of 0-1
Exclusion criteria	1. CNS disease unless radiation therapy and/or surgery has been completed and serial evaluation by CT (with contrast enhancement) or MRI over a minimum of 2 months demonstrates stable disease. Patient must be asymptomatic and without need for treatment with systemic corticosteroids or anti-epileptic medications 2. Malignant germ cell tumors other than that being treated in this study, including tumors with elements of mixed histology such as embryonal carcinoma, choriocarcinoma, yolk sac tumor or seminoma. Note – this refers to the histology at the time of enrollment, not the histology at the time of initial presentation 3. Pathologic evidence of malignant transformation 4. Concurrent malignancy other than teratoma within 3 years of randomization, with the additional exceptions of treated NSGCT from which teratoma has emerged,

[redacted]

	adequately treated basal or squamous cell carcinoma of the skin, curatively resected cervical cancer or curatively resected carcinoma *in situ* of any type 5. Prior treatment with any CDK4/6 inhibitor therapy 6. Any concurrent severe and/or uncontrolled medical condition that, in the investigator's judgment serves as a contraindication to patient participation (e.g., chronic pancreatitis, active hepatitis, viral hepatitis or known HIV positivity). Baseline HIV screening is not required 7. Patients who have not recovered to ≤ CTCAE grade 1 from the acute toxic effects (except for alopecia) of all prior chemotherapy, immunotherapy, or radiotherapy 6. Impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection) 9. Impaired cardiac function or any clinically significant cardiac disease, including any of the following ● Left ventricular ejection fraction (LVEF) < 45% or less than the institution's lower limit of normal as determined by multiple gated acquisition scan (MUGA) or echocardiogram (ECHO) ● Congenital long QT syndrome or family history of unexpected sudden cardiac death ● QT corrected with Fridericia's (QTcF) QTcF >450 msec for males and >470 msec for females on screening ECG ● Clinically significant heart disease such as CHF requiring treatment (NYH grade ≥ 2), unstable angina pectoris or myocardial infarction within the past 3 months. Any other clinically significant heart disease such as unstable arrhythmia, resting bradycardia, right bundle branch block, bifascicular block, or any heart disease that requires the use of a cardiac pacemaker ≤ 3 months prior to starting study drug ● Patients who are currently receiving medications with known risk of prolonging the QT interval or inducing Torsades de Pointes and are unable to discontinue or switch to an alternate medication 10. Concomitant therapy that precludes enrollment ● Systemic antineoplastic therapy or any experimental therapy within 3 weeks before the first dose of study drug (6 weeks for prior nitrosoureas, bevacizumab, or mitomycin C) ● Systemic corticosteroids within 2 weeks prior to starting study drug. Note: Corticosteroids are permitted for use as 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) 11. Major surgery within 2 weeks of the first dose of study drug (mediastinoscopy, insertion of a central venous access device, or insertion of a feeding tube is not considered major surgery) 12. Received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization, or patient has not recovered to ≤ CTCAE grade 1 related toxicity 13. Requirement for treatment with any of the prohibited medications including strong CYP3A inhibitors, strong CYP3A inducers, CYP3A substrates with a narrow therapeutic index, and medications with strong risk of QT prolongation 14. Have any of the following out-of-range laboratory values ● Absolute neutrophil count < 1.5× 10^9/L ● Platelet count < 100 × 10^9/L ● Hemoglobin <9.0 g/dL ● Potassium unless correctable by oral supplementation ● Calcium (corrected for serum albumin) unless correctable by oral supplementation ● Magnesium unless correctable by oral supplementation ● Serum creatinine ≥1.5 × ULN ● Alanine aminotransferase (AST) and aspartate aminotransferase (ALT) > 3 × ULN for age; for patients with liver metastases ≥ 5 × ULN for age. ● Total serum bilirubin >1.5 x ULN; or total bilirubin ≥3.0 × ULN with direct bilirubin within normal range in patients with well documented Gilbert's Syndrome ● INR ≥1.5

[redacted]

Investigational and reference therapy	LEE011
Efficacy assessments	Progression Free Survival (PFS) as per RECIST v1.1 (by local investigator assessment). Best Overall Response (BOR), Overall response rate (ORR), Duration of response (DOR), Disease Control Rate (DCR) at 4 months as per RECIST v1.1 and Overall Survival (OS) and OS rate at 12 months.
Safety assessments	Safety will be assessed using the following criteria: ● Adverse events (AEs) ● Serious Adverse Events (SAEs) ● Physical Exams ● Vital signs ● Laboratory assessments ● Performance Status ● Cardiac assessments
Other assessments	[redacted]
Data analysis	The primary endpoint of the study is PFS, defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS will be assessed via the local investigator assessment according to RECIST v1.1. If a patient has not had an event, PFS will be censored at the date of the last adequate tumor evaluation. The primary efficacy analysis will be performed when there are approximately 23 PFS events and all patients have been followed for PFS for at least 6 months or have discontinued prior to this time for disease progression or death, or have withdrawn consent to follow-up or have been lost to follow-up or if the study is terminated early. A secondary objective is to further assess the efficacy of LEE011 compared with placebo. The evaluations of tumor responses will be based on local investigator assessment according to RECIST v1.1. The following endpoints and analyses will be used to further assess the efficacy: ● OS, defined as the time from date of randomization of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive. ● BOR, defined as the best response recorded from the start of the treatment until disease progression/recurrence. Confirmation of complete and partial responses must be made at least 4 weeks apart. ● ORR, defined as the proportion of patients with a best overall response of CR or PR. ● DOR, defined for responder as the time between the date of first documented response (CR or PR) and the date of first documented progression or death due to underlying cancer. If progression or death due to underlying cancer has not occurred, then the patient is censored at the date of last adequate tumor assessment. ● DCR, defined as the proportion of patients with a best overall response of CR or PR or SD
Key words	Double blind randomized, Phase II, CDK 4/6 inhibitor, relapsed/refractory/incurable teratoma

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Disease pathogenesis

Teratomas consist of cell types derived from one or more of the germ layers (mesoderm, endoderm and ectoderm) and arise most commonly in the gonads or midline structures including the anterior mediastinum, retroperitoneum, sacrococcygeal region, and the pineal gland. Teratoma classification is dichotomized into benign and malignant. Benign teratomas are distinguished as mature or immature based on the proportion of differentiated tissue observed. Malignant teratomas include mature/immature teratomas that have metastasized or contain non-germinal malignant patterns (malignant transformation) such as carcinoma or sarcoma (Gatcombe et al 2004). Teratomas may also arise within other germ cell tumor (GCT) types, most commonly non-seminomatous germ cell tumors (NSGCT). Metastatic sites of NSGCT often contain teratomatous elements at diagnosis (Sheinfeld et al 2003).

Deregulation of the retinoblastoma tumor suppressor pathway in GCT has been well documented (Bartkova et al 2003). In the non-diseased state, cell cycle progression from $G_1 \rightarrow S$ is initiated by sequential phosphorylation at different sites of retinoblastoma protein (pRB) by both cyclin D-CDK4/6 complex and cyclin E-CDK2 complex and the subsequent release of bound E2F. The phosphorylation events mediated by CDK4/6 are prerequisites for those catalyzed by CDK2 (Bartek et al 1997). Upregulation of CDK4 and cyclin D2 is believed to be a central event in GCT tumorigenesis (Houldsworth et al 1997, Schmidt et al 2001). Although pRB expression is absent or grossly reduced in undifferentiated GCT, more differentiated NSGCT such as teratocarcinomas and teratomas demonstrate strong expression of pRB (Strohmeyer et al 1991, Bartkova et al 2003).

1.1.2 Epidemiology

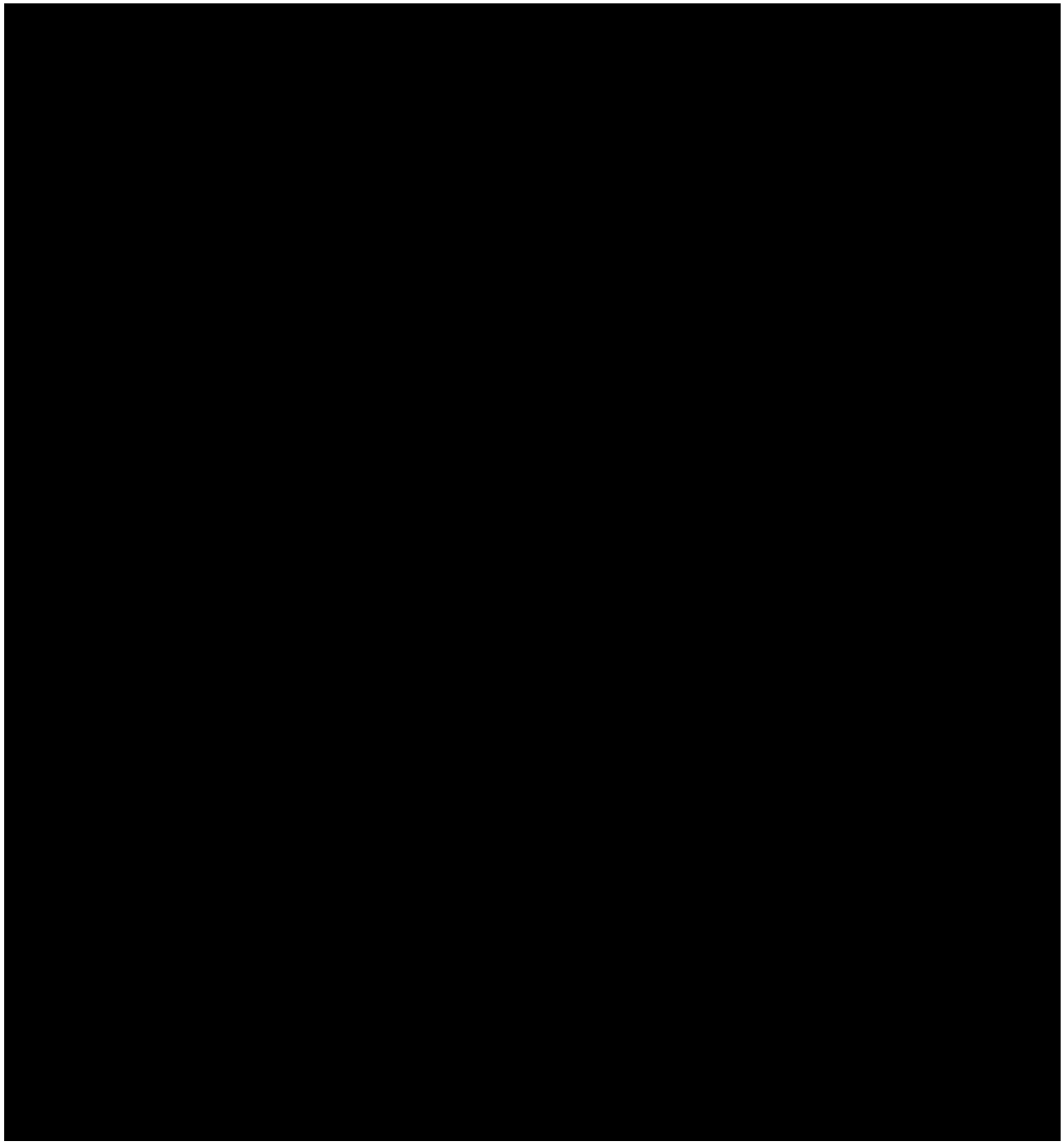
Malignant teratoma is rare in both pediatric and adult populations. Review of the Surveillance, Epidemiology, and End-Result (SEER) data revealed an incidence of 0.14/100,000 women-years with 531 cases identified over the 30 year period reviewed from 1973-2002 (Smith et al 2006). The frequency is higher in males. Growing Teratoma Syndrome (GTS), develops during or after treatment in about 2-7% of male patients with NSGCTs (Andre et al 2000). The US incidence of testicular GCT is 5.7/100,000 males (7,920 cases in 2013, SEER), this translates to about 355 cases of GTS annually. The incidence of testicular cancer is similar in Western Europe and Australia, but comparatively low in Asia and Africa at 1/100,000 males.

1.1.3 Current treatment

Unlike NSGCTs which are sensitive to cytotoxic chemotherapy, teratomas are highly chemo-resistant and optimally treated by complete surgical resection (Speiss et al 2007). More than 80% of cases of GTS are successfully managed by surgical resection. However, no standard therapy exists for progressive, unresectable teratoma in adult or pediatric patients (Andre et al 2000). Case reports of efficacy with various agents including interferon (van der Gaast et al

[redacted]

1991, Ornadel et al 1995, Rustin et al 1984) and bevacizumab (Mego et al 2007) have been published. Given the known deregulation of the RB tumor suppressor pathway in GCTs and that nearly all malignant teratomas stain positively for nuclear pRB (Strohmeyer et al 1991, Bartkova et al 2003), treatment of non-resectable malignant teratoma with a CDK 4/6 inhibitor such as LEE011 is a rational approach.



