A phase II study of LEE011 (Ribociclib) in patients with advanced neuroendocrine tumors of foregut origin

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List of abbreviations

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BID	bis in diem/twice a day
CK	Creatine Phosphokinase
Cmax	Maximum (peak) concentration of drug
Cmin	Minimum (peak) concentration of drug
CR	Complete Response
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria Adverse Events
DLT	Dose Limiting Toxicity
DoR	Duration of tumor Response
DMC	Data Monitoring Committee
DS&E	Drug Safety and Epidemiology
EC	Ethics committee
ECG	Electrocardiogram
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
FAS	Full Analysis Set
FFPE	Formalin-Fixed Paraffin-Embedded
GCP	Good Clinical Practice
Hgb	Hemoglobin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LLOQ	Lower limit of quantification
PD	Pharmacodynamics
PFS	Progression Free Survival
PK	Pharmacokinetics
QD	Quaque die/ once a day
REB	Research Ethics Board
RECIST	Response Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum glutamic oxaloacetic transaminase; aspartate aminotransferase; AST
SGPT	Serum glutamic pyruvic transaminase; alanine aminotransferase; ALT
TK	Toxicokinetics

WBC	White Blood cells
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being testing in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/healthy volunteer who enrolls in the study
Phase	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	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 treatment 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

1 Background

1.1 Overview of Neuroendocrine Tumors

Neuroendocrine tumors (NET) are thought to arise from cells at the interface of nerves and endocrine glands. While slow growing, these are nonetheless incurable and lethal when advanced. The incidence of these tumors is also steadily increasing. The traditional classification of these tumors is anatomical, based on site of origin into foregut, midgut and hindgut NETs. Foregut NETs include thymic, bronchopulmonary, gastric, duodenal and pancreatic NETs. Treatment options for metastatic pancreatic NETs (PNETs) continue to be limited as detailed below. Furthermore, treatment options for non-pancreatic metastatic foregut carcinoid tumors are severely limited with no FDA approved cytotoxic or targeted agents currently [1].

The phase III, randomized, double-blind, placebo controlled study of lanreotide in patients with gastroenteropancreatic NETs (GEP-NETs) randomized 204 patients with advanced, non-functioning, SSA naive GEP-NETs (45% were PNETs) with Ki-67 < 10% to lanreotide autogel 120 mg or placebo every 4 weeks for 96 weeks or until progressive disease or death. The primary endpoint was progression free survival (PFS). Secondary end points included percentage of patients without disease progression at weeks 48 and 96 and overall survival. At two years of treatment, median PFS was not reached with lanreotide vs 18 months with placebo (hazard ratio, HR 0.47; 95% CI 0.30-0.73; p = 0.0002). At end of 2 years of treatment, 62% of lanreotide treated patients vs 22% of placebo treated patients had not progressed or died. Very few serious treatment-related adverse events were noted [2].

The prospective, international, multicenter, randomized, placebo-controlled phase III RADIANT-3 trial randomized 410 patients with progressing low- or intermediate grade advanced PNET to everolimus 10 mg daily plus best supportive care (BSC) or placebo plus BSC. The primary endpoint was PFS. Treatment with everolimus demonstrated a 6.4 months prolongation of median PFS as assessed by the local investigators (11 months vs 4.6 months, HR, 0.35; 95% CI, 0.27-0.45; p < 0.0001) [3].

Sunitinib is an oral multi-tyrosine kinase vascular endothelial growth factor receptor inhibitor and was evaluated in a phase III prospective, multicenter, international, double-blind placebo controlled study of patients with advanced, well-differentiated PNETs who were randomized to best supportive care vs sunitinib 37.5 mg daily. The primary endpoint was PFS. The study was designed to enroll 340 patients but was terminated after 171 patients were accrued due to an unplanned interim analysis that showed more adverse events in the placebo arm. At the final analysis, PFS in the sunitinib arm was 11.4 months vs 5.5 months with placebo (HR 0.42; 95% CI 0.26 – 0.66; p < 0.001) [4].

The aim of this study is to evaluate the response rate of LEE011 in patients with metastatic foregut neuroendocrine tumors.

1.2 Overview of the G1 to S phase transition in mammalian cells

Normal mammalian cells proliferate in response to extracellular signals by transitioning through a series of tightly controlled phases that culminate in cell division. The commitment to transition from G1 to S phase and the initiation of cell cycle progression is regulated by the retinoblastoma protein (pRb). In the absence of appropriate growth stimuli, pRb, in its unphosphorylated state, binds and inhibits the activity of the E2F family of transcription factors, preventing these proteins from activating the genes required for S phase transition [5]. Upon mitogen stimulation, signaling through pathways such as the MAPK and PI3K pathways increases the abundance of D-cyclins, which bind and activate cyclin-dependent kinases (CDKs) 4 and 6 (CDK4/6). Cyclin D-bound CDK4/6 then phosphorylates the pRb protein to deactivate it and release bound E2F. Once freed, E2F activates S phase-specific genes in order to start cell cycle progression. Full deactivation of pRb requires its sequential phosphorylation at different sites by both cyclin D-CDK4/6 and cyclin E-CDK2. The phosphorylation events mediated by CDK4/6 are prerequisites for those catalyzed by CDK2 [6]. The kinase activity of CDK4/6 is in turn inhibited by p16, encoded by the INK4a gene [5, 7]. The CIP/KIP proteins, inhibitors of cyclin E-CDK2, also bind to the cyclin D-CDK4/6 complex, and this results in further activation of CDK2 by sequestering CIP/KIP proteins from their target [8]. Cyclin D-CDK4/6 is therefore a key enzyme complex that regulates the G1 to S phase transition.

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

The D-cyclin-CDK4/6-INK4a-pRb pathway is universally disrupted in cancer to favor cell proliferation. Eighty percent of human neoplasms maintain functional pRb but harbor aberrations that increase the activity of CDK4/6 to effectively inactivate pRb function. These aberrations include genetic or epigenetic changes that directly increase the kinase activity of CDK4/6 or defects that activate the upstream regulators [5, 9]. One of the most common events is the inactivation of p16 via mutations, deletion and epigenetic silencing. p16 inactivation is frequently observed in a significant portion of non-small cell lung cancer (NSCLC), melanoma, pancreatic cancer and mesothelioma [10-13]. Moreover, a specific mutation of the CDK4 gene (CDKR24C), that confers resistance to p16 binding, has been shown to play a causal role in rare cases of familial melanoma, suggesting that unchecked CDK4 activity is a key event in these cancers [14].

Translocations of the genes encoding D-cyclins to the immunoglobulin heavy chain locus are found in a majority of mantle cell lymphomas (MCLs) and in many cases of multiple myeloma [15]. These translocations lead to constitutive expression of D-cyclins, which result in enhanced CDK4/6 kinase activity and unchecked cell proliferation [16]. Amplification of cyclin D1 and overexpression of the protein have also been reported in approximately 50% of squamous cell esophageal cancers [17] and in 20-30% of breast cancers [18, 19], suggesting that activation of this pathway may play a role in the growth of these tumors. Furthermore, many of the receptor-mediated growth pathways that are activated in human cancers increase D-cyclin transcription and expression to drive cell proliferation. In mouse breast cancers driven by activated Ras or Her2/Neu oncogenes, cyclin D1 and CDK4 have been shown to be necessary for the tumorigenic phenotype in both initiation and maintenance phases, demonstrating that Cyclin-D1/CDK4 is the key effector enzyme complex for Ras- or Her2/Neu-driven cancers [20, 21]. Other activating aberrations of mitogen pathways such as V600E B-Raf in the MAPK pathway and PTEN deletions in the PI3K pathway also increase D-cyclins to achieve unchecked proliferation, suggesting that CDK4/6 may also be crucial for the cancers bearing these alterations [22, 23]. Finally, the genes encoding CDK4 and 6 are amplified in a subset of human neoplasms. The CDK4 gene is amplified in 100% of liposarcomas along with the MDM2 gene, while CDK6 is frequently amplified in T-lymphoblastic lymphoma and/or acute lymphoblastic leukemia [24].