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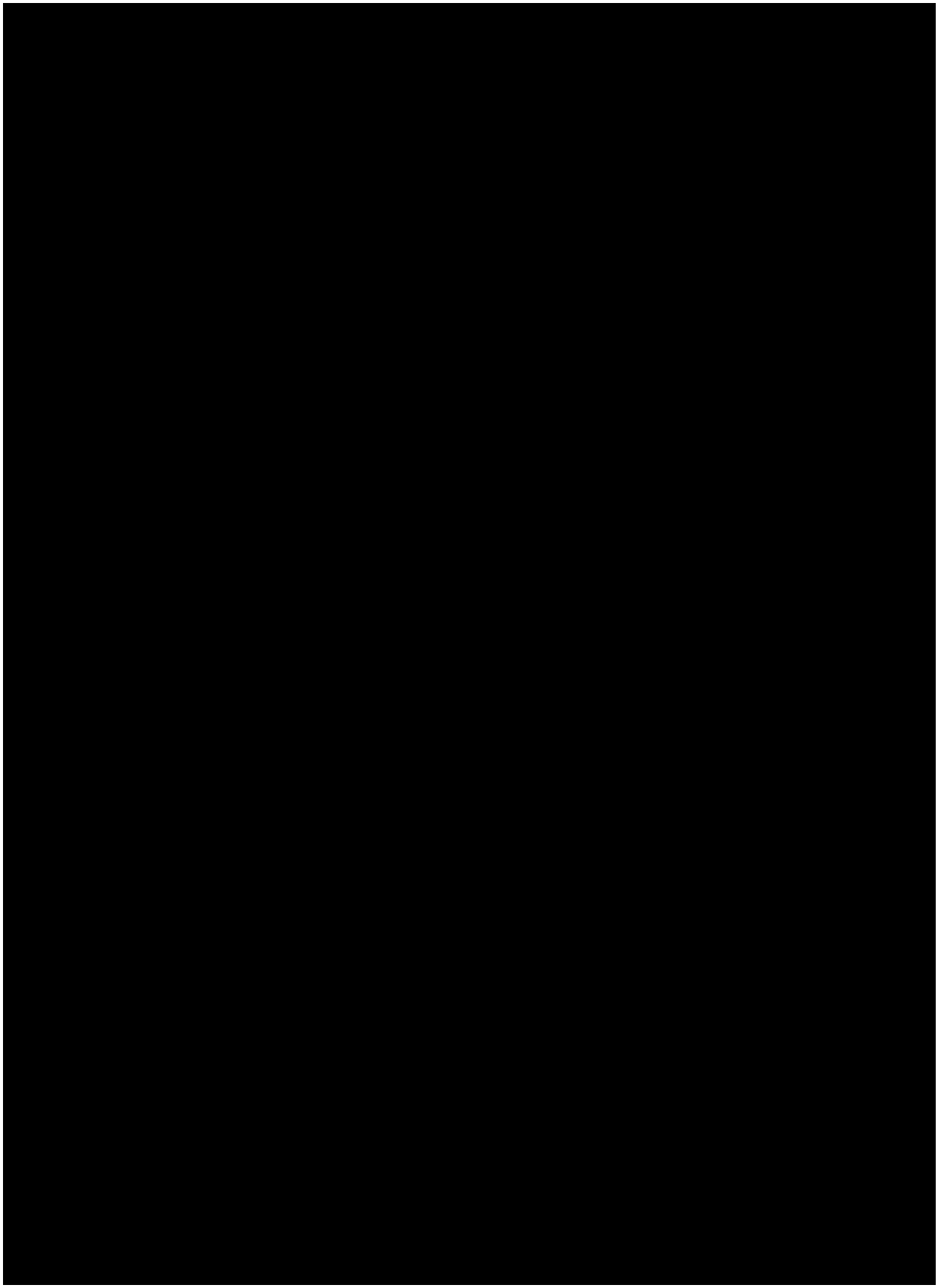

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2 Rationale

2.1 Study rationale and purpose

Deregulation of the retinoblastoma tumor suppressor pathway in GCT has been well documented (Bartkova et al 2003). Upregulation of CDK4 and cyclin D2 is believed to be a central event in GCT tumorigenesis (Houldsworth et al 1997, Schmidt et al 2001). Inhibition of CDK4/cyclinD1 and CDK6/cyclinD3 complexes prevents the phosphorylation of pRB and renders a cell unable to proceed through cell division. Differentiated NSGCT such as teratocarcinomas and teratomas demonstrate strong expression of pRB (Strohmeyer et al 1991, Bartkova et al 2003).

Treatment for relapsed/refractory/unresectable teratoma remains a high unmet medical need and use of a CDK 4/6 inhibitor such as LEE011 is a rational approach. A phase I study with palbociclib; another selective CDK 4/6 inhibitor, (PD-0332991) included 3 patients with progressive Growing Teratoma Syndrome (GTS) despite maximal surgical excision. Two patients maintained stable disease for 18 and 24 months at the time of the report, and the third had partial response and remained progression free on therapy at 22 months (Vaughn et al 2009).

The primary purpose of this study is to determine the anti-tumor activity of LEE011 for relapsed, refractory, progressive, incurable teratoma. Targeting the D-Cyclin-CDK axis to inhibit teratoma growth is driven by biological rationale, supporting clinical evidence, and the need for effective targeted therapy in this indication. Evidence of anti-tumor activity in this study will be used to inform future development of LEE011 in other tumors where this pathway may be critical for tumorigenesis.

2.2 Rationale for the study design

This is a randomized double blind (investigator and patient), placebo-controlled, phase II study of LEE011 in patients with progressive relapsed/refractory teratoma for whom standard therapeutic options are not available. The two-arm randomized design minimizes allocation bias, balancing both known and unknown prognostic factors in the assignment of treatment. Blinding will minimize the risk of overstating LEE011 effect. Given the variable growth rate of teratomas, documentation of radiologic progression within 12 weeks prior to enrollment (compared to a prior scan within 1 year) will be required.

A placebo-controlled design with crossover, at time of documented disease progression per RECIST v1.1, permits a more objective assessment of clinical improvement and radiologic response, while at the same time permitting all enrolled patients access to LEE011. There is no accepted standard therapy for patients eligible for enrollment in this study and case reports of individualized regimens are discouraging (van der Gaast et al 1991, Ornadel et al 1995, Rustin et al 1984). Patients will be randomized 2:1 to the experimental arm in order to

[redacted]

increase the probability of patients receiving active drug upfront and maximize collection of safety data. The presence of a placebo arm will also help to facilitate the evaluation of whether adverse events are related to LEE011. The use of a cross-over design will impact the ability to provide a robust estimate of overall survival, which is acceptable given the exploratory nature of this phase II study.

Preclinical and clinical studies suggest that the vast majority of teratoma have pRB (Bartkova et al 2003); therefore, pre-screening for pRB status will not be required but will be assessed retrospectively.

2.3 Rationale for dose and regimen selection

The LEE011 dose will be 600 mg QD for 21 days followed by a one week break as established in the [CLEE011X2101] study (28 day cycle). The MTD of LEE011 administered as single agent is 900 mg QD for 21 days followed by a one week break; however, the recommended dose for future development is 600 mg QD (3 weeks on/1 week off schedule) due to lower risk for QTcF prolongation, acceptable safety profile, adequate exposures, and preliminary evidence of clinical activity.

2.4 Rationale for choice of combination drugs

Not applicable

2.5 Rationale for choice of comparators drugs

Not applicable

[redacted]

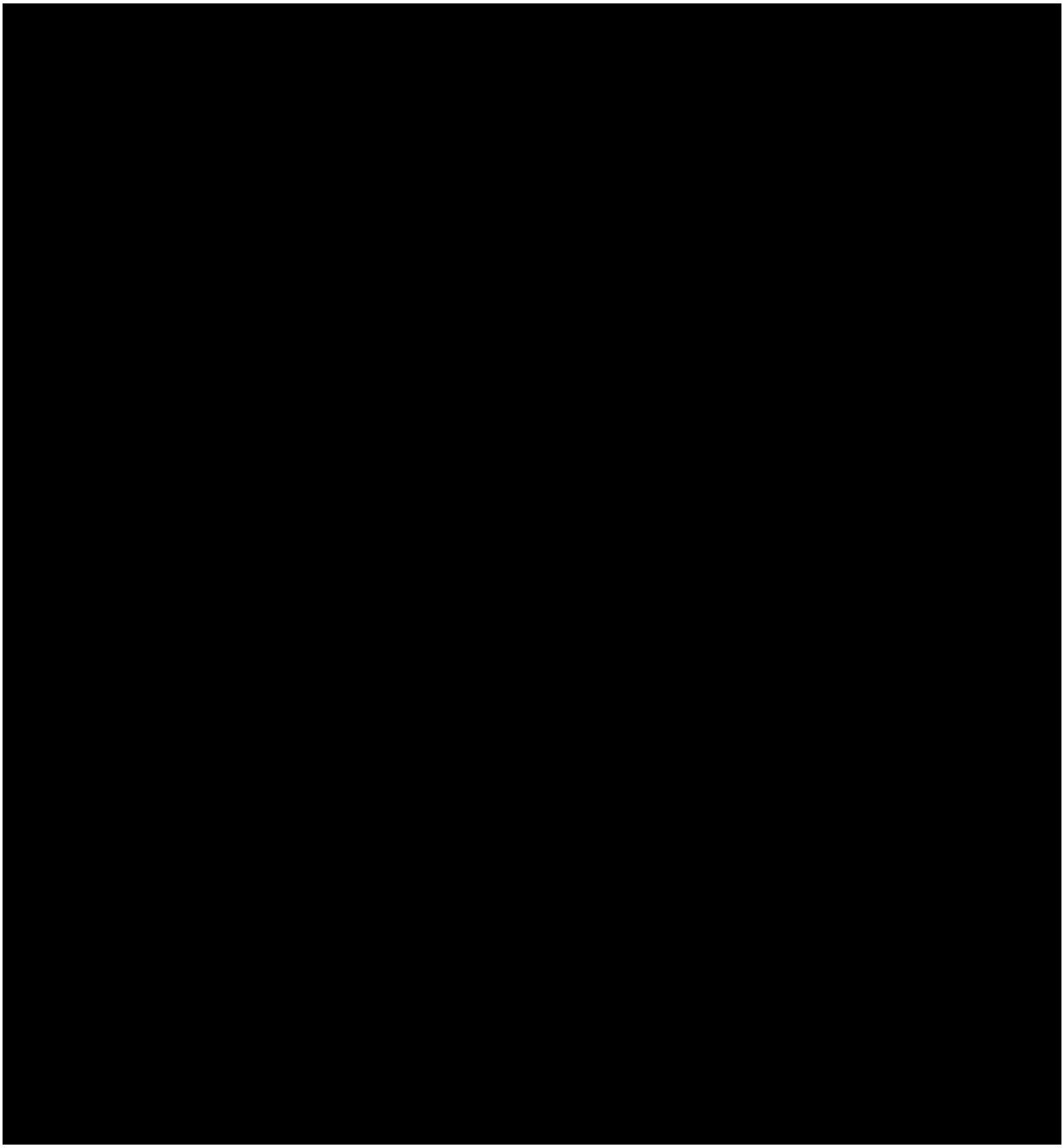
3 Objectives and endpoints

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

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To assess the efficacy of LEE011 compared to placebo in patients with relapsed/refractory teratoma with recent progression	PFS as per RECIST v1.1 (by local investigator assessment).	
Secondary		Refer to Section 10.5.2 and Section 10.5.3
To assess other measures of efficacy of LEE011 compared with placebo	BOR, ORR, DOR, DCR at 4 months as per RECIST v1.1 and OS, OS Rate at 12 months.	
To assess safety and tolerability of LEE011 compared with placebo	Incidence and severity of adverse events and serious adverse events, changes in laboratory values, electrocardiograms, and vital signs will be used to assess the safety as per CTCAE v.4.03. Dose interruptions and changes will be used to assess the tolerability.	
[redacted]		

4 Study design



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[redacted]

[redacted]

4.2 Timing of interim analyses and design adaptations

No formal interim analysis will be conducted for this study.

4.3 Definition of end of the study

The study data will be analyzed and a primary clinical study report (CSR) will be written based on all patients' data at the time when there are approximately 23 PFS events for the primary efficacy analysis and all patients have been followed for PFS for at least 6 months or have discontinued prior to this time for disease progression or death, or have withdrawn consent to follow-up, or have been lost to follow-up (see Section 10.4.2), or enrollment in the LEE011 rollover clinical trial (CLEE011X2X01B), or early study termination, whichever occurs first. Additional data for patients continuing on study or in any survival follow-up period past the data cutoff date for the primary CSR will be reported in a final CSR once the treatment period, safety follow-up, disease progression follow-up and survival follow-up periods have ended for all patients as described in Section 7.1.4. In the case when the study is terminated early (Section 4.4) and no CSR has been already reported, all data prior to the study termination will be reported in a final CSR (see Section 4.4).

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, patients should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.3 for an EOT/premature withdrawal 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 IRBs and/or ECs of the early termination of the study.

5 Population

5.1 Patient population

The study will be conducted in patients, 15 years old or older, with a diagnosis of teratoma that have radiographic progression within 12 weeks of enrollment.

Patients who do not meet all the inclusion or exclusion criteria can be re-screened once for consideration in the trial. If a patient is re-screened, the same patient ID number should be used.

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

[redacted]

5.2 Inclusion criteria

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

1. Age ≥ 15 years old at time of informed consent.
2. Diagnosis of teratoma for which no additional standard surgical or medical therapy exists.
3. Availability of an archival or newly obtained tumor sample (collected at diagnosis or progression) with accompanying pathology report.
   - Patients without a tumor sample may be permitted to participate after discussion between Novartis and the investigator.
4. Patients must have completed at least 1 prior line of chemotherapy for germ cell tumor (except patients who present with primary, pure teratoma who need not have received any previous chemotherapy)
5. Radiographic progression, defined by RECIST v.1.1, after the last cancer treatment and within 12 weeks prior to enrollment, compared with scans within 1 year of enrollment.
6. Measurable or evaluable extra-cranial disease as defined by RECIST v.1.1.
7. Patients must have ECOG performance status of 0-1.
8. Written informed consent/assent before any study-specific screening procedures. For pediatric patients, consent will be obtained from parent(s) or legal guardian(s) and the signature of at least 1 parent or guardian will be required. Investigators will also obtain assent of patients according to local, regional or national guidelines.

5.3 Exclusion criteria

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

1. CNS disease unless radiation therapy and/or surgery has been completed and serial evaluation by CT (with contrast enhancement) or MRI over a minimum of 2 months demonstrates stable disease. Patient must be asymptomatic and without need for treatment with systemic corticosteroids or anti-epileptic medications.
2. Malignant germ cell tumors other than that being treated in this study, including tumors with elements of mixed histology such as embryonal carcinoma, choriocarcinoma, yolk sac tumor or seminoma. Note – this refers to the histology at the time of enrollment, not the histology at the time of initial presentation.
3. Pathologic evidence of malignant transformation.
4. Concurrent malignancy other than teratoma within 3 years of randomization, with the additional exceptions treated NSGCT from which teratoma has emerged, of adequately treated basal or squamous cell carcinoma of the skin, curatively resected cervical cancer or curatively resected carcinoma *in situ* of any type.
5. Prior treatment with any CDK4/6 inhibitor therapy
6. Any concurrent severe and/or uncontrolled medical condition that, in the investigator's judgment serves as a contraindication to patient participation (e.g., chronic pancreatitis, active hepatitis, viral hepatitis or known HIV positivity). Baseline HIV screening is not required.
7. Patients who have not recovered to ≤ CTCAE grade 1 from the acute toxic effects (except for alopecia) of all prior chemotherapy, immunotherapy, or radiotherapy.

[redacted]

8. Impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drug (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
9. Impaired cardiac function or any clinically significant cardiac disease, including any of the following:
    - Left ventricular ejection fraction (LVEF) < 45% or less than the institution's lower limit of normal as determined by multiple gated acquisition scan (MUGA) or echocardiogram (ECHO)
    - Congenital long QT syndrome or family history of unexpected sudden cardiac death
    - QT corrected with Fridericia's (QTcF) QTcF >450 msec for males and >470 msec for females on screening ECG
    - Clinically significant heart disease such as CHF requiring treatment (NYH grade ≥ 2), unstable angina pectoris or myocardial infarction within the past 3 months. Any other clinically significant heart disease such as unstable arrhythmia, resting bradycardia, right bundle branch block, bifascicular block, or any heart disease that requires the use of a cardiac pacemaker ≤ 3 months prior to starting study drug.
    - Patients who are currently receiving medications with known risk of prolonging the QT interval or inducing Torsades de Pointes and are unable to discontinue or switch to an alternate medication.
10. Concomitant therapy that precludes enrollment:
    - Systemic antineoplastic therapy or any experimental therapy within 3 weeks before the first dose of study drug (6 weeks for prior nitrosoureas, bevacizumab, or mitomycin C).
    - Systemic corticosteroids within 2 weeks prior to starting study drug. Note: Corticosteroids are permitted for use as 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).
11. Major surgery within 2 weeks of the first dose of study drug (mediastinoscopy, insertion of a central venous access device, or insertion of a feeding tube is not considered major surgery)
12. Received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization, or patient has not recovered to ≤ CTCAE grade 1 related toxicity.
13. Requirement for treatment with any of the prohibited medications including strong CYP3A4/5 inhibitors, strong CYP3A4/5 inducers, CYP3A4/5 substrates with a narrow therapeutic index, and medications with strong risk of QT prolongation (Appendix 4).
14. Participation in a prior investigational study within 30 days prior to enrollment or within 5-half-lives of the investigational product, whichever is longer.
15. Have any of the following out-of-range laboratory values:
    - Absolute neutrophil count $\leq 1.5 \times 10^9$/L
    - Platelet count $\leq 100 \times 10^9$/L
    - Hemoglobin ≤9.0 g/dL
    - Potassium unless correctable by oral supplementation

[redacted]

- Calcium (corrected for serum albumin) unless correctable by oral supplementation
- Magnesium unless correctable by oral supplementation
- Serum creatinine ≥1.5 × ULN
- Alanine aminotransferase (AST) and aspartate aminotransferase (ALT) > 2.5 × ULN for age; for patients with liver metastases ≥ 5 × ULN for age.
- Total serum bilirubin > ULN except for patients with Gilbert's syndrome who may only be included if the total bilirubin is ≥1.5 × ULNINR ≥1.5

16. 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.
17. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during dosing and for 3 weeks after stopping dosing. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient), periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before starting study drug. In case of oophorectomy alone, only when the reproductive status of the female has been confirmed by follow-up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    - Combination of any two of the following (a+b or a+c, or b+c):
        a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
        c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception females should have been stable on the same oral contraceptive for a minimum of 3 months before starting study drug.

18. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.
19. Sexually active males, unless they use a condom during intercourse, while taking study drug and for 3 weeks after stopping study drug and should not father a child during this

[redacted]

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

All dosages of study drug prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

The investigator or responsible site personnel should instruct the patient to take the study drug as per protocol (promote compliance). Study drug accountability must be performed on a regular basis. Patients will be instructed to return unused study drug to the site at the end of each cycle. The site personnel will ensure that the appropriate dose of each study drug is administered at each visit and will provide the patient with the correct amount of drug for subsequent dosing.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Strength	Dose	Frequency and/or Regimen
LEE011	Capsule for oral use	200 mg/capsule	600 mg	Daily (21 days followed by one week break)
LEE011 matching Placebo	Capsule for oral use	N/A	N/A	Daily (21 days followed by one week break)

LEE011 and placebo will be supplied to investigational sites by Novartis or its designee as 200 mg hard gelatin capsules as individual patient supply packaged in bottles as double blind supply. Storage conditions are described on the medication label. Study drug will be taken orally, once a day for 21 consecutive days followed by a one week break as part of each 28-day cycle of treatment. The study drug will be administered as a flat-fixed dose, not by body weight or body surface area.

6.1.2 Study drug administration

Study drug should be taken as follows:

- Patients should be instructed to take his/her daily dose with a glass of water (~250 ml/8 oz.) in the morning at approximately the same time (+/- 1 hour). Patients may take study drug with or without food. Patients should be instructed to swallow capsules whole and not chew, crush or open, unless otherwise instructed. If patients cannot tolerate his/her daily dose in the morning, due to GI related side effects, then after cycle 1 it can be taken in the evening for the remainder of the study.
- [redacted]
- If vomiting occurs no re-dosing of the patient is allowed before the next scheduled dose.

[redacted]

- [redacted]
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped until the next day.

6.1.3 Guidelines for continuation of treatment

Not applicable

6.1.4 Treatment duration

Efficacy, safety and survival data will continue to be collected as per visit schedule (Table 7-1). Patients may continue treatment with study drug until disease progression as assessed by RECIST v1.1 (Appendix 1), occurrence of unacceptable toxicity that precludes any further treatment, or if treatment is discontinued at the discretion of the investigator or by patient's withdrawal of consent. Patients who progress on placebo may crossover to LEE011 and receive treatment until subsequent tumor progression, discontinuation at the discretion of the investigator or patient's withdrawal of consent (see Section 4.1.6). Patients receiving LEE011 may be allowed to continue treatment following progression if in the opinion of the investigator they are receiving clinical benefit. Details supporting continuation must be sent to Novartis for approval within 7 days of documented progression. For patients continuing on LEE011 after unblinding due to clinical benefit (not crossover patients), subsequent tumor assessments should be conducted according to local practice.

6.2 Dose modifications

6.2.1 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 drug. These changes must be recorded on the Dosage Administration Record eCRF. For patients undergoing a dose delay or reduction mid-cycle, upon restarting LEE011 during that cycle the, dosing should resume per the original cycle schedule. The planned 7-day break should begin on the originally planned date regardless of mid-cycle interruptions. Day 1 of subsequent cycles may be delayed if necessary to allow for toxicity resolution. If the study drug is delayed for more than 21 days due to drug toxicity, then study drug should be discontinued.

Severe or intolerable AEs may require dose reduction and/or interruption of study drug. Refer to Table 6-2 for guidance.

Table 6-2 Dose adjustments

Dose level	Daily dose	Frequency
*-2	200 mg	Daily (21 days), followed by one week break
*-1	400 mg	Daily (21 days), followed by one week break
1 (starting dose)	600 mg	Daily (21 days), followed by one week break

*Dose level-1 and -2 represent treatment doses for patients requiring a dose reduction from the starting dose level. No dose reduction below dose level -2 is permitted for this study.

[redacted]

Recommendations for dose reduction, interruption or discontinuation of study drug in the management of AEs are summarized in Table 6-3. Clinical judgment of the treating physician and an individualized risk/benefit assessment should guide the management plan for each patient. A maximum of two study drug dose reductions (minimum dose is 200 mg) is allowed before study drug must be discontinued. Once a dose reduction has occurred, the dose level may not be re-escalated until the adverse event resolves to grade 1 and dose change has been authorized by the Novartis team.

Table 6-3 Study drug dose adjustment and management recommendation for hematological adverse reactions

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 study drug 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 study drug at the same dose level. If toxicity recurs at grade 3: temporary dose interruption until recovery to grade ≤ 1 and reduce study drug to the next lower dose level.
Grade 4(< 25 x 10^9/L)	Dose interruption until recovery to grade ≤ 1. Re-initiate study drug at the next lower dose level. If toxicity recurs at grade 4: discontinue study drug.
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.
Grade 3 (≥ 0.5 - < 1.0 x 10^9/L)	Dose interruption until recovery to ≥ 1.0 x 10^9/L. Re-initiate study drug 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 in ≤ 7 days, then maintain dose level. If resolved in > 7 days, then reduce study drug 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 study drug 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 study drug at the next lower dose level.
Febrile neutropenia	
Grade 3 ANC < 1.0 x 10^9/L with a single temperature of > 38.3 ºC (101 ºF) or a sustained temperature of ≥ 38 ºC (100.4 ºF) 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 study drug.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue study drug
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.

[redacted]

Toxicity/Grade	Dose Adjustment and Management Recommendations
	Re-initiate study drug at the same dose.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue study drug.

Table 6-4 Study drug dose adjustment and management recommendation for 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 48-72h later)	Maintain dose level with LFTs monitored bi-weekly
Grade 2 (> 1.5 – 3.0 x ULN)	Dose interruption of study drug 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 study drug
Grade 3 (> 3.0 – 10.0 x ULN)	Dose interruption of study drug If resolved to ≤ grade 1 in ≤ 21 days, lower 1 dose level of study drug If resolved to ≤ grade 1 in > 21 days or toxicity recurs, discontinue study drug
Grade 4 (> 10.0 x ULN)	Discontinue study drug
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's Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert's 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 h 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 – 20.0 x ULN)	Dose interruption of study drug 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 study drug
Increase from baseline grade 0 or 1 to grade 3 (> 5.0 – 20.0 x ULN)	Dose interruption of study drug until resolved to ≤ baseline value, then lower 1 dose level of study drug If recovery to ≤ baseline value is > 28 days, discontinue study drug If toxicity recurs, discontinue study drug
Grade 4 (> 20.0 x ULN)	Discontinue study drug
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	Discontinue study drug

[redacted]

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
AST or ALT ≥ grade 3 (> 5 x ULN) in patients with grade 1 or 2 at baseline, and total bilirubin > 2 x ULN	
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.	

6.2.1.1 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's 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.
- 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 (Cytomegalovirus (CMV), Epstein Barr Virus (EBV) or Herpes Simplex Virus (HSV); autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis (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.

6.2.1.2 Additional follow-up for QTc prolongation

Table 6-5 Study drug dose adjustment and management recommendation

Grade	Dose Modification
For All Grades	● Check the quality of the ECG. ● Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If outside of the normal range, interrupt study drug 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.

[redacted]

Grade	Dose Modification
	● Check compliance with correct dose and administration of study drug
1 QTc 450-480 ms	No dose adjustment required.
2 QTc 481-500 ms	Interrupt study drug Perform a repeat ECG one hour after the first QTcF of ≥ 481 ms. If QTcF ≤ 481 ms, restart study drug at the same dose. No dose adjustment required for first occurrence. If QTcF remains ≥ 481 ms, repeat ECG as clinically indicated until the QTcF returns to < 481 ms. restart study drug at the same dose. No dose adjustment required for first occurrence. If QTcF ≥ 481 ms recurs, study drug should be reduced by 1 dose level. Refer to Table 6-2 for dosing schedule. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 481 ms
3 QTc ≥ 501 ms on at least two separate ECGs	Interrupt study drug. Transmit ECG immediately and confirm prolongation/abnormalities with central assessment. Perform a repeat ECG one hour after the first QTcF of > 501 ms. If QTcF remains ≥ 501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated, until the QTcF returns to < 481 ms. If QTcF returns to < 481 ms, study drug 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 (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 501 ms If QTcF of ≥ 501 ms recurs, discontinue study drug
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 study drug. ● Obtain local cardiologist consultation. ● 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 < 501 ms.

6.2.1.3 Guidance for all other adverse reactions

Consider performing an analysis of serum potassium, calcium, phosphorus, and magnesium for all adverse reactions, if indicated. If electrolyte values are below the lower limit of normal, interrupt study drug administration, correct electrolytes with supplements as soon as possible, and repeat electrolyte testing until documented normalization of the electrolytes.

Table 6-6 Study drug 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 study drug at the same dose. If the same toxicity recurs at grade 2, interrupt study drug until recovery to grade ≤1. Re-initiate study drug at the next lower dose level.
3	Dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate study drug at the next lower dose level. If toxicity recurs at grade 2: temporary dose interruption until recovery to grade ≤1 and reduce study drug dose the next lower dose level. If toxicity recurs at grade 3, discontinue study drug

[redacted]

Grade	Dose Adjustment and Management Recommendations
4	Discontinue study drug and treat with appropriate medical therapy.

6.2.2 Follow-up for toxicities

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

6.2.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria as well as specific dose modification and stopping rules are included in this protocol.

6.3 Concomitant medications

6.3.1 Permitted concomitant therapy

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as packed red blood cells (PRBC), pain medications, anti-emetics and anti-diarrheals are allowed. Hematopoietic growth colony stimulating factors may be used therapeutically or as secondary prophylaxis, see Appendix 4.

The patient (patient's guardian if appropriate) must be instructed to notify the treating physician of new medications after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including blood transfusions and physical therapy) administered within 30 days of first dose of study drug and during the study must be listed on the Concomitant Medications/Significant Non-Drug therapies eCRF as appropriate. Patients taking concomitant medications chronically should be maintained on the same dose and dosing schedule throughout the study, as medically feasible.

6.3.2 Permitted concomitant therapy requiring caution

The following therapies are permitted in this study; however, they should be used with caution:

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

6.3.3 Prohibited concomitant therapy

The following medications are prohibited during treatment in this study (Appendix 4):

- Strong inhibitors or inducers of CYP3A4/5
- Substrates of CYP3A4/5 with narrow therapeutic index

[redacted]

- Medications with a known risk for QT prolongation
- Other investigational and antineoplastic therapies
- Herbal medications
- Primary prophylactic hematopoietic growth factors
- Palliative radiotherapy
- Patients must avoid consumption of grapefruit, grapefruit hybrids, pummelos, star-fruit, Seville oranges or products containing the juice of each during the entire study and preferably for an additional 7 days before the first dose of study medications, due to potential CYP3A interaction with the study medications. Orange juice is allowed.

Refer to the LEE011 Investigator's Brochure and Appendix 4 for information on possible interactions with other drugs.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled for screening 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 to the investigator through the Oracle Clinical RDC interface.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Patient No. must not be reused for any other patient and the Patient No. for that individual must not be changed even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Disposition eCRF.

IRT must be notified within 2 days of a patient screen failure.

6.4.2 Treatment assignment or randomization

Patients will be randomized to 1 of the 2 treatment arms in a 2:1 ratio. LEE011 and placebo will be supplied to investigational sites by Novartis or its designee as hard gelatin capsules (200 mg) as individual patient supply packaged in bottles. Storage conditions are described on the medication label.

Block randomization will be used to allocate patients between treatment arms. The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management

[redacted]

using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

For patient's crossing over to LEE011, the investigator or his/her designee will call or log on to the IRT and confirm that the patient fulfills the criteria to crossover. The IRT will assign a unique medication number for the study drug to be dispensed to the patient.

The medication label will be in the local language and comply with the legal requirements of each country. The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms and a dose level. Responsible site personnel will identify the study drug package(s) to dispense to the patient by using the IRT and obtaining the medication number(s). Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drug as per protocol. Study drug 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.

6.4.3 Drug supply and storage

Study drug will be centrally supplied by Novartis DSM or a Novartis designated CRO, and must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, the study drugs should be stored according to the instructions specified on the drug labels and in the Investigator's Brochure.

6.4.4 Study drug compliance and accountability

6.4.4.1 Study drug compliance

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

6.4.4.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study drug 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

[redacted]

all unused study drug and packaging on a regular basis, at the end of the study and at the time of study drug 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 the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.4.4.3 Handling of other study treatment

Not applicable.

6.4.5 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility by the, Drug Supply group or third party, as appropriate. Drug supply is to be destroyed at the site only if permitted by local regulations and authorized by Novartis.

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.

No eCRF will be used as a source document.

After the screening period, all assessments have a ±3 day window unless otherwise indicated [redacted]

If study drug is being held due to toxicity, then the scheduled visits and assessments [redacted] should still be performed per protocol, unless otherwise specified. Additional assessments may be performed as clinically indicated.