1.4 LEE011

1.4.1 Overview of LEE011

LEE011 is an orally bioavailable, small molecule inhibitor of CDK4/6. LEE011 exhibits highly specific inhibitory activity against CDK4/cyclinD1 and CDK6/cylinD3 complexes, with concentration resulting in 50% inhibition (IC50) values of 10 nM and 39 nM, respectively, in isolated enzyme assays. It is inactive against the majority of other kinases. LEE011 is currently being tested in a first-in-human clinical study [CLEE011X2101] in adult patients with refractory cancer.

Pharmacology of LEE011

LEE011 inhibits the growth of many tumor cell types *in vitro* and *in vivo* including ER+ breast cancer. In a panel of human breast cancer cell lines, dose-dependent inhibition of proliferation was observed in ER+ breast cancer cell lines, with IC50 < 1μM being observed for most ER+ breast cancer lines. Regardless of the various genetic aberrations that may be present in the cancer cells, the anti-tumor activity of LEE011 requires the presence of functional retinoblastoma protein (Rb).

Nonclinical pharmacokinetics and metabolism of LEE011

Four different species were used to investigate the pharmacokinetics (PK) of LEE011: mouse, rat, dog and monkey. The absorption of LEE011 after oral administration was moderate for rats (48 to 84%). Bioavailability ranged between 10% and 65% across animal species. Time to maximum plasma drug concentration (Cmax) was between 2 and 4 hours. Terminal half-life (T 1/2) of LEE011 was moderate in rodents and monkeys (2 to 7 h), and was longer (18 h) in dogs.

The binding of LEE011 to plasma proteins was moderate (unbound fraction in human plasma for humans = 30). [^{3}H]-LEE011 and its metabolites are extensively distributed into the organs and tissues of rats including choroid, ciliary body and meninges with the exception of the brain. Radioactivity concentrations were highest in tissues such as the pituitary gland, pineal gland, spleen, kidney and adrenal medulla with remarkably high exposure in the thyroid gland. Distribution of LEE011 and/or its metabolites into melanin-containing structures was seen in pigmented rats.

Oxidative metabolism of LEE011 is dominated by CYP3A4 with a minor contribution of about 20% by flavin-containing monooxygenase 3 (FMO3). LEE011 is a moderate substrate of P-glycoprotein (P-gp). LEE011 is a time-dependent CYP3A4 inhibitor (KI 5.1 μM, kinact 0.0245 min^{-1}) and a reversible inhibitor of CYP1A2 at higher concentrations (Ki=16 μM). LEE011 inhibits the mitoxantrone-resistant protein (MXR; IC50=24 μM) and human bile salt export pump (BSEP; IC50=4.7 μM), but not the BSEP of rat or dog. LEQ803 (N-demethylation) is the main metabolite in humans, a major metabolite in the rat and monkey, and the only metabolite in dogs. This metabolite is weakly pharmacologically active; however, it interacts with hERG channels *in vitro*.

In rat ADME studies, LEE011 was predominantly excreted in the bile as metabolites, with limited excretion of unchanged drug in urine. The bulk of the administered dose (87%) was excreted within 24 h.

Overall, the elimination of LEE011 may potentially be affected by co-administered drugs that inhibit or induce CYP3A4. LEE011 may inhibit substrates of CYP3A4, CYP1A2, and BSEP, if sufficiently high concentrations are achieved *in vivo*.

Safety pharmacology and toxicology of LEE011

In vitro, LEE011 did not show mutagenic or phototoxic potential. Safety pharmacology studies conducted did not reveal any effects on CNS or respiratory functions. In the dog telemetry study, prolongation of the average QT and QTc was observed with the potential to induce PVCs at higher exposure levels. LEE011 and LEQ803 likely contributed to the QT prolonging effects seen *in vivo*.

In rats and dogs, LEE011 induced bone marrow hypocellularity, lymphoid depletion, atrophy of the skin and intestinal mucosa, decreased bone formation and testicular atrophy. The liver, bile system and gall bladder (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile) were identified as additional target organs of toxicity which are not likely related to the primary pharmacology of LEE011. Correlating hematological and/or biochemistry changes were seen for the effects described in the bone marrow, lymphoid system and liver. All of the described changes were fully reversible in rats and dogs.

Based on the mechanism of action and preclinical toxicology studies conducted, the major potential toxicities for LEE011 include myelosuppression, hepatic toxicity, and prolongation of the QT interval. The risk of these toxicities may be amplified by concomitant administration of strong inhibitors of CYP3A4.

Clinical Studies with LEE011

LEE011 is currently being investigated in patients as a single agent in 3 phase I studies: CLEE011X1101, CLEE011X2101, CLEE011X2102 and in combination in 10 studies: 8 phase Ib/II CLEE011X2105, CLEE011X2106, CLEE011X2107, CLEE011X2108, CLEE011A2112C, CMEK162X2114, CMEK162X2110, CLGX818X2102, a randomized phase II CLEE011A2201, and a randomized phase III CLEE011A2301. LEE011 is also being investigated in 3 clinical pharmacology studies in healthy subjects: CLEE011A2111, CLEE011A2101, and CLEE011A2106.

Single agent experience:

In single agent trials, a total of 179 patients have been treated: 132 in study CLEE011X2101 (in a Caucasian population, including 85 in the dose escalation), 15 in CLEE011X1101 (in Japanese patients, all in the dose escalation) and 32 in CLEE011X2102 (in patients under the age of 21 years, all in the dose escalation).

A total of 18 patients presented toxicities meeting the dose limiting toxicity (DLT) criteria (10 in CLEE011X2101, 4 in CLEE011X1101 and 4 in CLEE011X2102): these consisted of Grade 3 stomatitis, Grade 3 pulmonary embolism, Grade 3 hyponatremia, prolonged Grade 3/4 neutropenia (x2), prolonged Grade 2 elevated creatinine, Grade 4 thrombocytopenia (x5), Grade 3 asymptomatic QTcF prolongation with Grade 3 neutropenia, Grade 4 febrile neutropenia, Grade 3 febrile neutropenia (x2), Grade 3 electrocardiogram QT prolonged, Grade 3 fatigue, and Grade 3 asymptomatic QTcF prolongation with grade 4 neutropenia. The maximum tolerated dose (MTD) and recommended dose for expansion (RDE) from study CLEE011X2101 were declared as 900 mg qd and 600 mg qd on a 3 weeks on/1 week off schedule, respectively. At the RDE, the most common (in at least 2 patients) adverse events (AEs) related to study treatment were (all grades, Grade 3/4): neutropenia (46.3%, 28.4%), leukopenia (46.3%, 19.4%), nausea (44.8%, 1.5%), thrombocytopenia (34.3%, 9%), fatigue (32.8%, 3%), anaemia (28.4%, 3%), diarrhoea (26.9%, 3%), lymphopenia (22.4%, 17.9%), electrocardiogram QT prolonged (9%, 0%), hyponatremia (3%, 1.5%), and febrile neutropenia (1.5%, 1.5%). Preliminary data for clinical activity from study CLEE011X2101 show that out of 114 evaluable patients, 3 partial responses were seen at the 600 mg qd dose level: one in a BRAF/NRAS wild type, CCDN1 amplified melanoma patient, one in a CDKN2A loss head and neck acinar carcinoma patient, and one in an ER+/HER2-, PIK3CA

mutant, CCDN1 amplified breast cancer.

As of 28-Mar-2014, PK data were available from approximately 128 patients from the first-in human (FIH) study CLEE011X2101. Following oral dosing, LEE011 was rapidly absorbed with median Tmax ranging from 1 to 5 hours. LEE011 plasma exposure exhibited slightly over-proportional increases in exposure across the dose range tested (50 to 1200 mg), with no clear evidence of time-dependent auto-inhibition of its clearance mediated by CYP3A4. Steady-state was generally reached by Day 8 and the mean effective T1/2 based on accumulation ratio (i.e., T1/2,acc) ranged from 15.9 to 32.6 hours across the dose range tested. The accumulation ratio based on AUC obtained in a dosing interval (Racc) across the studied doses ranged from 1.55 to 2.52.

The MTD and RDE are still under evaluation for study CLEE011X1101 at the dose of 600 mg qd. In study CLEE011X2102, the MTD was determined to be 470 mg/m2 qd and the RDE was determined to be 350 mg/m^2 qd on a 3 week on/1 week off schedule in pediatric patients.
A food effect study conducted in healthy subjects CLEE011A2111 indicated that LEE011 administered as drug-in-capsule (DiC) can be taken without regard to meals.
A drug-drug interaction (DDI) study with ritonavir (a strong CYP3A4 inhibitor) and rifampicin (a strong CYP3A4 inducer) conducted in healthy subjects CLEE011A2101 indicated that concurrent use of strong CYP3A4 inhibitors or strong CYP3A4 inducers may markedly affect LEE011 exposure and should be avoided.
A DDI cocktail study with midazolam (a sensitive CYP3A4 substrate) and caffeine (a sensitive CYP1A2 substrate) was conducted in healthy subjects CLEE011A2106. Preliminary PK data indicate that LEE011 (400 mg) is a moderate inhibitor of CYP3A4, but did not have a substantial effect on CYP1A2 substrates in humans. Concurrent use of sensitive CYP3A4 substrates with a narrow therapeutic index should be avoided. Concurrent use of CYP1A2 substrates is not expected to lead to clinically important DDIs.

Combination trial experience:
LEE011 is being evaluated in several combination trials: letrozole (CLEE011A2201, CLEE011A2301]), letrozole and BYL719 CLEE011X2107, letrozole and buparlisib CLEE011A2112C, fulvestrant and buparlisib CLEE011X2108, everolimus and exemestane CLEE011X2106, LGX818 (CLEE011X2105, CLGX818X2102), MEK162 CMEK162X2114, or MEK162 and LGX818 CMEK162X2110. These trials are ongoing with the exception of CLEE011A2201 whose recruitment has been stopped on 28-July-2014. Phase I trials are still in the dose escalation phase. CLEE011A2201 and CLEE011A2301 are blinded trials and no safety data are available at the time of this update. The most recent DMC meeting was held for study CLEE011A2301 on 03-Sep-2014 after 86 patients have started treatment, and the IDMC recommended continuing the study without any changes.

Clinical pharmacokinetics of LEE011

The PK of LEE011 have been evaluated following single and repeat daily doses in the ongoing single agent, phase I study in patients with advanced solid tumors or lymphomas CLEE011X2101. Patients in all but one cohort received escalating doses of LEE011 once daily for 3 weeks followed by 1 week off schedule. In one cohort, patients received once daily

continuous dosing of 600 mg LEE011. PK sampling (pre-dose and 0.5, 1, 2, 4, 6, 8, and 24 h post-dose) was conducted on Days 1 and 18 or 21 of Cycle 1. Additional PK sampling (predose and 1, 2, and 4 h post-dose) was conducted on Days 8 and 15 of Cycle 1. Sparse samples were collected in Cycle 2 and subsequent cycles. Following oral dosing, LEE011 was rapidly absorbed with median Tmax ranging from 1 to 4 h. LEE011 exhibited slightly over-proportional increases in exposure (Cmax and AUC) across the dose range tested (50 to 1200 mg), with no clear evidence of time-dependent auto-inhibition of its clearance mediated by CYP3A4. Steady state was generally reached by Day 8 and mean T1/2, acc ranged from 15.9 to 32.6 h across the dose range (50 to 1200 mg). Mean Racc across the studied doses ranged from 1.55 to 2.52. At the 600 mg dose level, LEQ803, an active metabolite of LEE011, accounted for approximately 8% (geometric mean) of the LEE011 AUC0-24h after a single dose and after multiple doses. Further details regarding pharmacokinetics of single agent LEE011 and in combination with other agents is available in the IB.

1.5 Study purpose/rationale

Recent advances in molecular genetics have shed new light on the carcinogenesis of NETs. Evidence suggests aberrant cell cycle regulation due to aberrations in MENIN (MEN1), p27 (CDKN1B), p16 (CDKN2A), and Cyclin D1 (CCND1) is critical in the carcinogenesis and malignant progression of NETs.

The most common genetic cancer syndrome leading to the development of NETs is MEN1.[25] Germline mutation in MEN1 leads to the development of lung, thymic, and pancreatic NETs. Mutations in MEN1 appear to mediate carcinogenesis of NETs through dysregulation of p27, and p18.[26] Indeed, families with MEN1 phenotype without identifiable germline mutations in MEN1 have been found to have mutations in p27 (now called MENX syndrome).[27] This is further supported by the role of MENIN in regulating normal pancreatic islets. A study in mice showed that a physiologic function of MENIN is to regulate endocrine mass through p27.[28] During pregnancy, a down regulation of MENIN leads to suppression of p27, cell cycle progression, and an increase in pancreatic endocrine mass which serves to prevent gestational diabetes.

Somatic mutation in MENIN is also the most common genetic abnormality in sporadic foregut NETs and have been identified in approximately 40% of pancreatic and lung NETs.[29-32] We recently conducted exome sequencing of approximate 200 genes among 23 cases of advanced NETs treated with everolimus in our prior investigator-initiated phase 2 studies conducted at MDACC (unpublished data). In addition to confirming the presence of mutation in MEN1, we also identified the homozygous deletion of CDKN2A, CDKN2B (p15), as well as copy number amplification of CCND1. In addition, alterations in p16 may also be mediated by epigenetic modification. We previously also reported the methylation of p16 in 26% of NETs.

Studies have suggested that intact Rb function is a prerequisite for CDK 4/6 inhibitors activity. Multiple studies using various methods have documented this in foregut tumors [33-36]

Taken together, evidence suggests germ line mutations, somatic mutations and epigenetic silencing in NETs lead to dysregulation of CDK 4 and CDK 6 in a majority of patients with foregut NETs. This dysregulation leads to cell cycle progression, carcinogenesis and malignant progression. LEE011 is an inhibitor of CDK 4 and CDK 6. There is strong scientific rationale to study LEE011 in advanced NETs.