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Screening	Treatment Cycles							EOT	Crossover cycles							Crossover EOT	Follow-Ups		
				Cycle 1				Cycle 2		Subsequent Cycles		Cycle 1				Cycle 2		Subsequent Cycles		30-Day	Progression	Survival
Day of cycle			**-14 to-1**	**1**	**8**	**15**	**21**	**1**	**21**	**1**		**1**	**8**	**15**	**21**	**1**	**21**	**1**				
Obtain informed consent	D	7.1.1	X																			
[redacted]																						
IVRS/IRT registration	D	4.1	X																			
Demography	D	7.1.1.3	X																			
Inclusion/exclusion criteria	D	5.2 / 5.3	X									X										
Medical history	D	7.1.1.3	X																			
Diagnosis and extent of cancer	D	7.1.1.3	X																			
Prior antineoplastic therapy	D	7.1.1.3	X																			
Physical examination	S	7.2.2.1	X	X	X	X	X	X		X	X	X	X	X	X	X			X			
ECOG performance status	D	7.2.2.4	X	X				X		X	X	X				X		X	X			
Height	D	7.2.2.3	X																			
Weight	D	7.2.2.3	X	X				X		X	X	X				X		X	X			
Vital signs	D	7.2.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X			

[redacted]

	Category	Protocol Section	Screening	Treatment Cycles							EOT	Crossover cycles							Crossover EOT	Follow-Ups		
				Cycle 1				Cycle 2		Subsequent Cycles		Cycle 1				Cycle 2		Subsequent Cycles		30-Day	Progression	Survival
Day of cycle			**-14 to-1**	**1**	**8**	**15**	**21**	**1**	**21**	**1**		**1**	**8**	**15**	**21**	**1**	**21**	**1**				
Hematology	D	7.2.2.5.1	X	X		X	X	X	X	X	X	X		X	X	X		X	X			
Chemistry	D	7.2.2.5.2	X	X		X	X	X	X	X	X	X		X	X	X		X	X			
Thyroid panel	D	7.2.2.5.3	X								X								X			
Coagulation	D	7.2.2.5.4	X								X								X			
Pregnancy test	D	7.2.2.5.5	X	X				X		X	X	X				X		X	X			
ECG	D	7.2.2.6.1	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X			
[redacted]																						
Cardiac imaging (MUGA/ECHO)	D	7.2.2.6.2	X								X								X			
[redacted]																						
Collection of archival paraffin blocks/slides or newly obtained tumor sample	D	7.2.4.1	X																			
[redacted]																						
Tumor assessments	D	7.2.1	X	Every 8 weeks for first 12 months from C1D1, then every 12 weeks							X	Every 8 weeks for the first 12 months from C1D1, then every 12							X		X	

[redacted]

	Category	Protocol Section	Screening	Treatment Cycles							EOT	Crossover cycles							Crossover EOT	Follow-Ups		
				Cycle 1				Cycle 2		Subsequent Cycles		Cycle 1				Cycle 2		Subsequent Cycles		30-Day	Progression	Survival
Day of cycle			**-14 to-1**	**1**	**8**	**15**	**21**	**1**	**21**	**1**		**1**	**8**	**15**	**21**	**1**	**21**	**1**				
												weeks										
Study Drug administration	D	6.1.2		Continuous daily dosing days 1-21 of each cycle then one week break																		
Adverse Events	D	8.1	Continuous from signed ICF up to 30 days after last dose of study treatment.																			
Prior/concomitant medications	D	6.3	Continuous from consent to 30-Day follow-up																			
Assessment of Patient Disposition	D	7.1.3	X								X								X			
Antineoplastic therapy since discontinuation	D	7.1.5.2																		X	X	X
Survival Follow-up (telephone call/clinic visit every 12 weeks)	D	7.1.5.3																				X

[redacted]

7.1.1 Screening

The Study IRB/IEC approved Informed Consent Form (ICF) must be signed and dated before any screening procedures are performed; however, procedures that are part of the clinical routine during the initial diagnostic work-up of the patient may be performed before signing the ICF. A copy of the ICF must be given to the patient (or patient's guardian as appropriate). The Investigator or designee must record the date when the study informed consent was signed in the medical records of the patient.

For patients under 18 years of age, consent will be obtained from parent(s) or legal guardian(s) and the signature of at least 1 parent or guardian will be required. Investigators will also obtain assent of minor patients according to local, regional or national guidelines.

The screening period starts once a patient has provided written informed consent to participate in the study and ends on the day of first dose of study drug. Screening assessments have to be completed within 14 days prior to the first dose of study drug except for imaging and hematologic laboratories. Baseline tumor imaging may be done up to 28 days prior and hematologic laboratories (ANC, platelet count, and hematocrit) up to 72 hours prior to first dose of study drug.

Abnormal laboratory values of potassium, magnesium or calcium correctable by oral supplementation must document a normalized laboratory value prior to randomization.

7.1.1.1 Eligibility screening

When the patient is considered eligible for study treatment, the study site should enter the information into the IRT/IVRS system to register and randomize the patient.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to start on study drug for any reason will be considered a screen failure. The reason for not starting study drug will be entered on the Screening Phase Disposition eCRF. The demographic information, informed consent, and Inclusion/Exclusion eCRF must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experiences a Serious Adverse Event during the Screening Phase (See Section 8 for SAE reporting details). The IRT must be notified within 2 days of the screen failure.

7.1.1.3 Patient demographics and other baseline characteristics

Baseline data on patient characteristics to be collected includes: general demographics, relevant medical history, cancer diagnosis, tumor burden, and prior medications and antineoplastic therapies.

7.1.2 Treatment period

During the treatment period, the patient must follow the Investigator's instructions with regards to contraception, concomitant medications, and dosing regimen (see Section 6.1.1). There is no fixed treatment duration. Patients may continue study drug until disease progression, unacceptable toxicity, discretion of the investigator or patient withdrawal of

[redacted]

consent. At time of documented progression per RECIST v1.1, patients may be unblinded and those randomized to placebo will be evaluated for crossover to LEE011. Patients should receive LEE011 within 28 days of the last radiological assessment. Safety labs and assessment are not required to be repeated for patients who start crossover C1D1 within 14 days of completing treatment. Patients initially randomized to the LEE011 arm may be permitted to continue on LEE011, despite progression, if the investigator documents ongoing clinical benefit for the patient in the source documentation, in a comment in the eCRF, and discussed decision with CPL. Please refer to Section 4.1.6.

7.1.3 Discontinuation of Study Treatment

Patients may voluntarily discontinue from the study or be discontinued from the study at the discretion of the investigator at any time. If a patient decides to discontinue from the study treatment, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if he/she believes that continuation would be detrimental to the patient's well-being

If a patient discontinues study treatment, but continues study assessments, the patient remains on study until such time as he/she completes protocol criteria for ending study assessment. At that time, the reason for study completion should be recorded on the Study Phase Completion Disposition CRF page.

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

Patients who prematurely discontinue study drug should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the EOT visit will be performed (Table 7-1). This visit should take place no more than 14 days after the last dose of study drug. An EOT eCRF should be completed, giving the date and reason for stopping the study treatment. End of treatment/premature withdrawal visit is not considered as the end of study.

The investigator must contact the IRT to register the patient's discontinuation.

All patients who discontinue study drug should return for assessments according to Table 7-1 including: safety follow-up (Section 7.1.5.1), disease progression follow-up (if applicable, Section 7.1.5.2) and survival follow-up (Section 7.1.5.3).

An End of Phase Disposition eCRF should be completed upon completion of the Disease Progression Follow-Up Period.

Patients may be discontinued from the study drug if any of the following occur:

- Patient withdrew consent
- Adverse event
- Lost to follow-up
- Death
- Non-compliance with study drug

[redacted]

- Physician decision
- Progressive disease
- Protocol deviation
- Study terminated by sponsor
- Technical problems
- Patient/parent/guardian decision
- Transfer to another Novartis clinical study that continues to provide LEE011 (e.g. CLEE011X2X01B)

Patients must be withdrawn from the study drug if any of the following occur:

- Pregnancy
- Death

7.1.4 Withdrawal of Consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visit or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or a required by local regulations).

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information.

LEE011 must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow-up.

7.1.5 Follow-up Period

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient; e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow-up should be recorded as such on the appropriate Disposition CRF

7.1.5.1 Safety follow-up

All patients must have safety evaluations 30 days after the last dose of study drug, except, in the case of death, loss to follow-up, withdrawal consent, or discontinuation of study treatment to enroll in the LEE011 rollover clinical trial (CLEE011X2X01B). Information related to AEs (including concomitant medication taken for ongoing AEs) and initiation of anti-neoplastic treatments will be collected. All AEs suspected to be related to study drug should

[redacted]

be followed weekly, or as clinically indicated, until resolution or stabilization. Antineoplastic therapies and/or tumor directed surgical procedures initiated during the safety follow-up period must be recorded on the Antineoplastic Therapy since Discontinuation of Study Drug eCRF.

7.1.5.2 Disease progression follow-up

Patients who discontinue study drug for any reason other than disease progression will be followed for efficacy (i.e., tumor assessments) every 8 weeks during the first 12 months and every 12 weeks thereafter until disease progression, death, discontinuation from the study for any other reason (i.e., loss to follow-up or withdrawal of consent), the initiation of a new antineoplastic treatment, or until all patients have been followed for at least 18 months after their first dose of study drug, or early study termination, whichever occurs first. Antineoplastic therapies and/or surgical procedures initiated during the disease progression follow-up period must be recorded on the Antineoplastic Therapy since Discontinuation of Study Drug eCRF.

7.1.5.3 Survival follow-up phase

All patients will be followed for survival via a phone call (or during a clinic visit) every 12 weeks and up to one additional time per quarter if a survival update is required to meet safety or regulatory needs, until any of the following (whichever occurs first): death, withdrawal of consent, loss to follow-up, at least 18 months from when the last patient started treatment, or when 80% of patients have died or been lost to follow-up, or early study termination. Antineoplastic therapies or tumor directed surgical procedures initiated during the survival follow-up period must be recorded on the Antineoplastic Therapy since Discontinuation of Study Drug eCRF.

7.1.5.4 Replacement policy

Not applicable.

7.2 Assessment types

7.2.1 Efficacy assessments

All patients will have disease response assessments per the RECIST v 1.1 (Appendix 1). Each lesion that is measured at baseline (screening), must be measured by the same method throughout the study so that the comparison is consistent. Tumor response will be evaluated locally by the investigator according to the Novartis guideline (Version 3.0) based on RECIST v 1.1 (See Appendix 1).

The following assessments in Table 7-2 are required at screening/baseline (within 28 days of the start of treatment). FDG-PET scans are not required for this study. Sites may perform combined PET/CT scans per their local standard of care, provided the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and intravenous contrast media. If acquired according to local standard of care, FDG-PET may be relied upon to document progressive disease in accordance with RECIST v1.1.

[redacted]

Tumor assessments during the Blinded Treatment Period will be performed locally every 8 weeks (+/-3 days) for the first year following C1D1 and every 12 weeks thereafter until disease progression, death, discontinuation from the study for any other reason (i.e., loss to follow-up or withdrawal of consent) or initiation of a new antineoplastic treatment, whichever occurs first. Tumor evaluations may be performed sooner if there is clinical concern for disease progression. Tumor evaluation is required at EOT for patients who discontinue study drug before the first scheduled post-baseline tumor assessment and for patients whose previous tumor assessment did not demonstrate PD; however, if the last prior tumor evaluation was within 28 days of EOT, then tumor evaluations do not need to be repeated at EOT.

The primary investigator's or designee's assessment will be used for the primary endpoint analysis and for treatment decision making.

All radiological assessments obtained for all patients will be centrally collected and subjected to quality checks by an imaging CRO selected by Novartis. The site manual provided by the designated imaging CRO will provide further details regarding image collection. Additionally a central review of tumor assessments may be performed as supportive analysis if indicated.

Table 7-2 Disease assessment collection plan

Procedure	Screening: day−28 to day -1	Blinded Treatment phase	End of treatment*
CT or MRI (Chest, Abdomen, Pelvis)	Mandated	Every 8 weeks during the first 12 months then every 12 weeks thereafter	Mandated
Brain CT or MRI	Only if existing or suspected brain metastases	As clinically indicated	As clinically indicated
Whole body bone scan **	As clinically indicated	As clinically indicated	As clinically indicated
Bone X-ray, CT or MRI	Only if skeletal abnormalities identified by whole body bone scan at screening, which are not visible in the chest, abdomen, pelvis CT/MRI.	If bone lesion at screening, every 8 weeks during the first 12 months then every 12 weeks thereafter	Mandated only if bone lesion at screening
Skin color Photography	Only if skin lesions at screening	If skin lesions at screening, every 8 weeks during the first 12 months then every 12 weeks thereafter	Mandated if skin lesions at screening
CT or MRI of any disease outside of chest, abdomen and pelvis (e.g., neck)	Only if suspected lesion at screening	If lesion identified at baseline, every 8 weeks during the first 12 months then every 12 weeks thereafter	Mandated if lesion at screening
*Tumor evaluation at EOT is required for patients who discontinue study drug before the first scheduled post-baseline tumor assessment and for patients whose previous tumor assessment did not demonstrate PD and was done at least 8 weeks prior to EOT visit. ** Whole body bone scan according to institutional guidelines (e.g., Tc-99 bone scan, whole body bone MRI, sodium fluoride positron emission tomography (NaF PET) or fluorodeoxyglucose (FDG) PET).			

[redacted]

7.2.2 Safety and tolerability assessments

Safety and tolerability will be monitored by assessing the changes from baseline in physical exam, vital signs and laboratory measures and by collecting the AEs at every visit. All safety assessments should be performed pre-dose unless otherwise specified. For details on AE collection and reporting, see Section 8.2.

7.2.2.1 Physical examination

A complete physical examination that evaluates all major organ systems will be performed during the screening period. Subsequent physical examinations should be focused on sites of disease to explore clinical signs and symptoms. Significant findings that were present prior to the signing of informed consent must be included in the Medical History eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event eCRF.

Physical exams to be performed are outlined in Table 7-1.

7.2.2.2 Vital signs

Vital signs (heart rate, blood pressure and temperature) will be obtained in the same position, either sitting or supine, as appropriate prior to any blood collection.

Vital signs to be performed as per Table 7-1.

7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Assessments to be performed are outlined in Table 7-1.

7.2.2.4 Performance status

Assessment of ECOG performance status will be performed at screening and regularly throughout the study irrespective of the time of dosing (Appendix 2).

Performance status to be performed as per Table 7-1.

7.2.2.5 Laboratory evaluations

The clinical laboratory analyses described below are to be performed by the sites local laboratory according to the time points indicated in Table 7-1. More frequent assessments may be performed at the investigator's discretion if medically indicated and should be recorded on the Unscheduled Visit eCRF.

Abnormal laboratory values that are clinically relevant (e.g., require a dose modification and/or interruption of study drug, lead to clinical symptoms or signs, or require therapeutic intervention) must be documented in the Adverse Event eCRF.

Novartis must be provided with a copy of the site's local laboratory certification and tabulation of the normal ranges for each parameter required at study start and should be kept up to date on an ongoing basis if there are any changes. In addition, if at any time a patient has

[redacted]

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 for that laboratory.

For all visits, there is a ± 3 days window on assessments to take into account scheduling over public or religious holidays if not explicitly specified otherwise. Laboratory assessments that were completed within 72 hours before Cycle 1, Day 1 (C1D1) do not need to be repeated.

Table 7-3 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Platelets, Red blood cells, White blood cells with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils),
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Calcium, Chloride, Creatinine, Direct Bilirubin, Glucose, Indirect Bilirubin, Magnesium, Phosphate, Potassium, Sodium, Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN) or Urea
Coagulation	aPTT, Fibrinogen, INR ,PT
Thyroid	TSH; if indicated T3, T4 [free]
Pregnancy	Serum beta-HCG required at screening (only for women of child-bearing potential); subsequent testing may be serum or urine.

7.2.2.5.1 Hematology

Please refer to Table 7-3 for a list of tests to be performed. For timing of assessments, refer to Table 7-1.

7.2.2.5.2 Clinical chemistry

Please refer to Table 7-3 for a list of tests to be performed.

If during screening, an abnormal laboratory value of potassium, magnesium and/or calcium can be corrected by oral supplementation than a repeat blood test must be completed to confirm the abnormal laboratory value is within normal limits before the patient is allowed to randomize.

If total bilirubin elevation ≥ grade 2 then direct and indirect bilirubin should also be measured.

For timing of assessments, refer to Table 7-1.

7.2.2.5.3 Thyroid

Please refer to Table 7-3 for a list of tests to be performed. If TSH is elevated then T3 and T4 will be measured.

For timing of assessments, refer to Table 7-1.

7.2.2.5.4 Coagulation

Please refer to Table 7-3 for a list of tests to be performed.

For timing of assessments, refer to Table 7-1.

[redacted]

7.2.2.5.5 Pregnancy and assessments of fertility

When highly effective contraception is required, pregnancy testing is required at screening and as indicated in Table 7-1. At screening a serum pregnancy test must be performed. Urine or serum pregnancy tests are sufficient for all visits after screening.

Pregnancy tests are required at the following visits:

- Screening
- Day 1 of all cycles
- EOT Visit

If a patient becomes pregnant, the study drug must be stopped immediately. If a pregnancy test (urine or serum) is positive, but the patient is not thought to be pregnant the study drug should be held until it is determined that the test was false positive, and pregnancy is excluded. For females to be considered "of non-childbearing potential", the patient must meet one of the following:

- Prior to onset of menarche (pre-menarche)
- Surgically sterile (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before starting study drug. In case of oophorectomy alone, only when the reproductive status of the female has been confirmed by follow-up hormone level assessment.
- 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).

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of discovery. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology (DS&E). The pregnancy should be followed 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. Follow-up data should be recorded on the initial Clinical Trial Pregnancy Form and include an assessment of the possible relationship between any pregnancy outcome and the Novartis study drug. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed after the patient has been resting for 5-10 minutes prior to each time point indicated in Table 7-4. At screening between Day -14 and Day -1, triplicate ECGs should be taken approximately 2 minutes apart. The combined QTcF values from these triplicate ECGs will be averaged to provide a single baseline value for each patient.

[redacted]

Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF. Each ECG tracing should be transmitted to a central laboratory and will be centrally reviewed by an independent reviewer. Clinically significant abnormalities at screening should be recorded on the relevant medical history/current medical conditions eCRF. Clinically significant findings must be discussed with Novartis 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.

Table 7-4 ECG collection plan

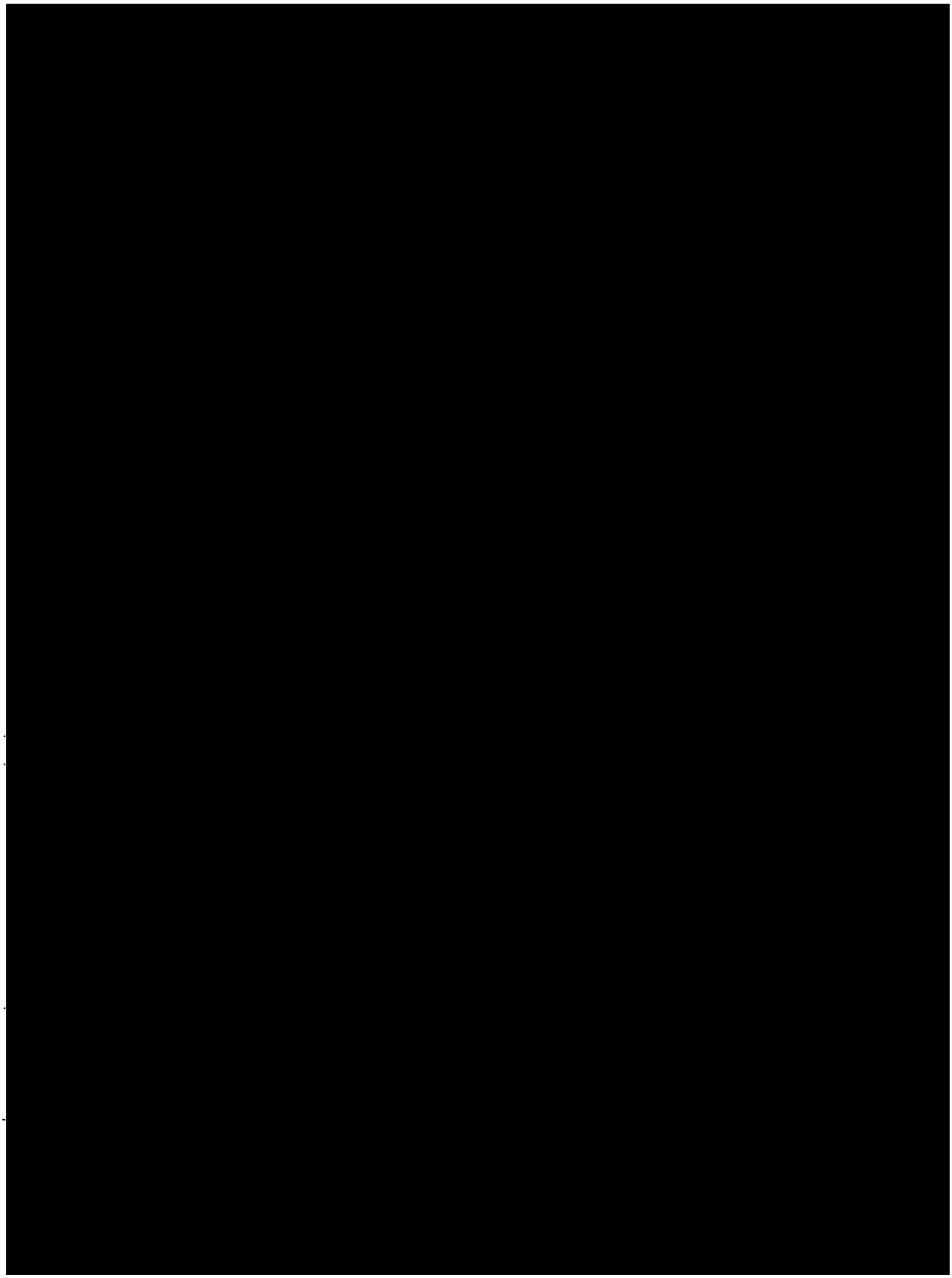
Scheduled time points (hours)		
Screening		**Anytime during the screening period**
Cycle	**Day**	**Sampling Time**
1	1	Pre-dose
1	8	Pre-dose
1	8	2h post-dose (±30 min)
1	8	4h post-dose (±30 min)
1	15	Pre-dose
1	15	2h post-dose (±30 min)
1	15	4h post-dose (±30 min)
2	1	Pre-dose
2	21	Pre-dose
2	21	2h post-dose (±30 min)
3	1	Pre-dose
3	1	2h post-dose (±30 min)
4-5	1	Pre-dose
6	1	Pre-dose
6	1	2h post-dose (±30 min)
All other cycles[a]	1	Pre-dose
9 and every 3rd cycle[b]	1	Pre-dose
9 and every 3rd cycle[b]	1	2h post-dose (+/- 30 min)
Unscheduled		As clinically indicated
EOT		Within 14 days of last dose
[redacted]		

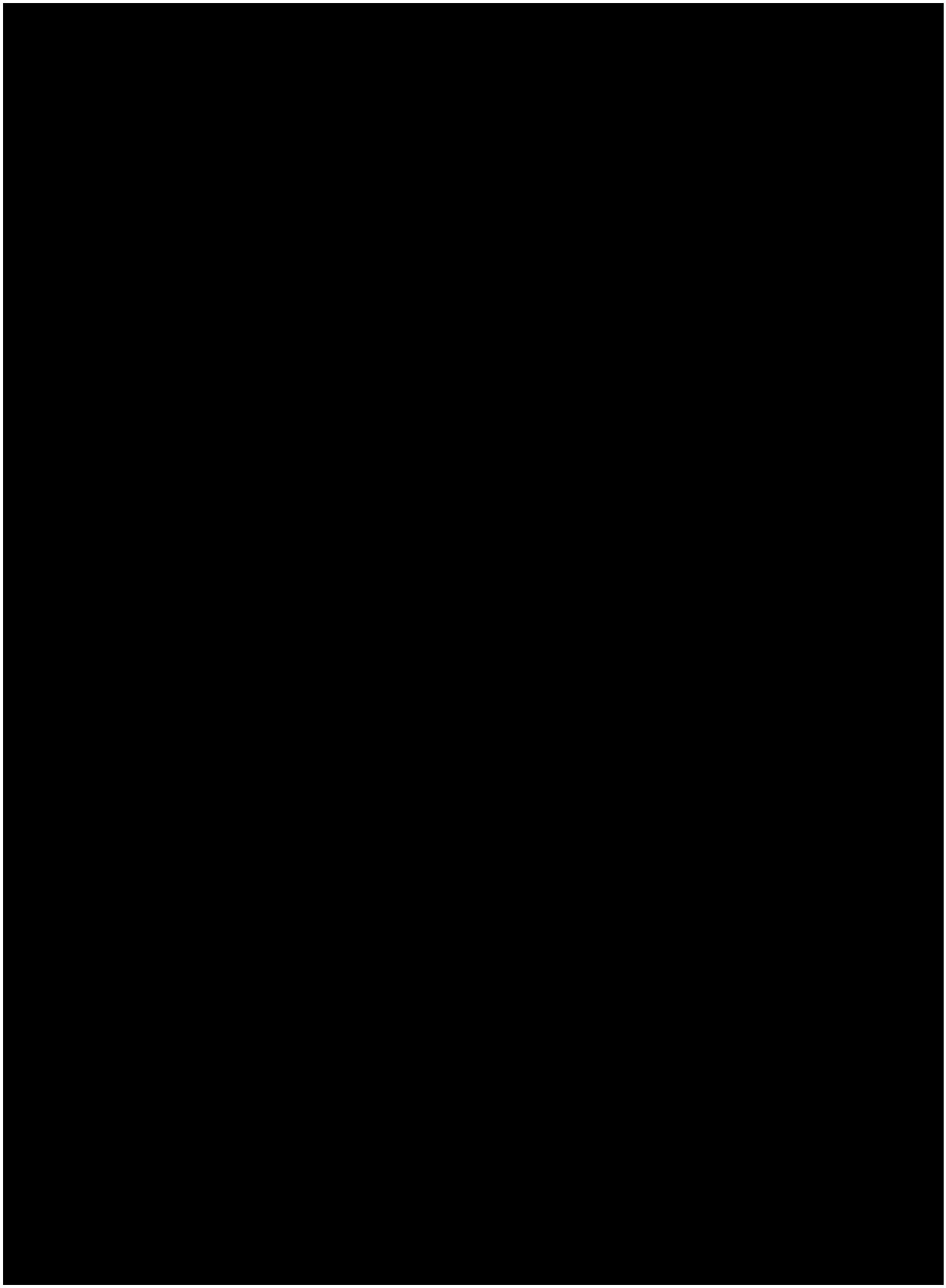
[a] Patients with QTcF ≥ 481 ms at any time prior to cycle 7;
[b]Perform pre-dose ECG on the first day of every cycle. Additionally, 2 h post-dose in every 3rd cycle (Cycle 9, 12, 15, 18 etc)

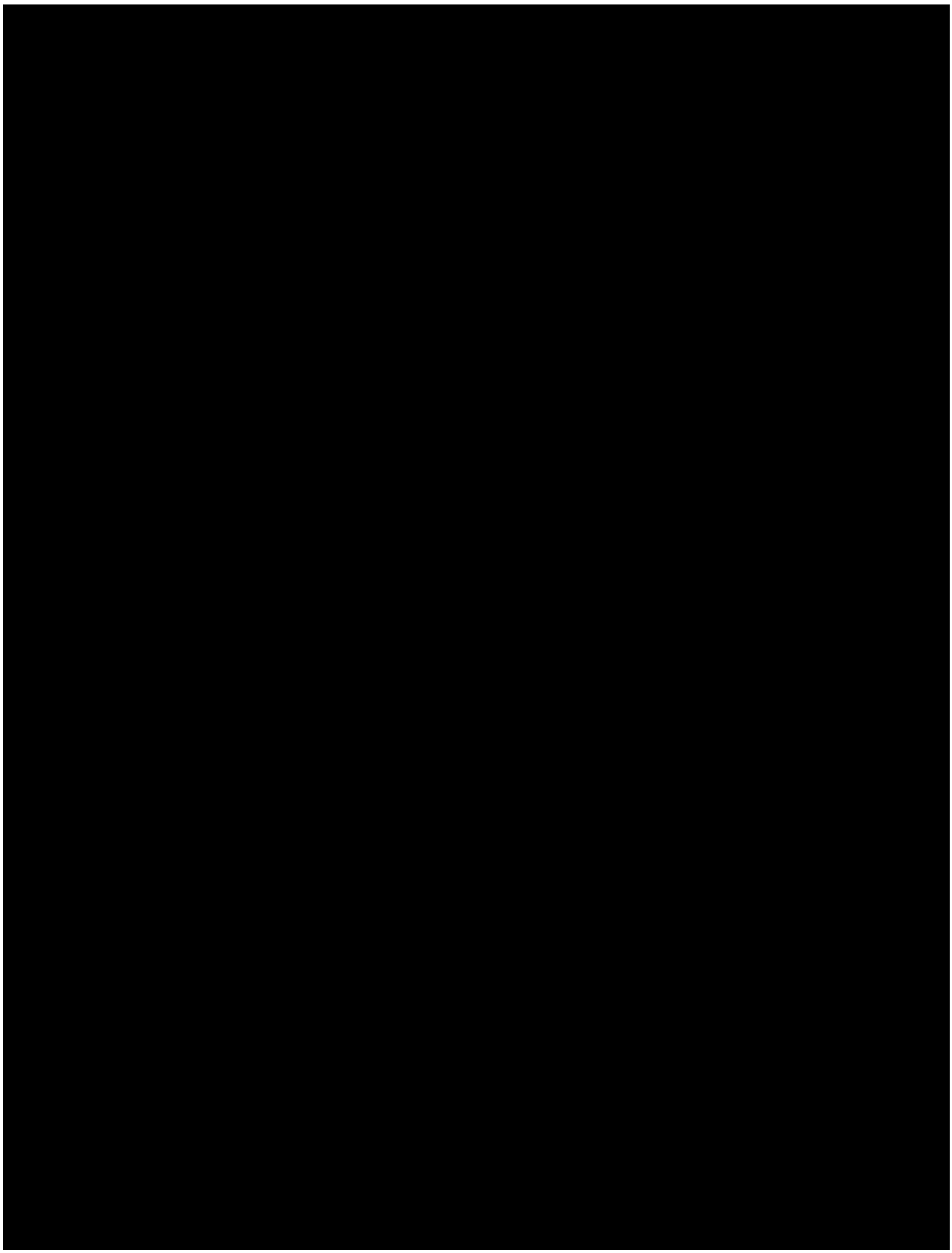
7.2.2.6.2 Cardiac imaging – ECHO (echocardiogram) or MUGA (multiple gated acquisition) scan