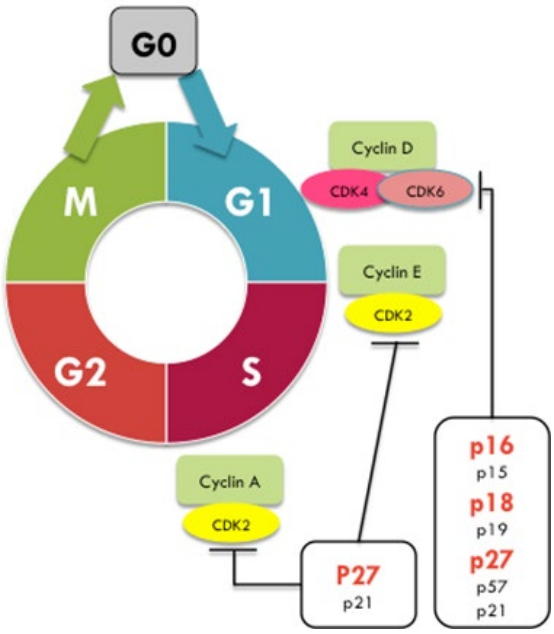

Figure 1: Regulation of CDK4, CDK6 and cell cycle by MENIN, p27, p18, and p16

2 Objectives and endpoints

Primary objective

- To estimate the RECIST (per version 1.1) objective response rate of LEE011 among patients with advanced foregut NETs

Secondary objectives

- To evaluate the progression free survival duration of LEE011 among patients with advanced foregut NETs
- To evaluate the safety and tolerability of LEE011 in patients with advanced foregut NETs

- To determine clinic benefit rate at 6 months (defined as complete response plus partial response plus stable disease) with LEE011 among patients with advanced foregut NETs

Explorative objectives

- To determine baseline molecular markers (mutations, deletions, and amplifications in MEN1, p27, p16 and CCND1) in archival tumor that may predict clinical benefit at 6 months from LEE011
- To determine potential mechanisms / markers of resistance
- To determine early chromogranin and neuron specific enolase responses in patients with elevated levels at baseline
- To determine the pharmacodynamic changes including Ki-67 and pRb upon treatment with LEE011 in patients with advanced foregut NETs

Objectives and related endpoints are described in the table below.

Table Objectives and related endpoints

	Objective	Endpoint	Analysis
Primary	RECIST objective response rate of LEE011 among patients with advanced foregut NETs	Radiographic RECIST (ver 1.1) response rate, ORR	Response rate with corresponding confidence interval
Secondary	Progression free survival duration of LEE011 among patients with advanced foregut NETs	PFS	Kaplan Meier estimate of median PFS with corresponding confidence interval
	Safety and tolerability	CTCAE v 4.0	Descriptive statistics of event rates for all grade and G3/4 events
Exploratory	Early CgA response rate	Early response as defined by a 30% decrease from baseline at week 4 among patients with elevated values at baseline	Response rate with corresponding confidence interval
	Early NSE response rate	Early response as defined by a 30% decrease from baseline at week 4 among	Response rate with corresponding confidence interval

		patients with elevated values at baseline	
	Baseline molecular markers in archival tumor that may predict clinical benefit at 6 months from LEE011	Mutations, deletions, and amplifications in MEN1, p27, p16 and CCND1	Descriptive statistics
	Pharmacodynamic effect of LEE011 on Ki 67, pRB	Paired measurement of Ki 67, pRB	Descriptive statistics including mean and median. Comparison will be made with paired-sample T-test or non-parametric test as appropriate

3 Investigational plan

3.1 Overview of Study Design

This is an open-label, single center, phase II study of LEE011. Patients with **advanced, progressive pancreatic NET and foregut carcinoids** and adequate organ function, performance status will be recruited. **Patients will be treated with LEE011 600 mg po daily 3 weeks on/1 week off in 28 day cycles.** This dose is based on prior phase I trials of this drug. Patients will be allowed to remain on study until disease progression or unacceptable toxicities. Toxicity evaluations will be conducted at the beginning of each cycle while radiographic tumor evaluations will be carried out at baseline and every 3 cycles thereafter.

The primary objective of the study is objective response rate and secondary objectives include progression free survival, safety analyses. Baseline molecular markers in archival tumor tissue will be evaluated for potential predictive markers to LEE011 therapy as exploratory objectives. A response rate of <5% will be considered unacceptable i.e. the signal for further, larger studies with LEE011 in this patient population is ≥ 1 response. Refer to the statistical analysis section for greater detail.

3.2 Investigational treatment

The investigational study drug used in this trial is LEE011, which is supplied as capsules.

3.3 Treatment arm

Patients with histologically or cytologically confirmed, advanced, unresectable well differentiated neuroendocrine tumors (low or intermediate grade) that have progressed in the last 12 months will be accrued. They will consist of patients with advanced PNET who have progressed on prior therapy or (non-pancreatic) advanced foregut carcinoids with progressive disease in the last 12 months.

3.4 Treatment duration

Patients will continue on therapy until progressive disease or unacceptable toxicities or other criteria as listed below:
-Evidence of recurrent or progressive disease
-Second malignancy
-Development of unacceptable toxicity during treatment
-Anaphylactic reactions to LEE011
-Non-adherence to the protocol
-Refusal of therapy
-Physician decides it is in the best medical interest of the patient
-Positive pregnancy test after receipt of study agent
-Completed all planned therapy

Off Study Criteria:
-Death
-Lost to follow-up
-Enrollment on another therapeutic study or non-protocol therapy for disease
-Withdrawal of consent
-Authorizes consent but does not receive study agent(s) due to development of significant health disorder or change in health status

3.5 Rationale for the study design

This is a single center, exploratory study evaluating the activity of LEE011 in patients with advanced foregut neuroendocrine tumors i.e. carcinoid tumors and pancreatic NETs.

4 Population

Patients with radiographically measurable, advanced, unresectable PNETs with progression after prior therapy, and other foregut carcinoids with evidence of progression in the past 12 months prior to screening will be eligible for this study.

4.1 Inclusion criteria

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

1. Histologically or cytologically confirmed low or intermediate grade, unresectable well differentiated foregut neuroendocrine tumors (thymic, bronchopulmonary, gastric, duodenal and pancreatic). Patients with multiple neuroendocrine tumors associated with MEN1 syndrome will be eligible.
2. Patients must have radiographically measurable disease.
3. Pancreatic neuroendocrine patients must have had progression after prior therapy. Patients with other foregut neuroendocrine tumors must have had progressive disease over the last 12 months, irrespective of prior therapy. Patients with both functional (who may continue somatostatin analogues as required for control of related symptoms) and non-functional tumors are eligible. In patients who have previously received therapy, the number of prior lines of therapy should not be more than 2 lines of systemic therapy not including somatostatin analogues.
4. Written informed consent must be obtained prior to any screening procedures
5. Age ≥ 18 years.
6. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 1.
7. A sufficient interval must have elapsed between the last dose of prior anti-cancer therapy (including cytotoxic and biological therapies and major surgery) and enrollment, to allow the effects of prior therapy to have abated:
   a. Cytotoxic or targeted chemotherapy: ≥ the duration of the cycle of the most recent treatment regimen (a minimum of 3 weeks for all regimens, except 6 weeks for nitrosoureas and mitomycin-C)
   b. Biologic therapy (e.g., antibodies): ≥ 4 weeks
8. Patients must have adequate organ function, as defined by the following parameters:
   a. Bone marrow:
      - Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L
      - Hemoglobin (Hgb) ≥ 9 g/dL
      - Platelets ≥ 100 x 10^9/L
   b. Hepatic function:
      - Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN) Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT]) and ALT (SGPT) ≤ 2.5 x ULN, except in patients with tumor involvement of the liver who must have AST and ALT ≤ 5 x ULN
   c. Renal function:
      - Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 mL/min
      - Serum potassium, sodium, magnesium, phosphorus and total calcium (corrected for serum albumin) must be within clinically relevant limits (e.g., a patient can be enrolled if a lab value may be outside the normal laboratory range but the abnormality is not clinically relevant or can be repleted.)

9. Negative pregnancy test (serum β-HCG) within 7 days of starting study treatment is required in women of childbearing potential. β-HCG may be secreted by a small percentage of NETs and be a tumor marker. Thus, NET patients with positive β-HCG are eligible if pregnancy can be excluded by vaginal ultrasound or lack of expected doubling of β-HCG.

4.2 Exclusion criteria

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

1. Patient has a known hypersensitivity to LEE011 or any of its excipients.
2. Patients with known or suspected brain metastases. However, if radiation therapy and/or surgery has been completed and serial evaluation by CT (with contrast enhancement) or MRI over a minimum of 3 months demonstrates the disease to be stable and if the patient remains asymptomatic, then the patient may be enrolled. Such patients must have no need for treatment with steroids or anti-epileptic medications.
3. Patients with concurrent malignancies or malignancies within 3 years prior to starting study drug (with the exception of tumors common to a single genetic cancer syndrome, i.e. MEN1, MEN2, vHL, TSC etc., or adequately treated, basal cell skin cancer, squamous cell carcinoma, non-melanoma skin cancer or curatively resected cervical cancer).
4. Patient is not able to swallow oral medication and/or has impairment of 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).
5. Known diagnosis of human immunodeficiency virus (HIV) or hepatitis C (testing is not mandatory)
6. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, contraindicate patient participation in the clinical study (e.g. chronic pancreatitis, chronic active hepatitis, etc.).
7. Patient who has received radiotherapy within ≤ 4 weeks or limited field radiation for palliation within ≤ 2 weeks prior to starting study drug, and who has not recovered to grade 1 or better from related side effects of such therapy (exceptions include alopecia) and/or in whom ≥ 30% of the bone marrow was irradiated.
8. Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects (tumor biopsy is not considered as major surgery).
9. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
    a. History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis < 12 months prior to screening
    b. History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    c. Documented cardiomyopathy

d. Patient has a Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO) at screening
e. History of ventricular, supraventricular, nodal arrhythmias, or any other cardiac arrhythmias, long QT Syndrome or conduction abnormality within 12 months prior to starting study drug
f. Congenital long QT syndrome or a family history of QTc prolongation
g. On screening, inability to determine the QTcF interval on the ECG (i.e.: unreadable or not interpretable) or QTcF >450 msec (using Fridericia's correction). All as determined by screening ECG (mean of triplicate ECGs)

10. Systolic blood pressure >160 mmHg or <90 mmHg at screening.
11. Patients who are currently receiving treatment with agents that are known to cause QTc prolongation or inducing Torsades de Pointes in humans and are unable to discontinue or switch to an alternate medication.
12. Patients who are currently receiving treatment (within 5 days prior to starting study drug) with agents that are known strong inducers or inhibitors of CYP3A4/5, or that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.
13. Patients with concurrent severe and/or uncontrolled concurrent medical conditions that could compromise participation in the study (e.g., uncontrolled diabetes mellitus defined by a glucose > 1.5 ULN in spite of adequate medical treatment, clinically significant pulmonary disease, clinically significant neurological disorder, active or uncontrolled infection)
14. Patient has a history of non-compliance to medical regimen or inability to grant consent.
15. Pregnant or 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 (> 5 mIU/mL).
16. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception throughout the study and for 8 weeks after study drug discontinuation. 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 taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
    - Combination of any of the two following (a+b or a+c or b+c)
        a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository

In case of use of oral contraception, women should have been stable on the same pill before taking study treatment.

Note: Oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction.

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.

17. Sexually active males unless they use a condom during intercourse while taking the drug and for 21 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
18. Patients unwilling or unable to comply with the protocol.
19. Patient is currently receiving warfarin or other coumarin-derived anticoagulant for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH) or fondaparinux is allowed.

5 Treatment

5.1 Treating the patient

The investigator needs to instruct the patient to take the study drug as per protocol. All dosages prescribed and dispensed to the patient and any dose change or interruption must be recorded as appropriately.

5.1.1 Administration

Table 5-1 Treatment and treatment schedule

Study treatment	Pharmaceutical form and route of administration	Dose	Frequency and/or regimen
LEE011	Capsule for oral use	600 mg	Daily (21 days with 7 days of rest)

LEE011 will be taken orally, once a day for 21 consecutive days followed by a 7 day planned break. LEE011 will be dosed on a flat dosing scale of 600 mg/day, irrespective of size and weight. Medication labels will be in the local language and comply with the legal requirements.

5.1.2 Dosing and treatment schedule

The following general guidelines should be followed for LEE011 administration:

- Patients should be instructed to take their once-a-day dose at approximately the same time each day. LEE011 can be taken without regard to meals.
- Each daily dose of LEE011 should be taken with a glass of water and consumed over as short a time as possible unless otherwise instructed
- Patients should be instructed to swallow capsules whole and to not chew or open them unless otherwise instructed.
- If vomiting occurs during the course of the treatment, then no re-dosing of the patient is allowed before the next scheduled dose
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.
- Patients should inform the study team of any missed or delayed doses
- Patients must avoid grapefruit products/juice, and Seville (sour) oranges/juice during the entire study. Orange juice is allowed.
- On a day of lipid panel sampling, patients must be fasting from all food and drink for at least 8 hours overnight. Water is allowed during all fasting periods; however coffee, tea and juice are not permitted during the fasting period.

5.1.3 Dose modification and dose delay

Investigators should follow the guidelines described below for the modification of LEE011 treatment. Toxicities will be graded per the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Any plan to deviate from these guidelines in view of the patient safety must be previously discussed with Novartis unless there is an urgent need for action.

All dose modifications should be based on the worst preceding toxicity. If study treatment is being held due to toxicity, scheduled visits and all assessments should continue to occur except the dosing of the study drug. If the patient requires a dose interruption of > 21 days from the previous dose, then the patient must be discontinued from study treatment. Patients who discontinue the treatment due to an adverse event or an abnormal laboratory value must be followed until resolution or stabilization of the event. All dose changes or interruptions must be recorded appropriately. Provisional dose levels can be found in the table below.

Table 5-2 Dose Modification Guidelines

	LEE011	
	Dose	**Number of capsules & strength**
Starting dose	600 mg	3 x 200 mg capsules
First dose reduction	400 mg	2 x 200 mg capsules
Second dose reduction	200 mg	1 x 200 mg capsules

Table 5-3 Recommended Dose Modifications and Dose Delays for suspected LEE011 treatment-related toxicities (except for Hematologic toxicities & QTC Prolongation as outlined in subsequent tables)

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

Table 5-4 Study drug dose modification and management recommendation for hematological AEs