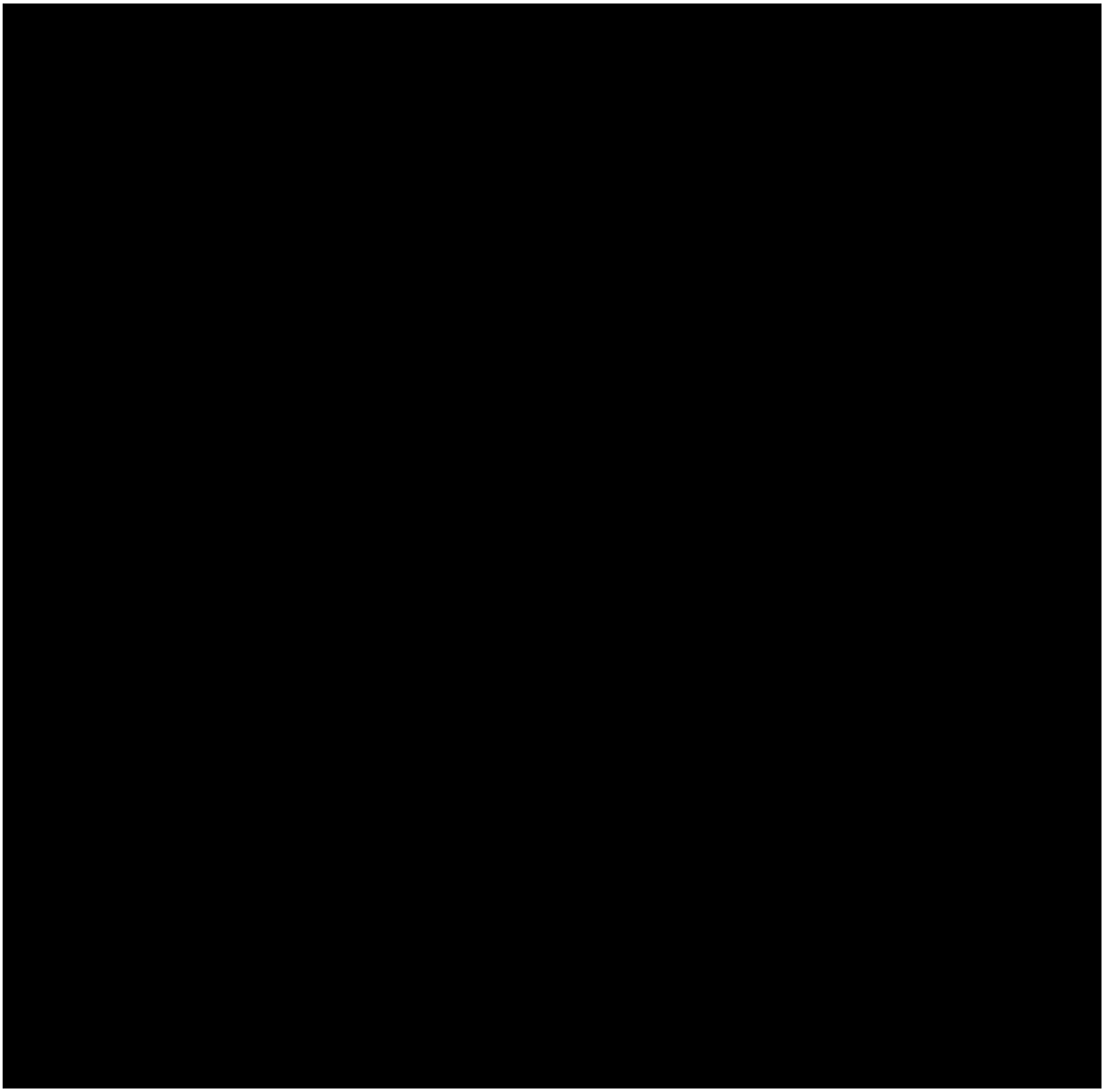
Ventricular heart function will be evaluated by ECHO or MUGA at Screening and at the EOT visits. The same imaging modality should be used throughout the study.

[redacted]









7.2.6 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 a patient's signed informed consent has been obtained.

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 (or 5 half-lives, whichever is longer) 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 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 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 or Ongoing at End of Study
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 was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a SAE is defined as in Section 8.2.

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 AE 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 (for example, as per RECIST criteria), should not be reported as a serious 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

[redacted]

progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an AE 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 CRF. 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 AE, 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 AE, should not be reported as such. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a 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 in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

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
    - 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
    - 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

For patients who sign the ICF, SAE collection starts at time of study informed consent whether the patient is a screen failure or not. 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.

SAEs considered by the investigator to be possibly related to a biopsy procedure will be indicated as such in the AE eCRF. This information will be followed up for 30 days after the biopsy procedure

Any SAEs experienced after this 30 day 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 is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to each site. 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.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. 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. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

[redacted]

8.3 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential for effective treatment of the patient. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IRT. When the investigator contacts the IRT to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Lead that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study treatment name if available, patient number and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable. However, if a mechanism is already in place to ensure that the investigator and/or back-up can always be reached in case of emergency then the procedure above is not required.

Study drug must be held if emergency unblinding is required.

An assessment will be completed by the appropriate site personnel and the CPL after an emergency unblinding to assess whether or not study drug must be discontinued and whether the patient will be eligible for crossover from placebo to LEE011, if 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 Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment for any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must 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

[redacted]

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

An independent data monitoring committee will not be formed for this phase II study. Patients will be closely monitored for safety by participating study sites and Novartis clinical study team. Teleconferences with investigators will be held for reviewing reported safety data on individual patients as necessary. The Novartis clinical study team will distribute minutes of these meetings, including a description of any potential safety signals, to all participating investigators.

8.7 Steering Committee

A Steering Committee consisting of members of the Oncology Translational Medicine Leadership Team will be formed for this study. If at any time the monitoring of the study data requires a decision to be taken on the continuation of the study, the relevant data (e.g., safety data or primary analysis and predictive probability of success (PPOS)) will be communicated to the Steering Committee for decision making purposes.

9 Data collection and management

9.1 Data confidentiality

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

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

In the event that a patient revokes authorization to collect or use PHI, the investigator and sponsor, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the patient experienced any new or worsened AEs) 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.

Prior to entering key sensitive personally identifiable information (Patient Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If

[redacted]

the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Patient Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the patient satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, 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 CRFs must be traceable to source documents in the patient's medical record. 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 CRF 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 CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (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.

[redacted] ECG data collected during the study will be reviewed and processed centrally by a specialist CRO. Tumor histology samples collected during the study will be retrospectively reviewed by a central pathologist.

Designated investigational site staff will enter the information required by the protocol into the appropriate eCRF and/or designated laboratory requisition forms. Field monitors will

[redacted]

review the eCRFs and laboratory paper requisition forms for accuracy and completeness and will instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample(s) by the field monitor or by the designated investigational site staff, and one copy will be retained at the investigational site.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or 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) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis personnel (or designated CRO). The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and the treatment codes will be unblinded and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Oncology Translational Medicine.

For EDC studies, 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

This is a multi-center, randomized, double blind (investigator and patient), placebo controlled phase II study to determine the efficacy and safety of treatment with LEE011 versus placebo in patients with progressive relapsed, refractory incurable teratoma. Patients will be randomized at a 2:1 ratio to LEE011 or placebo.

[redacted]

Data will be analyzed by Novartis and/or designated CRO. Any data analysis carried out independently by the investigator must be submitted to Novartis before publication or presentation.

It is planned that the data from participating centers in this protocol will be combined, in the final safety and efficacy analysis. Data will be summarized with respect to demographic and baseline characteristics, efficacy and safety observations and measurements and all relevant [redacted] measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data).

The primary clinical study report (CSR) will be written based on all patients' data at the time when there are approximately 23 PFS events for the primary efficacy analysis and all patients have been followed for PFS for at least 6 months or have discontinued prior to this time for disease progression or death, or have withdrawn consent to follow-up or have been lost to follow-up. Additional data for patients continuing on study or in any follow-up period past the data cutoff date for the primary CSR will be reported in a final CSR once the treatment period, safety follow-up, disease progression follow-up and survival follow-up periods have ended for all patients as described in Section 7.1.4. In the case when all patients are discontinued from study treatment to be enrolled in the LEE011 rollover clinical trial (CLEE011X2X01B), or when the study is terminated early (Section 4.4) and no CSR has already been reported, all data prior to study termination will be reported in a final CSR.

Data will be analyzed by the two treatment arms unless stated otherwise.

All data collected during the optional crossover to LEE011 from placebo will be listed separately. This data will be summarized within the planned analyses. The data will not be pooled with the data from patients receiving LEE011 from the outset of the study unless otherwise specified below. Data collected after progression on LEE011 (in the situation which a patient continues to receive the study drug due to clinical benefit) will be listed but will not be pooled in analyses with data collected prior to disease progression.

Further details of statistical analysis and reporting will be described in the RAP.

For screen failure patients the eCRF data collected (Section 7.1.1.2) will not be included in any analysis but will be reported in the CSR as separate listings.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study drug were assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment arm assigned at randomization.

The FAS2 will consist of all patients from the placebo arm who had progression per RECIST and crossed over to the LEE011 arm and received at least one dose of LEE011.

FAS will be the primary population for the analysis of efficacy endpoints.

[redacted]

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study drug.

The statement that a patient had no AEs on the AE eCRF constitutes a valid safety assessment. Patients will be classified according to treatment received, where treatment received is defined as:

- The treatment assigned if it was received at least once, or
- The first study drug received when starting therapy with study treatment if the assigned treatment was never received.

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) will consist of a subset of patients from the safety set who have an adequate tumor assessment at baseline, a follow-up tumor assessment ≥8 weeks after starting treatment (unless disease progression is observed before that time), and no major protocol deviations.

All major protocol deviations leading to exclusion from the PPS will be detailed in the RAP. Patients will be classified according to treatment received.

The PPS will define the patients used in the sensitivity analysis of the primary endpoint (Section 10.4). If the PPS and the FAS are identical, then analyses described by the PPS below will not be performed.

[redacted]

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be summarized descriptively by treatment arm for the FAS and FAS2 Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles (if appropriate), minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study Treatment

The actual dose and duration in days of the study drug as well as the dose intensity (computed as the ratio of actual dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration), will be listed and summarized by means of descriptive statistics in the clinical study report. The summary data will be presented for all study days as a single category. The FAS and FAS2 will be used.

[redacted]

10.3.2 Concomitant therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized by summarized by ATC term and treatment arm by means of contingency tables. The FAS and FAS2 will be used.

10.3.3 Compliance

Compliance to the protocol will be assessed by the number and proportion of patients with protocol deviations. These will be identified prior to database lock and will be listed and summarized by treatment arm.

10.4 Primary objective

The primary objective of the study is to assess the efficacy of LEE011 compared to placebo in patients with relapsed/refractory teratoma with recent progression

10.4.1 Variable

The primary endpoint of the study is PFS, defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS will be assessed via the local radiology assessment according to RECIST v1.1. If a patient has not had an event, PFS will be censored at the date of the last adequate tumor evaluation (Appendix 1).

10.4.2 Statistical hypothesis, model, and method of analysis

The primary efficacy endpoint, PFS will be formally analyzed at the final analysis time point (Section 10.8).

If the estimated hazard ratio at the final analysis is 0.48 or below, it will be considered as evidence of clinically relevant efficacy of LEE011 over placebo.

To claim the superiority of LEE011 to placebo, both criteria below need to be satisfied:

- The log-rank test p-value (one-sided) is below 0.05
- The estimated HR is 0.48 or smaller

The distribution of PFS between the two treatment arms will be compared using the log-rank test. The HR will be estimated using the Cox proportional hazard regression model. The estimated HR and related two-sided 90% confidence interval (CI) will be provided.

In addition, PFS will be analyzed using Kaplan-Meier estimates (Kaplan and Meier 1958) (including graphical representation) with two-sided 90% confidence interval for median survival and survival probabilities for specific time-points (3, 6, 9, 12, 15, 18, 21 and 24 months) will be presented for each treatment arm.

The final primary analysis of PFS will be conducted when a total of 23 PFS events are observed (See Section 10.8 for sample size calculation) and patients have been followed for PFS for at least 6 months or have discontinued prior to this time for disease progression or death, or have withdrawn consent to follow-up or have been lost to follow-up. This event number is associated with 80% power when the underlying hazard ratio is 0.33

[redacted]

(corresponding to 2 months median PFS for placebo versus 6 months median PFS for LEE011).

10.4.3 Handling of missing values/censoring/ discontinuations

For the analysis of PFS, patients without documented disease progression or death are censored at the time of last valid tumor assessment documenting non-progression (one of complete response, partial response, or stable disease). Patients without any valid post-baseline tumor assessment response (one of CR, PR, SD, or PD) will be censored on the randomization date. Patients who have a PFS event (progression or death) after two or more consecutive missing assessments from the last valid tumor assessment will be censored on the last valid tumor assessment (or on the date of randomization among those without a post-baseline tumor assessment).

For patients who have a PFS event (progression or death) after a single missing or non-adequate tumor assessment, actual date of event will be used.

For patients who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event with the appropriate censoring as described in the above paragraph. The reason for discontinuation from study treatment will be summarized and listed.

Other missing data will simply be noted as missing on appropriate tables/listing.

10.4.4 Supportive analyses

The primary analyses described above will also be repeated using the PPS if it differs from the FAS.

10.5 Secondary objectives

Please refer to Table 3-1 for the secondary objectives. The following subsections describe the analyses of related secondary objectives.

10.5.1 Key secondary objective(s)

None

10.5.2 Other secondary efficacy objectives

A secondary objective is to further assess the efficacy of LEE011 compared with placebo. The evaluations of tumor responses will be based on local investigator assessment according to RECIST v1.1.