Toxicity	Grade	Dose Adjustment and Management Recommendations
Thrombocytopenia	1 ≥75 x 10^9/L	No dose adjustment required.
	2 50 x 10^9/L - <75 x 10^9/L	Dose interruption until recovery to grade ≤1. Re-initiate LEE011 at the same dose.
	3 25 x 10^9/L - <50 x 10^9/L	Dose interruption until recovery to grade ≤1. Re-initiate LEE011 at the same dose level. • If toxicity recurs at grade 3: temporary dose interruption until recovery to grade ≤1 and reduce LEE011 to the next lower dose level.
	4 <25 x 10^9/L	Dose interruption until recovery to grade ≤1. Re-initiate LEE011 at the next lower dose level. • If toxicity recurs at grade 4: discontinue LEE011.
Absolute neutrophil count (ANC)	1 ≥1.5 x 10^9/L	No dose adjustment required.
	2 1.0 - <1.5 x 10^9/L	No dose adjustment required.
	3 0.5 - <1.0 x 10^9/L	Dose interruption until recovery to >1.0 x 10^9/L. Re-initiate LEE011 at the same dose level. • If toxicity recurs at grade 3: temporary dose interruption until recovery to >1.0 x 10^9/L and reduce LEE011 dose to the next lower dose level.
	4 <0.5 x 10^9/L	Dose interruption until recovery to >1.0 x 10^9/L. Re-initiate LEE011 at the next lower dose level. • If toxicity recurs at grade 4: temporary dose interruption until recovery to >1.0 x 10^9/L and reduce LEE011 at the next lower dose level.
Febrile neutropenia	3 ANC <1.0 x 10^9/L with [a single temperature of >38.3°C (101°F) or a sustained temperature ≥38°C (100.4°F) for more than one hour]	Dose interruption until improvement of ANC ≥ 1.0 x 10^9/L and no fever. Restart at the next lower dose level. • If febrile neutropenia recurs, discontinue LEE011.
	4 Life-threatening consequences; urgent intervention indicated	Discontinue LEE011.
Anemia (Hemoglobin)	1 10.0 – LLN g/dL	No dose adjustment required.
	2 8.0 – 10.0 g/dL	No dose adjustment required.
	3 <8.0 g/dL	Dose interruption until recovery to grade ≤ 2. Re-initiate LEE at the same dose.
	4 Life-threatening consequences; urgent intervention indicated	Discontinue LEE011.

Table 5-5

Recommended Dose Modification guidance in case of QT prolongation

Grade	Dose Modification
For all grades	• Check the quality of the ECG. • Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If below the lower limit of normal, interrupt LEE011 administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. • Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. • Check compliance with correct dose and administration of LEE011.
1 QTc 450-480 ms	No dose adjustment required.
2 QTc 481-500 ms	Interrupt LEE011 Perform a repeat ECG one hour after the first QTcF of ≥418ms • If QTcF <481 ms, restart LEE011 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 LEE011 at the same dose level. No dose adjustments required for first occurrence. • If QTcF ≥481 ms recurs, LEE011 should be reduced by 1 dose level (please refer to the dosing schedule table) • Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patient who has therapy interrupted due to QTcF ≥481 ms
3 QTc ≥501 ms on at least two separate ECGs	Interrupt LEE011 • Consider consulting a local cardiologist. Perform a repeat ECG one hour after the first QTcF of ≥501 ms. • If QTcF remains ≥501 ms, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to <481 ms. • If QTcF returns to <481 ms, LEE011 should be reduced by 1 dose level (please refer to the dosing schedule table) • Repeat ECGs 7 days and 14 days after dose resumption for any patient who has therapy interrupted due to QTcF ≥501 ms • If QTcF of ≥501 ms recurs, discontinue LEE011
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 LEE011 • 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.

5.1.4 Concomitant therapy

The investigator should instruct the patient to notify the study team about any new medications including herbals and supplements he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be recorded appropriately.

In general, medications required to treat AEs, manage cancer-related symptoms including pain medications are allowed at investigator's discretion. Medications which are being used to manage underlying medical conditions (except for those medications specifically mentioned in the inclusion/exclusion criteria) at study entry will be allowed to continue at investigator's discretion. Concomitant medications will be recorded in PDMS/CORe.

Concomitant therapy requiring caution

The following therapies are permitted when used with caution:

- Moderate inhibitors or inducers of CYP3A4/5
- Sensitive substrates of CYP3A4/5 that do not have narrow therapeutic index
- Strong inhibitors of BSEP
- Medications that carry a possible risk for QT prolongation
- Sensitive substrates of the renal transporters, MATE1 and OCT2, and sensitive substrates of BCRP.

Table 5-6 : Medications to be used with caution during LEE011 therapy

Category	Drug Name
Moderate CYP3A4/5 inhibitors	Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, darunavir, diltiazem, dronedarone, fluconazole, fosamprenavir, grapefruit juice (citrus paradisi fruit juice), imatinib, Schisandra sphenanthera[1], tofisopam, verapamil
Moderate CYP3A4/5 inducers	Bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, talviraline, thioridazine
Sensitive CYP3A4/5 substrates[1]	Alfentanil, aAlpha-dihydroergocryptine, aplaviroc, aprepitant, atorvastatin, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, sildenafil, simvastatin, ticagrelor, tolvaptan, triazolam, vardenafil, vicriviroc
Strong BSEP inhibitors	Bosentan, fusidate, glibenclamide, lovastatin, sulindac, troglitazone (TGZ-sulfate)
MATE1 Medications that carry a possible risk for QT prolongation[2]	Alfuzosin, amantadine, atazanavir, chloral hydrate, clozapine, dolasetron, dronedarone, eribulin, escitalopram, famotidine, felbamate, fingolimod, foscarnet, fosphenytoin, gatifloxacin, gemifloxacin, granisertron, iloperidone, indapamide, isradipine, lapatinib, levofloxacin, lithium, moexipril, nicardipine, nilotinib, octreotide, ofloxacin, ondansetron, oxytocin, paliperidone, pasireotide, quetiapine, ranolazine, risperidone, roxithromycin, sertindole, sunitinib, tamoxifen, tizanidine, vardenafil, venlafaxine, ziprasidone
MATE1 and OCT2 substrates[3]	Acyclovir, amantadine, amiloride, cephalexin, cephradine, cimetidine, famotidine, fexofenadine, memantine, metformin (also a substrate for OCT1, MATE1, and MATE2K), pindolol, procainamide, ranitidine, and varencicline
BCRP substrates	Daunorubicin, doxorubicin, rosuvastatin, sulfasalazine, topotecan

[1] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.

[2] Source: www.crediblemeds.org

[3] Source: FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and implications for Dosing and Labeling (February 2012) and Yonezawa and Inui (2011) Importance of the multidrug and toxin extrusion MATE/SLC47A family to pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics. Br J Pharmacology 164:1817-25

5.1.5 Prohibited concomitant therapy

Other anti-neoplastic therapy is prohibited. Concurrent somatostatin analogue given for control of hormonal syndrome is allowed.

Other investigational therapies

Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatment must not be given to patients while the patient is on the study medication.

Strong CYP3A inhibitors and inducers

Patients receiving concomitant medications including vitamins, supplements and herbal supplements known to strongly inhibit and/or induce CYP3A4/5 and that are deemed medically necessary should be excluded from the study. Patients should be instructed not to take grapefruit, Seville oranges or products containing the juice of each while receiving LEE011 treatment throughout the study due to its potential for CYP3A4/5 inhibition.

Table 5-7 List of prohibited medications during LEE011 treatment

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

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

5.2 Study drug(s)

5.2.1 Packaging and labeling

LEE011 hard gelatin capsule will be supplied by Novartis as 200-mg hard gelatin capsules for oral use, packaged in bottles, and will be administered on a flat scale of mg/day.

Medication will be labeled for Clinical Trial use and will include storage conditions for the drug and the medication number but no information about the patient.

Table Packaging and labeling

Study drugs	Packaging	Labeling (and dosing frequency)
LEE011	hard gelatin capsules in bottles (200 mg)	Labeled as ”LEE011”

5.2.2 Supply, receipt and storage

Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, LEE011 should be stored according to the instructions specified on the drug labels. Study medication will be dispensed by an authorized person at the investigator’s site.

Patients will be provided with adequate supply of LEE011 for self-administration at home until at least their next scheduled study visit.

5.2.3 Drug compliance and accountability

Drug accountability

Clinical drug supply must be accounted for and patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and, as appropriate during the course of the study, the Investigator will return all unused study drug (except as indicated in section 5.2.4), packaging, drug labels, and a copy of the completed drug accountability ledger to Novartis.

5.2.4 Disposal and destruction

The drug supply will be destroyed at a Novartis facility, or at MD Anderson, as appropriate. Study drug destruction at MD Anderson will only be permitted if authorized by Novartis. The unused study drug will be destroyed per MD Anderson Cancer Center standard policy.

6 Visit schedule and assessments

6.1 Study flow and visit schedule

The table below lists all of the assessments and indicates with an "X" the visits when they are performed.

Note: All assessments should be performed within ± 3 days, unless otherwise specified as in the case of restaging radiographic evaluation which may be done within 7 days of the end of every 3rd cycle. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Screening tests may be done between days -28 to -1. For cycle 1 day 1 treatment, screening laboratory values, medical history, physical exam may be used if done within 10 days .

Table 6-1 Visit evaluation schedule

	Screening	Treatment				Subsequent cycles	End of Treatment	End of Post Treatment Follow-Up
		Cycle 1		Cycle 2		Cycle 3 +		
Day of cycle	**Screening**	**1**	**15**	**1**	**15**	**1**	**EOT**	**30 days after last dose**
Informed consent	X							
Inclusion/ exclusion criteria	X							
Relevant medical history[9]	X	X		X		X		
Physical exam[9]	X	X	X	X		X	X	
Vitals[9]	X	X	X	X		X	X	
Hematology[9]	X	X	X	X		X	X	
Biochemistry[9]	X	X	X	X		X	X	
Coagulation[1]	X	X		X		X	X	
Urinalysis[2]	X						X	
Lipid Panel[13]	X					X	X	
ECG[11]	X		X	X	X	X	X	
Echo / MUGA[12]	X						X	
Pregnancy Test[3]	X							
Archival Tumor Tissue[4]	X							
Tumor Biopsy[5]	X			X			X[6]	
Blood for genomic DNA[10]	X							
Radiographic Evaluation[7]	X					X[7]		
Serum Tumor Markers[8]	X			X		X		
LEE011 dosing		Continuous (21 days with 7 days of rest)						
Concomitant medications		**Continuous monitoring**						
Progression free survival		**Continuous monitoring**						

	Screening	Treatment				Subsequent cycles	End of Treatment	End of Post Treatment Follow-Up
		Cycle 1		Cycle 2		Cycle 3 +		
Day of cycle	**Screening**	**1**	**15**	**1**	**15**	**1**	**EOT**	**30 days after last dose**
Adverse events		**Continuous Monitoring (up to 30 days post treatment discontinuation)**						
	1 Coagulation profile includes a prothrombin time (PT) or International normalized ratio (INR), activated partial thromboplastin time (aPTT) and fibrinogen at baseline and as required per treating physician discretion every cycle in patients on anticoagulation 2 Urinalysis includes specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes and blood 3 Women with child-bearing potential will be screened with serum β-HCG. In patients with positive serum β-HCG, pregnancy can be excluded by vaginal ultrasound or lack of expected doubling of β-HCG (every 3 days). 4 Treatment need not be held until procurement of archival tissue 5 Mandatory pre-treatment and cycle 2 day 1 tumor biopsies in all patients in whom they may be obtained safely. Post treatment biopsies may be obtained +/- 3 days of cycle 2 day 1. 6 Optional EOT biopsies will be obtained in patients with initial response or prolonged stable disease (>6 months) 7 Radiographic evaluation will be with CT, MRI and/or Octreoscan and will be obtained at baseline and at the end of every 3 cycles subsequently. Choice of radiographic test (including octreoscans) per discretion of physician; For patients with known or suspected brain metastases, CT head with contrast or MRI at baseline and as clinically indicated thereafter. Confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response. 8 Serum tumor markers including chromogranin-A, neuron specific enolase will be obtained at baseline, cycle 2, Day 1, cycle 4 day 1 and every 3 cycles thereafter. These tests may be obtained more frequently per treating physician's discretion 9Physical exam with vitals, weight and performance status will be obtained at each clinic visit. All evaluations during and after cycle 3 will be obtained on day 1 +/- 3 days except for radiographic evaluations which will be obtained at the end of every 3 cycles within a window of 7 days. Hematology tests: CBC with platelets and differential; Serum biochemistry tests: BUN, Creatinine, direct and indirect bilirubin, total protein, alkaline phosphatase, albumin, ALT, AST, glucose, electrolytes including, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus. 10Blood for genomic DNA will be obtained at baseline. 11 ECGs will be performed as per section 6.2.1 and Table 6.2 after the patient has been resting for 5-10 minutes prior to each time point. If an abnormal ECG is obtained at any time, patient's electrolytes must be reviewed and repeat ECG measurements must be done after correction of electrolyte abnormalities. For patients with QTcF ≥481 ms, interrupt study treatment and follow the procedures described in the "LEE011 Dose Modification" section. If treatment is resumed, repeat ECGs 7 days and 14 days after dose resumption (and then as clinically indicated). ECGs will be performed according to the schedule in (Table 6-2). 12 Echocardiogram or MUGA scan in patients with prior history of heart failure who have not had LVEF evaluated in the past 6 months or in patients with clinical signs / symptoms suggestive of heart failure. 13. Fasting lipid panel including triglycerides, total cholesterol, HDL, LDL at baseline and every 4 cycles.								

6.1.1 Screening Examination

The screening examination must start with the Informed Consent procedure. The investigator is obliged to give the patient thorough information about the study and the study related assessments, and the patient should be given ample time to consider his or her participation. The investigator must not start any study related procedure before ICF is signed and dated by both patient (and impartial witness, if applicable) and investigator.

6.2 Assessment types

6.2.1 Electrocardiogram

Standard twelve-lead ECGs should be obtained after the patient has been resting for 5-10 minutes prior to each time point indicated. All ECGs should be recorded with the patient in the same physical position. Screening ECGs should be obtained in triplicate approximately 2 minutes apart.

If an abnormal ECG is obtained at any time, patient's electrolytes must be reviewed and repeat ECG measurements must be done after correction of electrolyte abnormalities. For patients with QTcF ≥481 ms, interrupt study treatment and follow the procedures described in the "LEE011 Dose Modification" section. If treatment is resumed, repeat ECGs 7 days and 14 days after dose resumption (and then as clinically indicated). ECGs will be performed according to the schedule in (Table 6-2).

Table 6-2 ECG Collection Schedule

Scheduled time points		
Screening		Anytime during the screening period. Triplicate ECGs approximately 2 minutes apart
Cycle	**Day**	**Sampling time**
1	15	pre-dose
2	1	pre-dose
2	15	pre-dose, 2-4 hours post dose
3	1	pre-dose, 2-4 hours post dose
4 -6	1	Predose up to cycle 6
Unscheduled		As clinically indicated
End of Treatment		Within 14 days of last dose
All measurement times are relative to dose of LEE011 unless otherwise specified.		

6.2.2 Efficacy

Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response after 3 cycles +/- 1 week. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response. The PI will be responsible for determining each participants' response to treatment. The PI will document the response to treatment on a protocol-specific response form. The PI will sign the form and it will be included as part of the patient's medical record.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter for non-nodal lesions and short axis for nodal lesions to be recorded) as $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan, or $\geq$10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. In order for such lesions to be considered measurable, the radiation must be greater than 6 months prior to the study initiation, and there must have been subsequent evidence of disease progression in the radiated tumor lesions.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in short axis when assessed. At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts 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 non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation 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.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should

not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

d.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of 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 progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	

SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Response Review

The PI will be responsible for determining each participant's response to treatment. All imaging will be done with no thicker than 2.5 mm reconstruction as per the standard of care for our institutional imaging.