The following endpoints and analyses will be used to further assess the efficacy:

- Overall Survival (OS), defined as the time from date of randomization of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.
- Best Overall Response (BOR), defined as the best response recorded from the start of the treatment until disease progression/recurrence. Confirmation of complete and partial responses must be made at least 4 weeks apart.

[redacted]

- Overall Response Rate (ORR), defined as the proportion of patients with a best overall response of CR or PR.
- Duration of Response (DOR), defined for responder as the time between the date of first documented response (CR or PR) and the date of first documented progression or death due to underlying cancer. If progression or death due to underlying cancer has not occurred, then the patient is censored at the date of last adequate tumor assessment.
- Disease Control Rate (DCR), defined as the proportion of patients with a best overall response of CR or PR or SD.

CT/MRI assessments will be used for all efficacy assessments of anti-tumor activity on study.

BOR, ORR, and DCR at 4 months will be summarized as point estimate and corresponding 95% exact confidence interval according to Clopper-Pearson method (Clopper and Pearson 1934). The Kaplan-Meier plots for DOR will also be produced and the median DOR will be estimated for all patients who achieve a response of CR or PR.

OS will be analyzed using Kaplan-Meier estimates (including graphical representation) with confidence intervals of median survival for each treatment arm. The OS rate at 12 months and related 95% CI will be presented for each treatment arm. In addition, median OS and related 95% CI will be presented for each treatment arm.

10.5.3 Safety objectives

Another secondary objective is to characterize the safety and tolerability of LEE011 compared to placebo. Incidence and severity of AEs and SAEs, changes in laboratory values, electrocardiograms and vital signs will be used to assess the safety of LEE011 compared to placebo. Dose interruptions and changes will be used to assess the tolerability of LEE011 compared to placebo.

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the Safety Set will be used. All listings and tables will be presented by treatment arm with patients classified according to treatment received.

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study drug
2. on-treatment period: from day of first dose of study drug to 30 days after last dose of study drug
3. post-treatment period: starting at day 31 after last dose of study drug.

10.5.3.2 Adverse events (AEs)

All AEs recorded during the study will be summarized. The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by primary system organ class, severity based on CTCAE version 4.03, type of adverse event, and relationship to treatment arm. Any other information collected (e.g., start/end dates and duration of adverse event, severity or relatedness to study medication) will be listed as appropriate. If applicable, these will be specified in the RAP.

[redacted]

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

If the lower limits of normal ranges used in CTCAE definitions are missing, then they have to be replaced by clinical meaningful limit. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- frequency table for newly occurring on-treatment CTCAE Grade 3 or 4 toxicities
- 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

In addition to the above mentioned tables and listings, [redacted]

10.5.3.4 Other safety data

Any other safety information collected will be listed and notable values will be flagged. Any statistical tests performed to explore the data will be detailed in the RAP modules. Additionally, the following outputs will be produced:

ECG

Definitions of notably abnormal resulted detailed in the RAP.

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality

Cardiac Imaging

- Left ventricular heart function evaluations will be summarized and listed.

Vital signs

Definitions of notably abnormal results detailed in the RAP.

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points

[redacted]

10.5.3.5 Tolerability

The tolerability of the study drug will be assessed by summarizing the number of dose interruptions or changes. The reason for dose interruption and dose reduction and dose change will be listed by patient and summarized by arm.

Cumulative dose, dose intensity and relative dose intensity of LEE011 and placebo will be listed by patient and summarized. Categories for relative dose intensity of LEE011 and placebo will be specified as < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of patients within each category will be presented.

[redacted]

[redacted]

[redacted]

10.7 Interim analysis

No formal interim analyses are planned.

10.8 Sample size calculation

The sample size is determined based on the primary efficacy endpoint PFS.

Under the hypothesis in Section 10.4.2, 23 PFS events are required for a one-sided type I error of $\alpha = 0.05$ and 80% power to reject H_0 when the true log hazard ratio is HR = 0.33 using a log-rank test. It is assumed the median PFS for placebo is 2 months and median PFS for LEE011 is 6 months. Under an exponential survival model, a 3-fold increase of PFS (or a 66.7% reduction in the hazard rate) is expected on treatment of LEE011 against placebo.

Patients will be randomized in a 2:1 ratio of LEE011 to placebo. It is assumed that the anticipated patient accrual rate will remain constant at 1.5 patients per month for the entire study. To observe 23 PFS events by the end of study, 36 patients are required. Assuming a 15% drop-out rate, a total of approximately 42 patients will be randomized.

The expected study duration is approximately 24 months (completed study) (inflated by 3 months in order to take into account for a 15% drop-out rate).

The sample size calculation was performed using software package EAST 5.4

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 ICH Harmonized Tripartite Guidelines for Good Clinical Practice, 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.

[redacted]

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. 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 patient's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH 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/REB approval.

Women of child bearing potential 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. If there is any question that the patient will not reliably comply, they should not be entered in the study.

[redacted]

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 4.4.

[redacted]

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 patients. 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, patients' 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 patient 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 case report form (CRF) 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 CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

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.

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.

[redacted]

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 are 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 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 at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

[redacted]

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[redacted]

14 Appendices

14.1 Appendix 1 – Guidelines for response duration of overall response, TTF, TTP, progression free survival and overall survival (based on RECIST v1.1) harmonization of efficacy analysis of solid tumor studies

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Release date:	29-Nov-2011
Authors (Version 3.1):	[redacted]
Authors (Version 3):	[redacted]
Authors (Version 2):	[redacted]
Authors (Version 1):	[redacted]

Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
LPLV	Last patient last visit
MRI	Magnetic resonance imaging
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

[redacted]

14.1.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 14.1.2 and the definition of best response in Section 14.1.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.1.18 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 14.1.28 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

14.1.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

14.1.3 Definitions

14.1.4 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 14.1.26.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

[redacted]

- **Cystic lesions:**
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

14.1.5 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.1.26.

14.1.6 Methods of tumor measurement – general guidelines

In this document, the term "contrast" refers to intravenous (i.v) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm 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 baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication 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.

[redacted]

- 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, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline with 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 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 CT 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.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions

[redacted]

and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).

- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.1.7 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions**: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target:** Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 14.1.4**.**
- **Nodal target**: See Section 14.1.4

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- Non-target lesions: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

14.1.8 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 14-1) and non-target lesions (Table 14-2) identified at baseline. These

[redacted]

evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-3) as well as the presence or absence of new lesions.

14.1.9 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

14.1.10 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are patient to substantial “partial volume” effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

14.1.11 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a “non-zero size” will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

[redacted]

14.1.12 Determination of target lesion response

Table 14-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of 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[2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

1. SOD for CR may not be zero when nodal lesions are part of target lesions
2. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
3. Methodology change (see Section 14.1.6).

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However,

[redacted]

in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.

- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0" mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

[redacted]

14.1.13 Determination of non-target lesion response

Table 14-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

1. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.1.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.1.14 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- 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 (see Section 14.1.15).
- 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. **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.1.6.

14.1.15 Evaluation of overall lesion 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 shown below in Table 14-3.

Table 14-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK1
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

1. This overall lesion response also applies when no non-target lesions are identified at baseline.
2. Once confirmed PR was achieved, all these assessments are considered PR.
3. As defined in Section 14.1.8

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

14.1.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.1.26 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

[redacted]

14.1.17 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status

[redacted]

other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD.

[redacted]

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of (Dent and Zee 2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

14.1.18 Time to event variables

14.1.19 Progression free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

14.1.20 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

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

14.1.21 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

[redacted]

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

14.1.22 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

14.1.23 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by (Morgan 1988)

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in (Ellis et al 2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

[redacted]

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

14.1.24 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.1.23. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

14.1.25 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the

[redacted]

assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

Start dates

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.1.25).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

14.1.26 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires

[redacted]

special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-4.

Table 14-4 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD1	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 14.1.8.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

14.1.27 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

[redacted]

Based on definitions outlined in Section 14.1.25, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 14-5 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after exactly one missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after two or more missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

1. =Definitions can be found in Section 14.1.25.
2. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.25.
3. =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.
- In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.
- **Situation E: Treatment discontinuation due to 'Disease progression' without documented progression**: By default, option (1) is used for situation E as patients

[redacted]

without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

- **Situation F: New cancer therapy given**: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.
- **Additional suggestions for sensitivity analyses**
- Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:
- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.
- In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

14.1.28 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

14.1.29 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

14.1.30 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee 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.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

[redacted]

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Patient/parent/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)
- Transfer to another Novartis clinical study that continues to provide LEE011 (e.g. CLEE011X2X01B)

14.1.31 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Patient/parent/guardian decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor
- Transfer to another Novartis clinical study that continues to provide LEE011 (e.g. CLEE011X2X01B)

14.1.32 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK)

[redacted]

and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

14.1.33 Programming rules

The following should be used for programming of efficacy results:

14.1.34 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

14.1.35 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 14.1.25). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

14.1.36 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

[redacted]

14.1.37 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

14.1.38 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

14.1.39 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-5)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 14.1.25. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason "Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

[redacted]

14.1.40 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47

Ellis S, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465

FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005

FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18

Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16

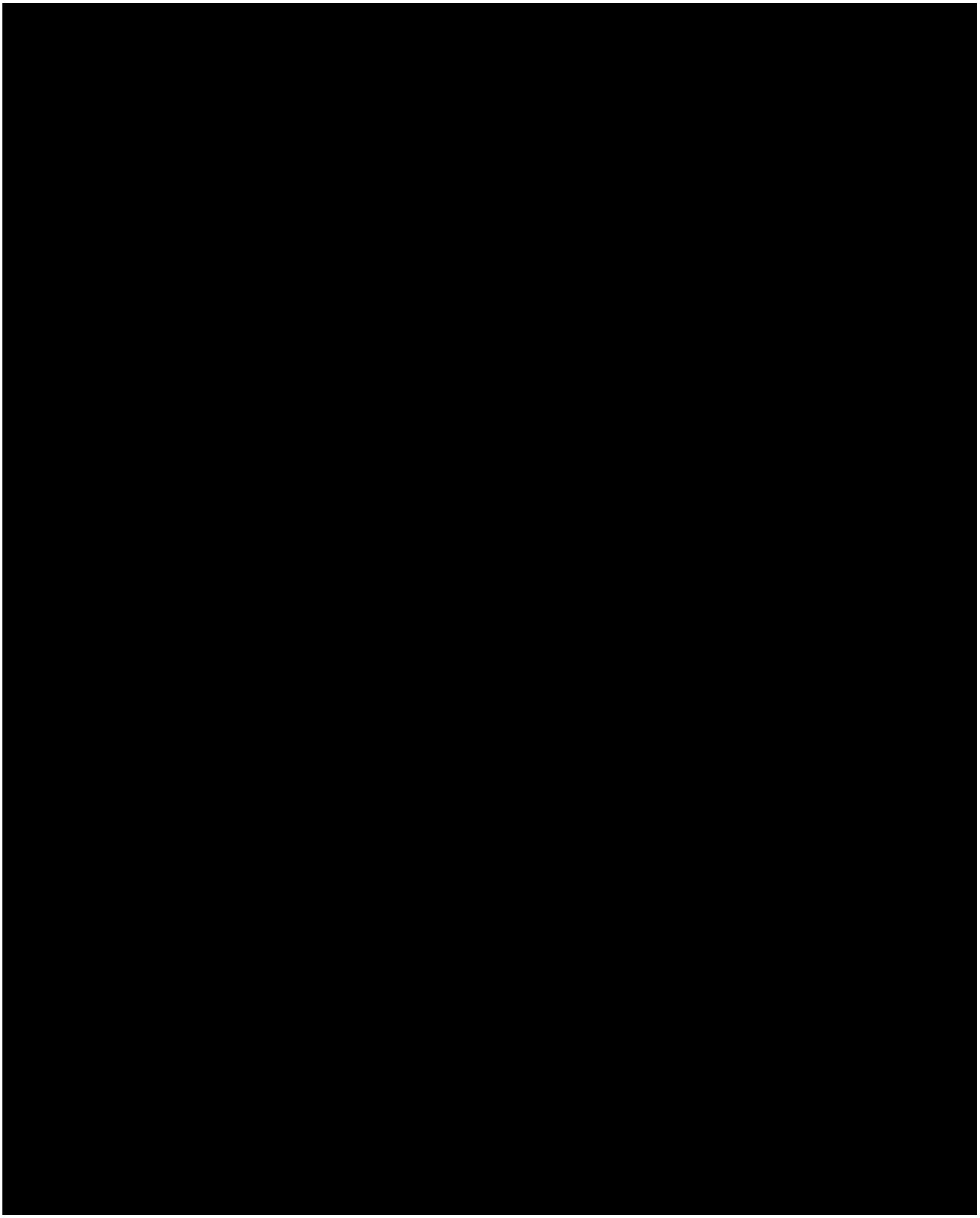
[redacted]

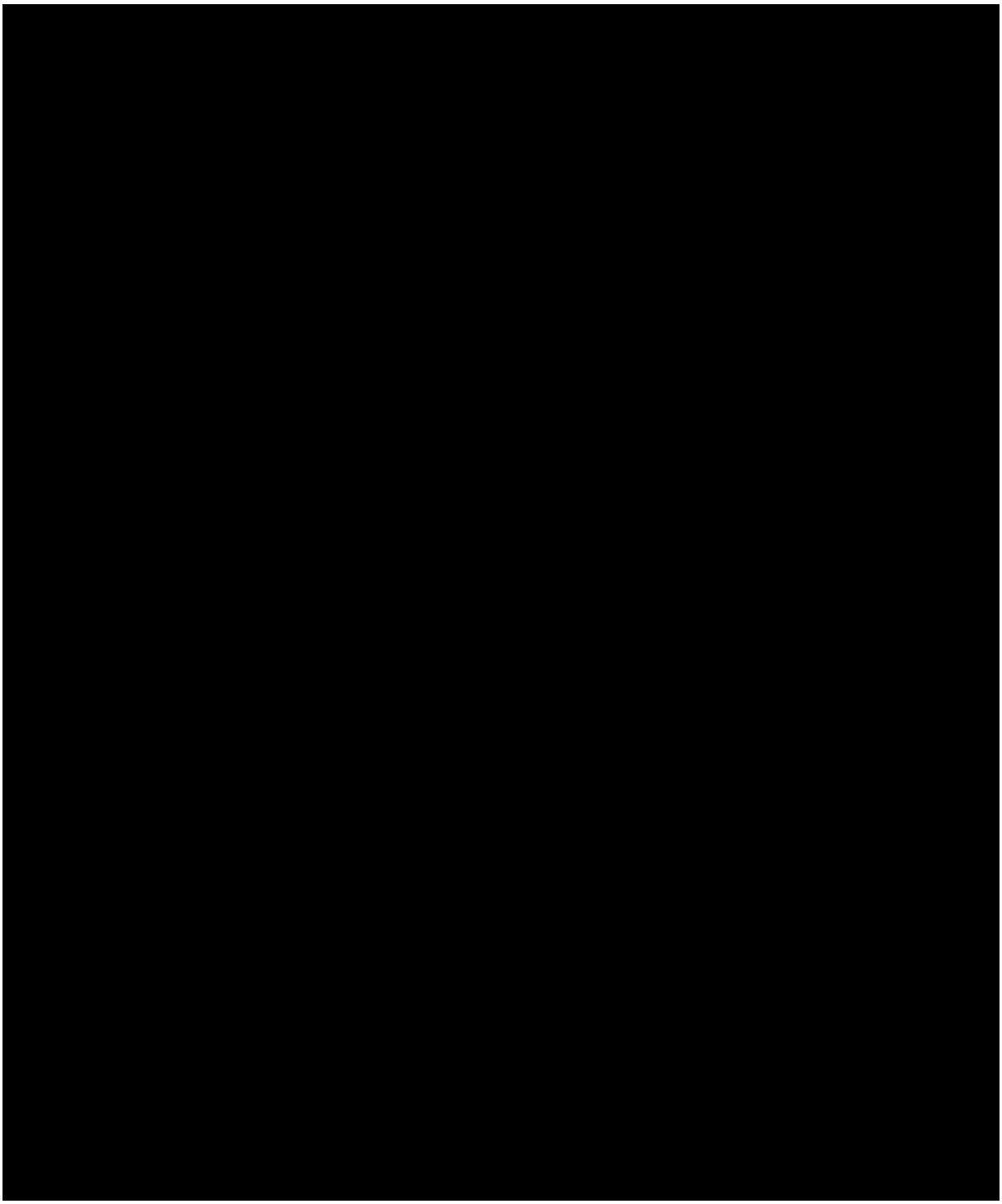
14.2 Appendix 2 - ECOG/WHO performance status scale