6.2.3 Safety

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the monitoring of hematology, blood chemistry, ECG and the regular monitoring of vital signs, and physical exam including weight; and performance status.

6.2.4 Biomarkers

Biomarkers (from blood and/or tissue as indicated on Table 6.1) will be obtained for the following objectives:

1) To evaluate efficacy of target inhibition with LEE011 therapy
2) To evaluate for predictors of response to LEE011
3) To evaluate for markers of resistance to LEE011 therapy

Archival tumor tissue equivalent to at least 2 core biopsies will be collected prior to initiation of treatment. Paired pre- and post- treatment tumor biopsy will be obtained from all patients (required). Pre-treatment biopsy will be obtained within 4 weeks before initiating therapy. Post-treatment tumor biopsy will be obtained on day 1 (+ / - 3 days) of cycle 2. All FNA biopsies to be used for molecular profiling will be frozen immediately. Tissue will be picked-up by the laboratory personnel of Funda Meric-Bernstam. Tissue biomarker studies will be performed at the laboratory of Funda Meric-Bernstam, University of Texas M. D. Anderson Cancer Center.

This tumor tissue will be used to asses Ki67 and levels of pharmacodynamics markers including but not limited to pRB and cyclin D1 cyclin E, p16, p21 and p27 at baseline and at cycle 2 day 1. Marker expression will be assessed by a pathologist blinded to outcomes and treatment status. Level of marker expression will be assessed by H score, incorporating both intensity (0 to 3), and percentage of cells stained; thus providing a score of 0-300. For IHC, we will compare the H-score at baseline to H-scores on-treatment.

In addition, genomic profiling including methylation, mutations, deletions and amplifications in the CDK 4/6 pathway genes including but not limited to *MEN1*, Cip/Kip protein genes such as *CDKN1B* (coding for p27), INK4 protein genes such as *CDKN2A* (coding for p16), D-cyclin genes such as *CCND1, CCND2, CCND3* (coding for cyclins D 1-3), *CDK4, CDK6* will be also be performed.

Optional biopsies will be taken at the end of study in patients who are willing and have demonstrated partial response or prolonged progression free survival. These biopsies will be analyzed with additional targeted sequencing in addition to other assays such as FISH, RNA seq, IHC, RPPA, methylation assays, rearrangement assays through the MD Anderson unusual responders program.

Blood for genomic DNA will be collected at baseline.

Serum tumor markers including chromogranin-A, neuron specific enolase will be obtained at baseline, cycle 2, Day 1, cycle 4 day 1 and every 3 cycles thereafter. These tests may be obtained more frequently per treating physician's discretion.

Descriptive statistics will be presented by response category in an attempt to characterize these changes with respect to efficacy.

7 Safety monitoring and reporting

7.1 Adverse Events

7.1.1 Definitions and reporting

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (LEE011), even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded.

Information about all serious adverse events will be collected and recorded on the FDA MedWatch 3500a form for reporting to the supporting drug company, Novartis. To ensure patient safety each serious adverse event must also be reported to Novartis within 24 hours of learning of its occurrence. Please refer to Section 7.1.2 for the definition of a serious adverse event.

Events not considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, should also be reported on the serious adverse event form and Novartis Clinical Study Pregnancy Form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Safety monitoring and reporting

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

Protocol specific data and adverse events will be documented in the medical record and entered into PDMS/CORe. PDMS/CORe will be used as the electronic case report form (CRF) for this protocol.

Adverse events

Definitions and reporting

Adverse events that begin or worsen after informed consent should be recorded in PDMS/CORe. Conditions that were already present at the time of informed consent should be recorded in the Medical History section of PDMS/CORe. . 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.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during 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 if continuing at the Safety Follow-up Visit)
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, hospitalized, 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 sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section7.1.2.

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drugs can be found in the [Investigators' Brochure]. This information should be included in the patient informed consent and should be discussed with the patient during the study as needed.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment

Laboratory test abnormalities

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

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per 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 and is still, by definition, an adverse event.

7.1.2 Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- (**Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last study treatment/intervention, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

7.2 Communications between Investigator and Novartis

7.2.1 Reporting responsibility

The principal investigator has the obligation to report all serious adverse events to Novartis Drug Safety and Epidemiology (DS&E)

7.2.2 Reporting procedures to Novartis

The investigator must complete the FDA MedWatch 3500a form and Novartis SAE coversheet in English, assess the relationship to study treatment and send the initial completed MedWatch form and Novartis SAE coversheet by fax 1.888.299.4565 within 24 hours to the local Novartis Drug Safety and Epidemiology (DS&E). The investigator must then ensure that the form and coversheet are accurately and fully completed with follow-up information and fax those to Novartis Drug Safety and Epidemiology (DS&E) within 2 to 3 calendar days for deaths or life-threatening events and 5 calendar days for other serious adverse events. The original and the duplicate copies of the FDA MedWatch form, Novartis SAE coversheet, and the fax confirmation sheet must be kept with the case report forms at the study site.

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The MedWatch form, Novartis SAE coversheet, and fax confirmation sheet must be retained. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

7.2.3 Pregnancies

Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also 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 birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology (DS&E) department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8 Statistical methods and data analysis

This is a single arm, open-label exploratory/ phase II study. Since no effective treatments are available in this setting, a response rate of 15% (within 95% CI) is considered acceptable – i.e., the signal for launching further, larger studies with LEE011 in this patient population is ≥ 1 response in the current study. If no response is observed, the treatment LEE011 is considered ineffective. A total of 20 patients will be enrolled and treated to rule out a response rate of 15% of less when at least one response is observed with 96% power. In other words, with twenty patients treated, the probability of observing at least one response is more than 96% if the response rate is at least 15%. Descriptive statistics including with 90% confidence interval will be computed. Observed response profile, clinical benefit rate at 6 months and PFS along with relevant confidence intervals will be used to guide future development decisions.

Total evaluable patients	Number of responders	Response rate	Lower 90% CI	Upper 90% CI
20	0	0%	0	13.9
20	1	5%	0.3	21.6
20	2	10%	1.8	28.3
20	3	15%	4.2	34.4
20	4	20%	7.1	40.1
20	5	25%	10.4	45.6
20	6	30%	14	50.8
20	7	35%	17.7	55.8
20	8	40%	21.7	60.6
20	9	45%	25.9	65.3
20	10	50%	30.2	69.8
20	>10*	>50%	>34.7%	>74.1%

* Actual response rate with corresponding CI will be calculated. Exact confidence interval was calculated for all responses.

Kaplan-Meier method will be used to compute the survival rate for the time-to-event endpoints such as PFS. The efficacy in biomarker subgroups will be summarized by descriptive statistics.

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9 Ethical considerations and administrative procedures

9.1 Ethics and good clinical practice

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
4. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

9.2 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Any amendments to the protocol, must be approved by Novartis, the IND office, and this committee.

9.3 Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

Fertile men and 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.

9.4 Discontinuation of the study

Novartis reserves the right to discontinue support for any study under the conditions specified in the clinical trial agreement.

9.5 Amendments to the protocol

Any change or addition, including administrative aspects, to this protocol requires a written protocol amendment that must be approved by Novartis, the IND office and the IRB before implementation. A copy of the written approval of the IRB/IEC/REB, must be sent to Novartis.

9.6 Publication of results

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and prior to any outside submission. Novartis must receive copies of any intended communication in advance of publication (at least twenty-one working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Novartis' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Novartis and, in accord with the trial contract and shall not permit disclosure of Novartis confidential or proprietary information.

9.7 Disclosure and confidentiality

The investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Novartis (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

9.8 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

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