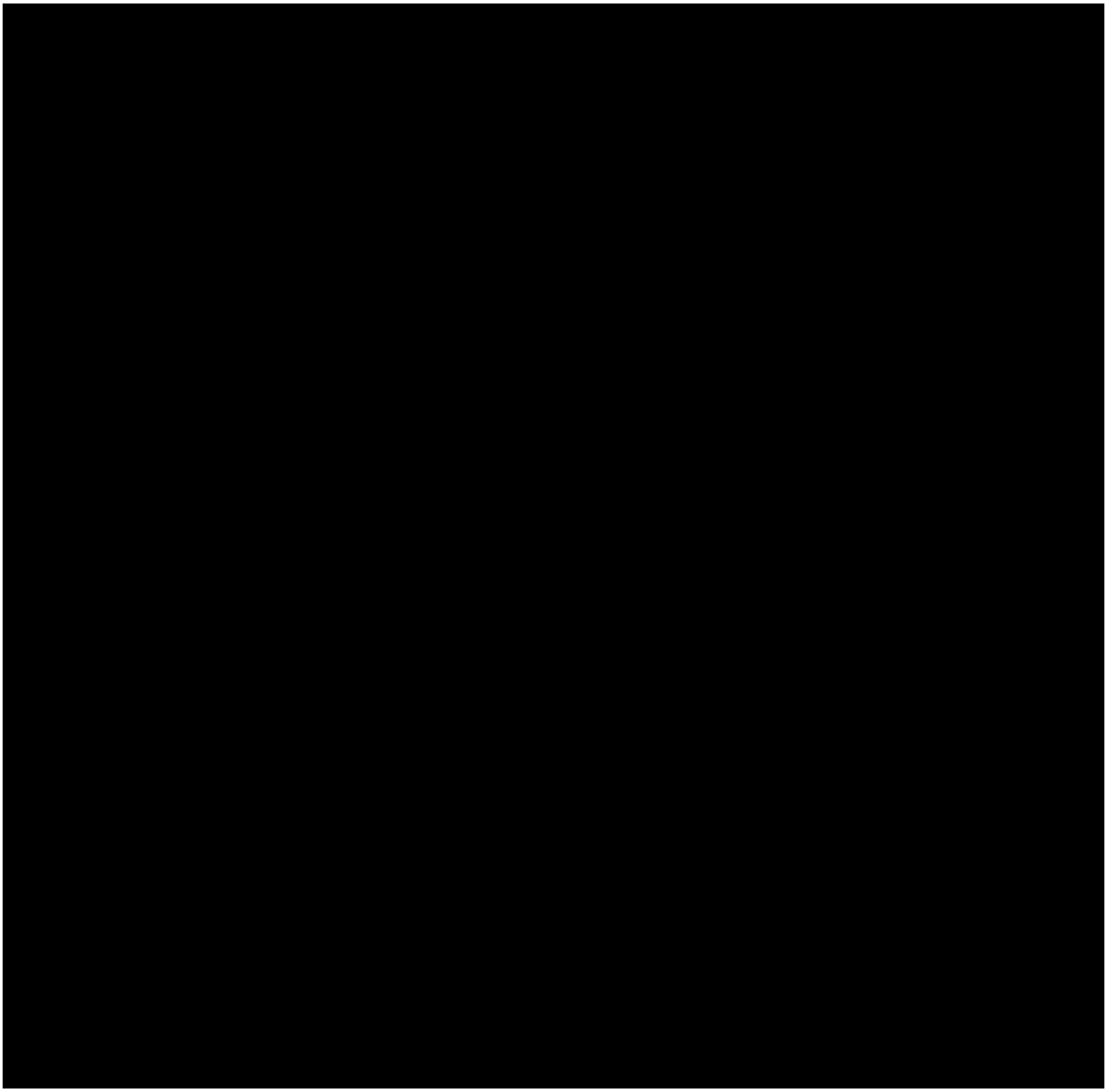
Table 14-6 ECOG performance status

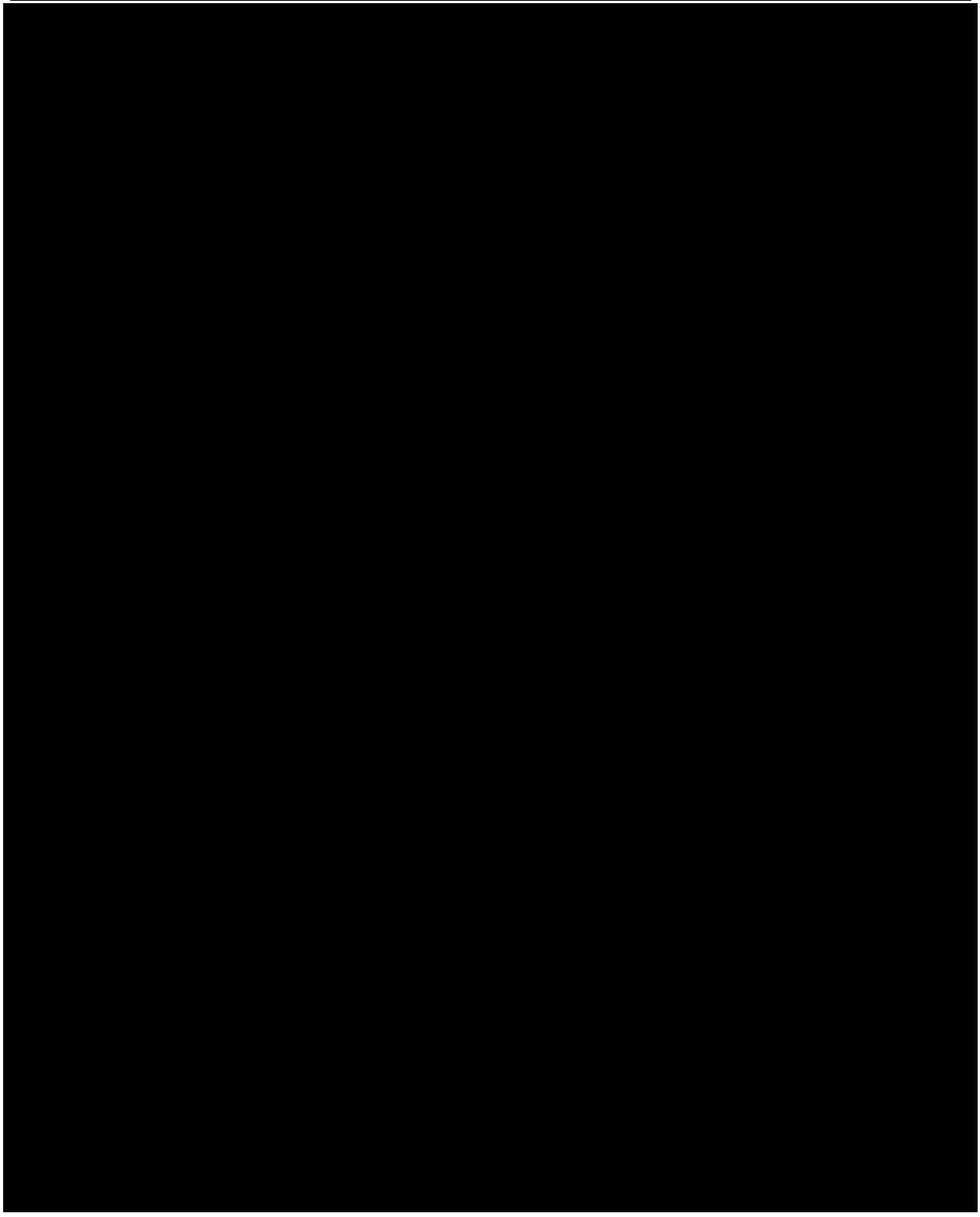
Grade	ECOG status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable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

[redacted]









14.4 Appendix - 4 Prohibited 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. Administration of study drug could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or LEE011.

The following lists are based on the Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: 29 Oct 2012), which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database. These lists are not comprehensive and are only meant to be used as a guide. Please contact the medical monitor with any questions.

14.4.1 Prohibited medications

Table 14-7 List of prohibited medications during LEE011 treatment

Category	Drug Name
Strong CYP3A Inhibitors	boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, sequinavir/ritonavir, telaprevir, telithromycin, voriconazole, indinavir/ritonavir, tipranoavir/ritonavir, cobicistat, troleandomycin, danoprevir/ritonavir, eltegravir/ritonavir
Strong CYP3A Inducers	avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort[2], rifabutin, phenobarbital, mitotane, enzalutamide
CYP3A substrates with NTI[1]	quinidine, astemizole, terfanadine, cyclosporine, sirolimus, tacrolimus, diergotamine, cisapride, ergotamine, pimozide, alfentanil, fentanyl, thioridazine, diergotamine, dihydroergotamine, ergotamine
Medications that carry a strong risk for QT prolongation/TdP	amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cisapride, citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone, dronedarone, droperidol, erythromycin, escitalopram, flecainide, grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl, mesoridazinet), methadone, moxifloxacin, ondansetron, pentamidine, pimozide, probucol, procainamide, quinidine, sevoflurane, sotalol, sparfloxacin, sulpiride, terfenadine, thioridazine, vandetanib
Other investigational and antineoplastic therapies	Other investigational anticancer therapies including chemotherapy, biologic or radiation therapy, and surgery must not be used while the patient is on the study. If such agents are required for a patient then the patient must be discontinued from the study.
Herbal medications	Herbal preparations/medications are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, 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.
Hematopoietic growth factors	Hematopoietic growth factors (e.g. erythropoietins, G-colony stimulating factor (CSF) and GM-CSF) are not to be administered for primary prophylaxis. Use of these drugs should be reserved to patients with severe neutropenia and anemia as per the labeling of these agents or as dictated by local practice (see also the guidelines established by the American Society of Clinical Oncology (ASCO)).
Palliative radiotherapy	Local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture

[redacted]

Category	Drug Name
	may be carried out if required. Whenever possible, these patients should have a tumor assessment of the lesion(s) before they actually receive the radiotherapy in order to rule out progression of disease. In case of PD, patients should discontinue treatment. No dose modification of study treatment is needed during radiotherapy.
[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 P-gp inducer	

Table 14-8 List of medications to be used with caution[1] during LEE011 treatment

Category	Drug Name
Moderate CYP3A Inhibitors	amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, nilotinib imatinib, tofisopam, cyclosporin, ciprofloxacin, verapamil, dronedarone, crizotinib, casopitant, amprenavir, atazanavir/ritonavir, duranavir, netupitant, schisandra sphenanthera[4] , cimetidine, lomitapide
Moderate CYP3A Inducers	bosentan, efavirenz, etravirine, modafinil, nafcillin, genistein, ritonavir, thioridazine, tipranavir, semagacestat, talviraline, lopinavir, lersivirine
Sensitive CYP3A Substrates[2]	alpha-dihydroergocryptine, alfentanil, almorexant, aplaviroc, aprepitant, atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, conivaptan, danoprevir, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, elvitegravir, eplerenone, everolimus, felodipine, fluticasone, ibrutinib, indinavir, ivacaftor, levomethadyl, lomitapide, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simeprevir, simvastatin, ticagrelor, terfenadine, ticagrelor, tilidine,tipranavir, tolvaptan, triazolam, vardenafil, vicriviroc, voclosporin
Known inhibitors of BSEP	atorvastatin, cerivastatin, cyclosporine, glyburide, reserpine, rifampicin, troglitazone, valinomycin,
Sensitive substrates of MATE1 and OCT2	acyclovir, cimetidine, ganciclovir, fexofenadine[1], metformin[1], procainamide, topotecan, glycopyrronium[1], topotecan, 6-beta-hydroxycortisol, amantadine, carboplatin, cisplatin, histamine, lamivudine, linagliptin, metformin, oxyplatin, oxybutynin, phenformin, picoplatin, pramsorafenib, tropisetron, trospium, varenicline, umeclidinium
Sensitive substrates of BCRP	rosuvastatin and sulfasalazine
Medications that carry a possible risk for QT prolongation	alfuzosin, apomorphine, aripiprazole, atazanavir, bedaquiline, bortezomib, bosutinib, clozapine, crizotinib, dabrafenib, dasatinib, dexmedetomidine, dihydroartemisinin+piperaquine, dolasetron, eribulin, famotidine, felbamate, fingolimod, foscarnet, fosphenytoin, gatifloxacin, gemifloxacin, granisetron, iloperidone, isradipine, lapatinib, lithium, mifepristone, mirabegron, mirtazapine, moexipril/hctz, nicardipine, nilotinib, norfloxacin, ofloxacin, olanzapine, oxytocin, paliperidone, pasireotide, pazopanib, perflutren lipid microspheres, pipamperone, promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin, saquinavir, sertindole, sorafenib, sunitinib, tacrolimus, tamoxifen, telavancin, telithromycin, tetrabenazine, tizanidine, tolterodine, toremifene, vardenafil, vemurafenib, venlafaxine, vorinostat, ziprasidone
[1]Any drug mentioned in the above list should be contraindicated if they are excluded based on any other exclusion criteria as specified in of the Study Protocol or listed in Table 14-1 [2]Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when coadministered 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).	

[redacted]